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JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the
American Society of Clinical Oncology

2017 ASCO Annual Meeting Proceedings

53rd Annual Meeting
June 2-6, 2017
McCormick Place
Chicago, IL

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ASCO

53rd
Annual Meeting of the American Society of Clinical Oncology
June 2-6, 2017

Chicago, Illinois

2017 Annual Meeting Proceedings

(a supplement to the *Journal of Clinical Oncology*)

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Supplement to May 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

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CONTENTS

2017 ASCO ANNUAL MEETING PROCEEDINGS

Special Award Lecture Abstracts 1s

Plenary Session
(Abstracts LBA1 - LBA4) 4s

Special Clinical Science Symposia
(Abstracts LBA100 - 109) 6s

Breast Cancer—Local/Regional/Adjuvant
Scheduled presentations (Abstracts LBA500 - TPS595) 9s

Breast Cancer—Metastatic
Scheduled presentations (Abstracts 1000 - TPS1127) 32s

Cancer Prevention, Hereditary Genetics, and Epidemiology
Scheduled presentations (Abstracts 1500 - TPS1592) 63s

Central Nervous System Tumors
Scheduled presentations (Abstracts 2000 - TPS2086) 86s

Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics
Scheduled presentations (Abstracts 2500 - TPS2621) 107s

Developmental Therapeutics—Immunotherapy
Scheduled presentations (Abstracts 3000 - TPS3116) 138s

Gastrointestinal (Colorectal) Cancer
Scheduled presentations (Abstracts 3500 - TPS3633) 167s

continued on following page

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Gastrointestinal (Noncolorectal) Cancer
Scheduled presentations (Abstracts 4000 - TPS4154) 199s

Genitourinary (Nonprostate) Cancer
Scheduled presentations (Abstracts 4500 - TPS4601) 237s

Genitourinary (Prostate) Cancer
Scheduled presentations (Abstracts 5000 - TPS5097) 263s

Gynecologic Cancer
Scheduled presentations (Abstracts 5500 - TPS5615) 287s

Head and Neck Cancer
Scheduled presentations (Abstracts 6000 - TPS6099) 316s

Health Services Research, Clinical Informatics, and Quality of Care
Scheduled presentations (Abstracts 6500 - TPS6626) 341s

Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant
Scheduled presentations (Abstracts 7000 - TPS7075) 373s

Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
Scheduled presentations (Abstracts 7500 - TPS7579) 392s

Hematologic Malignancies—Plasma Cell Dyscrasia
Scheduled presentations (Abstracts 8000 - TPS8058) 412s

Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers
Scheduled presentations (Abstracts 8500 - TPS8586) 427s

Lung Cancer—Non-Small Cell Metastatic
Scheduled presentations (Abstracts 8509 - TPS9107) 448s

Melanoma/Skin Cancers
Scheduled presentations (Abstracts 9500 - TPS9600) 476s

Patient and Survivor Care
Scheduled presentations (Abstracts LBA10000 - TPS10129) 501s

Pediatric Oncology
Scheduled presentations (Abstracts LBA10500 - TPS10579) 534s

Sarcoma
Scheduled presentations (Abstracts 11000 - TPS11082) 554s

Tumor Biology
Scheduled presentations (Abstracts 11500 - TPS11628) 575s

First Author Index 608s

American Society of Clinical Oncology
53rd Annual Meeting

2017 Abstracts

Descriptions of Scientific Sessions

Plenary Session
The Plenary Session includes abstracts selected by the Scientific Program Committee as having practice-changing findings of the highest scientific merit.

Highlights of the Day Sessions
Highlights of the Day Sessions invite expert discussants to provide an overview of the previous day's Oral Abstract presentations, focusing on key findings and putting abstracts into clinical context.

Oral Abstract Sessions
Oral Abstract Sessions include didactic presentations of abstracts of the highest scientific merit, as determined by the Scientific Program Committee. Experts in the field serve as discussants and provide comprehensive themed discussions of the findings from the abstracts.

Clinical Science Symposia
Clinical Science Symposia provide a forum for science in oncology, combining didactic lectures on a specific topic with abstract presentations. Experts in the field serve as discussants, placing studies in the appropriate context and critically discussing the applicability of the conclusions in clinical practice. Three special Clinical Science Symposia will be designated around specific topics that cut across cancer types.

Poster Discussion Sessions
Select posters from the Poster Sessions will be discussed by expert discussants, with the abstract authors participating in a question and answer period as panel members. These sessions will be followed by networking with the discussants and authors.

Poster Sessions
Poster Sessions include selected abstracts of clinical research in poster format. Trials in Progress (TPS) abstracts are presented within a track's Poster Session.

Publication-Only Abstracts
Publication-only abstracts were selected to be published online in conjunction with the Annual Meeting, but will not be presented at the Meeting.

All presented and publication-only abstracts are citable to this Journal of Clinical Oncology *supplement. For citation examples, please see the Letter from the Editor.*

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2017 Annual Meeting. Abstracts selected for electronic publication only are available in full-text versions online through ASCO.org and JCO.org. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Annual Meeting Program or the iPlanner, the online version of the Annual Meeting Program, available at am.asco.org.

Dates and times are subject to change.
All modifications will be posted on am.asco.org.

Letter From the Editor

The *2017 ASCO Annual Meeting Proceedings* (a supplement to *Journal of Clinical Oncology*) is an enduring record of the more than 2,400 abstracts selected by the ASCO Scientific Program Committee for presentation at the 53rd ASCO Annual Meeting. Accepted abstracts not presented at the meeting are included in the online supplement to the May 20 issue of *Journal of Clinical Oncology* at JCO.org.

The majority of abstracts selected for presentation are included here in full and are categorized by scientific track. Abstracts can be also accessed online through ASCO abstracts website (abstracts.asco.org) or Meeting Library (meetinglibrary.asco.org). Online abstracts include the full list of abstract authors and their disclosure information.

Late-Breaking Abstracts are represented here by abstract title and first author only. The full-text versions of these abstracts will be publicly released during the Annual Meeting. Print versions of these abstracts will be available onsite at the Annual Meeting in the *ASCO Daily News*.

All abstracts carry *Journal of Clinical Oncology* citations. The following are citation examples for print and electronic abstracts:

J Clin Oncol 35:5s, 2017 (suppl; abstr LBA1)

J Clin Oncol 35, 2017 (suppl; abstr e12000)

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Michael A. Carducci, MD
Editor, *2017 ASCO Annual Meeting Proceedings*

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5. Single-issue price: $40 US, $50 international.
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7. Except on consortia orders, the publisher allows for a 5% discount on Tiers 1-3 to recognized subscription agents.

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- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Friday, June 2, will be publicly released Friday, June 2, through ASCO.org at 2:00 PM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Saturday, June 3, will be publicly released Saturday, June 3, through ASCO.org at 7:30 AM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Sunday, June 4, will be publicly released Sunday, June 4, through ASCO.org at 7:30 AM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Monday, June 5, or Tuesday, June 6, will be publicly released Monday, June 5, through ASCO.org at 7:30 AM (EDT).

Late-Breaking Abstracts will be available in Section D of *ASCO Daily News* on the day of their scientific presentation, with the exception of abstracts presented on Friday (these will appear in the Saturday issue) and those presented on Tuesday (these will appear in the Monday issue).

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on ASCO.org.

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As the CE provider for the Meeting, ASCO is committed to balance, objectivity, and scientific rigor in the management of financial interactions with for-profit health care companies that could create real or perceived conflicts of interest. Participants in the Meeting have disclosed their financial relationships in accordance with ASCO's Policy for Relationships with Companies; review the policy at asco.org/rwc.

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ABSTRACTS
American Society of Clinical Oncology
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SPECIAL AWARD LECTURE ABSTRACTS

David A. Karnofsky Memorial Award and Lecture
Saturday, June 3, 9:30 AM

Driving new CARs for cancer: PACE CARS, NASCARs, and SWEET CARs.

Carl H. June, MD; University of Pennsylvania, Philadelphia, PA

The emergence of immune-oncology as the first broadly successful strategy for metastatic cancer will require clinicians to integrate this new pillar of medicine with the pillars of chemotherapy, radiation, and targeted small molecule compounds. Chimeric antigen receptor (CAR) T cells have proven that engineered immune cells can serve as a powerful new class of cancer therapeutics. Adoptive immunotherapy retargeting T cells to CD19 via a chimeric antigen receptor (CAR) is an investigational treatment capable of inducing complete tumor regression of B-cell malignancies when there is sustained survival of infused cells. Clinical experience has helped to define the major challenges that must be met to make engineered T cells a reliable, safe, and effective platform that can be deployed against a broad range of tumors. The emergence of synthetic biology approaches for cellular engineering is providing us with a broadly expanded set of tools for programming immune cells. I will discuss how these tools could be used to design the next generation of smart T-cell precision therapeutics.

Science of Oncology Award and Lecture
Sunday, June 4, 1:00 PM

Lessons learned from the development of imatinib.

Brian J. Druker, MD; Oregon Health & Science University, Portland, OR

Imatinib (Gleevec) exemplifies the successful development of a rationally designed, molecularly targeted therapy for the treatment of a specific cancer. Imatinib is an inhibitor of the ABL, platelet-derived growth factor receptor, and KIT tyrosine kinases. Given the pathogenetic role of the BCR-ABL tyrosine kinase in chronic myeloid leukemia (CML), this was the first disease selected for clinical trials with imatinib, and the development of imatinib for CML from preclincal to clinical results will be summarized. In patients with CML who acquire resistance to imatinib, mutations in the kinase domain of ABL are the most common mechanism of resistance, and the development of second generation drugs targeting these mutations will also be reviewed. Imatinib has now been successfully used in other malignancies driven by each of the targets of imatinib, and the extension of imatinib to other diseases will be described. Unfortunately, targeted therapies for most advanced cancers have not yielded results as dramatic as those observed with imatinib for CML. There are numerous reasons for these less remarkable results, including accumulation of molecular defects with clonal evolution and disease heterogeneity in more advanced disease. Potential paths forward to extend the success of imatinib to other cancers, including combination therapy and treatment earlier in the course of disease, will be discussed.

ASCO–American Cancer Society Award and Lecture
Monday, June 5, 11:30 AM

Cancer prevention as continuum of oncologic diagnostic and therapeutic disciplines: Targeting the eicosanoid system as an example.

Dean E. Brenner, MD, FASCO; University of Michigan Medical Center, Ann Arbor, MI

Our deepening understanding of the carcinogenesis process enables identification of targets for interventions that span the entire cancer process. Because of its pivotal role in normal and pathologic physiology including carcinogenesis biology, we have used the eicosanoid system as both therapeutic anticarcinogenesis target and as biomarkers of individual carcinogenesis risk. We chose to study the lower GI tract because it has an endoscopically accessible dysplastic lesion (adenoma) and a well described molecular carcinogenesis process, with high incidence and mortality. Our initial trials of aspirin in the colon documented potent inhibition of colonic mucosal prostaglandins at low doses (80 mg every 48 hrs), reduction of crypt proliferation, and shifting of the crypt lectin

binding profile. Subsequent work from other investigators has demonstrated aspirin-induced reduction in colonic adenoma formation, molecular biomarkers for aspirin's preventive activity, and activity as an inhibitor of metastatic progression in patients with stage III colorectal cancer. Because of nonsteroidal therapeutic index concerns for long-term, chronic treatment in otherwise healthy populations, we identified polyphenolic dietary components with strong anticarcinogenesis activity (curcumin, resveratrol, gingerols) and found that their strong in vitro eicosanoid and stem cell self-renewal inhibitory activity could not be replicated in humans, primarily due to bioavailability limitations. Most recently, we have translated new data showing that fatty acid binding to the cyclooxygenase-2 catalytic dimer is limited to the ω6 arachidonic acid or the ω3 eicosapentaneoic acid. Other common saturated and unsaturated fatty acids that bind to the allosteric cyclooxygenase-2 dimer can alter catalytic dimer activity, regulating prostaglandin synthesis. Translation to humans permits optimal individualization of ω3 fatty acid dosing using prostaglandin E_2 and other eicosanoid products as biomarker endpoints in normal weight but not in obese populations. These insights are driving new investigations into the biological linkage between obesity, carcinogenesis, and cancer prevention.

B. J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology
Monday, June 5, 3:00 PM

Has the time come to develop the concept of global geriatric oncology?

Jean Pierre Droz, MD, PhD; Centre Hospitalier Andrée Rosemon, Cayenne, French Guiana

Global oncology is focused on cancer care, research, and care delivery issues unique to countries and settings with limited healthcare resources. Projections of the world population through 2050 indicate that the population of persons over 60 increases. The elderly people population will rise from 0.2 billion in 2008 to 0.4 billion in 2050 in the more developed countries, whereas it will rise, during the same period, from 0.4 billion to 1.6 billion in the less developed countries. Between 2016 and 2035, the estimated number of new cancers in patients older than 65 in less developed countries should increase from 3.2 million to 7.5 million. During the same period, the estimated number of cancer patients younger than 65 should increase from 4.8 million to 7.2 million. This demonstrates that geriatric oncology is a real challenge in less developed countries, where cancers have some specific characteristics: late diagnosis, more advanced stages and consequently increased mortality; particular biological features like frequency of triple-negative breast cancers and *BRCA1-2* mutations; frequent microorganisms implicated in the carcinogenesis. Conversely, knowledge on the aging characteristics in these populations is still scarce. Principles of contemporary geriatric oncology are not always enforceable to patients from these areas: This is often due to cultural differences, different comorbidities, different socioeconomic environment, and a lack of geriatricians and health professional education. It is therefore important to make efforts to develop geriatric oncology in this part of the world mostly through the development of adapted screening tools of frailty and the establishment of a decision-making process to suit resources and cultures and based on simple standardized screening tools and clinical exams, health professional training, and production of scientific knowledge. In conclusion, the development of the concept of global geriatric oncology is important and should be advisable.

Pediatric Oncology Award and Lecture
Monday, June 5, 1:15 PM

Recognizing when less is more: Progress in management of childhood Hodgkin lymphoma.

Michael P. Link, MD, FASCO; Stanford University School of Medicine, Palo Alto, CA

The improvement in outcome of children with Hodgkin lymphoma has been a spectacular achievement of the past four decades. Although the biology and clinical behavior of Hodgkin lymphoma in children closely resembles the adult counterpart, successful therapies designed for children are based on the unique concerns of the growing child as host. Early studies designed to reduce the dose and volume of radiation to minimize the impact on bone and soft tissue growth relied on the administration of chemotherapy to "substitute" for the omitted radiation. An unexpected result was improvement in overall disease control—particularly in children with advanced stage disease—over what would be expected from management with high-dose extended-field irradiation, which had been routine. Treatment strategies centered on chemotherapy and reduced radiation doses and volumes have emerged as the standard of care. More recent studies have provided further refinements of this approach, with long-term event-free survivals now exceeding 90%. Advances in imaging technologies have facilitated expeditious and accurate staging, while eliminating the need for meticulous surgical staging. With increasing numbers of children cured of Hodgkin lymphoma, late complications related to therapy that compromise quality of life and survival emerged as key concerns, particularly because children cured of cancer have a lifetime ahead of them to manifest the long-term toxicities of therapy. Secondary radiation-related cancers in survivors stimulated more recent studies of approaches designed to eliminate irradiation as a component of therapy for most children. The focus of modern studies is minimizing therapy for children with the most favorable prognosis, while reserving more

intensive therapy for children with advanced stage disease at higher risk of relapse. New agents under study promise to contribute to improved therapy for such children with high-risk disease. As has been true in the management of all childhood cancers, improvements in therapy have resulted from multi-institutional and interdisciplinary collaborations focused on achieving high cure rates while reducing the acute and long term toxicities of therapy.

Gianni Bonadonna Breast Cancer Award and Lecture
Saturday, June 3, at 4:45 PM

Advances in HER2+ breast cancer: Can we score the ultimate goal.

Eric P. Winer, MD, FASCO; Dana-Farber Cancer Institute, Boston, MA

Over the last two decades, we have seen dramatic advances in the treatment of HER2+ breast cancer. There are now four approved anti-HER2 agents—trastuzumab, lapatinib, pertuzumab, and T-DM1—and others likely to be approved in the near future. For women with stage II/III HER2+ disease, the clinical outcome is excellent with distant recurrences arising in no more than 10-20% of patients who are treated with contemporary anti-HER2 regimens. The outcome is even more promising for women with stage I disease, many of whom can be successfully treated with regimens that have limited toxicity. In the metastatic setting, patients with HER2+ disease are living far longer than in the past and with much better quality of life. In spite of all the good news, we face multiple challenges. There are still thousands of women who lose their lives to HER2+ breast cancer each year. Some of these women are unable to access medical care, and for these individuals social and behavioral changes are essential. Many others, however, lose their lives because of drug resistance. Many HER2+ cancers simply outsmart the drugs that we have available. In addition, central nervous system disease remains a vexing problem for many patients. Approximately half of all women with HER2+ metastatic disease develops CNS metastases, and for many of these women CNS disease is the cause of death. There are challenges related to drug delivery in the CNS and there may well be important differences in the tumor microenvironment. Translational and clinical research need to focus on approaches to overcome both drug resistance and CNS relapse. On the other end of the spectrum, there are also many patients in 2017 who are receiving far more treatment than they need, and this overtreatment leads to unnecessary toxicities. If we are going to de-escalate therapy, we will need to design thoughtful and creative clinical trials that seek to minimize excessive treatment while ensuring that we do not compromise the excellent results that have been achieved. Finally, the challenge we face, beyond science and research funding, is that some believe that we have solved the problem of HER2+ breast cancer and it is time to move on to other areas. Although other areas are important, we need to maintain a focus on the ultimate goals—the elimination of mortality and minimization of unnecessary toxicity.

Allen S. Lichter Visionary Leader Award and Lecture
Monday, June 5, 1:15 PM

Heroes, mentors, role models, and friends.

Patrick J. Loehrer, MD, FASCO; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

The development of leaders is as varied as the human genome. This is in part because of the uniqueness of individuals in the various roles of leadership and the uniqueness of the times. For over a half century, the American Society of Clinical Oncology has been a conclave for the best and the brightest individuals in the field of oncology. The seven original founders sought a home for clinical investigators to share accomplishments in cancer research and to educate an emerging workforce for what was becoming a new discipline. ASCO has now evolved to become the preeminent, international leader in cancer research, education and advocacy. Today, its membership, over four thousand fold greater than at its inception, looks to its future through a cautionary lens. A legacy of the Lichter era was that of professional development. ASCO's Leadership Development Program, just one of Dr. Lichter's brainchilds, links senior and younger physicians from various disciplines and geographic locations for an intense year of collective learning on leadership skills important for our society and beyond. One of its lessons is that leadership begins with conversations, delineates the cause (or the project), asks for commitment, and in the end, affects change. Ultimately, our society is only as strong as its members and the causes they choose to champion. Our vision, *"A world where cancer is prevented or cured, and every survivor is healthy"* lays the gauntlet down. This lecture will highlight the professional and personal journey of one of its members through three decades of the society, built upon the shoulders of mentors, role models, and friends.

ABSTRACTS
American Society of Clinical Oncology
53rd Annual Meeting
June 2-6, 2017
McCormick Place
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LBA1 **Plenary Session, Sun, 1:00 PM-4:00 PM**

Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): The IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration. *First Author: Qian Shi, Mayo Clinic Cancer Center, Rochester, MN*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, June 4, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News.*

LBA2 **Plenary Session, Sun, 1:00 PM-4:00 PM**

Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *First Author: Ethan M. Basch, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, June 4, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA3 **Plenary Session, Sun, 1:00 PM-4:00 PM**

LATITUDE: A phase III, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naive prostate cancer. *First Author: Karim Fizazi, Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, June 3, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA4 **Plenary Session, Sun, 1:00 PM-4:00 PM**

OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients (pts) with HER2-negative metastatic breast cancer (mBC) and a germline *BRCA* mutation (gBRCAm). *First Author: Mark E. Robson, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Sunday, June 4, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA100 **Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

Routine molecular screening of advanced refractory cancer patients: An analysis of the first 2490 patients of the ProfilER Study. *First Author: Olivier Tredan, Département d'Oncologie Médicale, Centre Léon Bérard, Lyon, France*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, June 3, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

101 **Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

Clinical application of comprehensive next generation sequencing in the management of metastatic cancer in adults. *First Author: Erin Frances Cobain, University of Michigain Health System, Ann Arbor, MI*

Background: Next generation sequencing (NGS) platforms are frequently utilized in the care of patients (pts) with metastatic cancer to identify tumor genomic alterations that may serve as therapeutic targets. Biomarker driven clinical trials, such as NCI-Molecular Analysis for Therapy Choice (MATCH) and Targeted Agent and Profiling Utilization Registry (TAPUR) have augmented clinicians' ability use this strategy in clinical practice. **Methods:** From 2011-2015 over 500 adult pts with metastatic solid tumors of diverse lineage underwent biopsy for whole exome and transcriptome sequencing of tumor and matched normal sample through the Michigan Oncology Sequencing Center (Mi-Oncoseq). Genomic alterations identified were reviewed at Precision Medicine Tumor Board and tiered according to their clinical relevance. Alterations were also classified as being identifiable or not identifiable by a commercially available NGS assay such as Oncomine Focus or FoundationOne. **Results:** Genomic alterations identified by Mi-Oncoseq provided rationale for enrollment in a clinical trial in 72% (n = 360) of cases. The percentage of pts who did receive therapy informed by NGS results increased over time (5% in 2012 versus 11% in 2015). 11% of pts (n = 55) had a pathogenic germline variant (PGV) conferring increased cancer risk identified, none of which were known prior to study entry. Numerous pts had clinically relevant molecular alterations identified by Mi-Oncoseq that would not have been identifiable utilizing targeted NGS assays, including PGVs and activating/deleterious gene fusions. **Conclusions:** Comprehensive NGS, including DNA and RNA sequencing, readily identifies potentially actionable alterations in the vast majority of pts beyond what is observed with use of targeted NGS platforms. Observed modest increase in utilization of NGS results to direct subsequent therapy over time is due to clinician employment of this strategy earlier in the therapeutic algorithm, increased availability of biomarker driven clinical trials and changes in physician referral patterns. Comprehensive NGS identified many unanticipated PGVs of clinical importance for pts and their families. Clinical trial information: HUM00067928.

102 **Clinical Science Symposium, Sat, 8:00 AM-9:30 AM**

Next generation sequencing in community oncology practice: Beneficial or economical burden? *First Author: Natraj Reddy Ammakkanavar, Community Cancer Center, Indianapolis, IN*

Background: Precision genomics medicine is a fast growing in cancer care. Targeted therapy has yielded substantial benefit when appropriately used. With next generation sequencing (NSG) use increasing in non-academic setting outside clinical trial, we need to consider benefits and economical burden of this. **Methods:** Retrospective chart analysis of cancer patients (pts) treated at a large community practice was undertaken. With IRB approval, demographic, clinical and NSG data were collected for 209 pts who had NSG in 2015 and 2016. Pts were placed in 1 of 4 categories based on NSG results with available drug for specific mutation and change in management (CIM): a) CIM for current, b) Potential to CIM with subsequent therapy, c) No CIM due to poor performance status, d) No CIM due to lack of new target and/or drug. Alternate economical standard test for the mutation noted. Statistical analysis was done using chi-square and fisher's exact test. **Results:** Median age was 64yr. Most common tumor types tested where as listed in table 96% had stage 4 disease. 82% had ≥1 prior systemic therapy. Pts were assigned to categories as per table below. When RAS mutation status where accounted by standard testing, none of the colon cancer pts benefited from NSG test. 6 of 54 pts who had CIM had alternate test option. Financial responsibility for these tests is approximately $1.21 million. 18 pts in 2015 and 17 pts in 2016 where billed for test after exhausting insurance and support option. More financial data may be available at time of presentation. **Conclusions:** NGS tumor test might benefit small group of selective pts at time of testing. It is likely not prime time to use for colon cancer. Benefits with later therapy are difficult to predict. NSG should be used more judiciously due to financial implications.

	Total Pt. N=209 (%)	Lung Cancer N = 63(%)	Colonrectal Cancer N= 31(%)	Ovarian /Endometrial cancer N= 23(%)	Breast cancer N=15(%)	Pancreatic N=9(%)	Other cancer N=68(%)
CIM for current	22(11)	8(12.7)	0	4(17.4)	1(6.7)	0(0)	9(12.5)
CIM with subsequent	32(16)	7(11.1)	0	5(21.7)	5(33.3)	2(22)	13(20.3)
No CIM due to poor performance	15(7)	5(7.9)	3(12)	0(0)	2(13.3)	0(0)	5(7.8)
No CIM due to no new target /drug	137 (66)	43(68.3)	28(88)	14(60.9)	7(46.7)	7(78)	41(59.4)

103 **Clinical Science Symposium, Sun, 9:45 AM-11:15 AM**

The effect of pembrolizumab in combination with CD19-targeted chimeric antigen receptor (CAR) T cells in relapsed acute lymphoblastic leukemia (ALL). *First Author: Shannon L. Maude, Cancer Immunotherapy Program, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: CD19-targeted CAR T cells show CR rates of 70-95% in B-ALL. Yet a subset of patients do not respond or relapse due to poor CAR T cell expansion and persistence. We hypothesized that PD-1 checkpoint pathway inhibition may improve CAR T cell expansion, function and persistence. **Methods:** Four children with relapsed B-ALL treated with murine (CTL019) or humanized (CTL119) anti-CD19 CAR T cells received 1-3 doses of the PD-1 inhibitor pembrolizumab (PEM) for partial/no response or prior history of poor CAR T cell persistence starting 14d-2mo post CAR T cell infusion. **Results:** PEM increased and/or prolonged detection of circulating CAR T cells in all 4 children, with objective responses in 2/4. It was well tolerated, with fever in 2 pts and no autoimmune toxicity. Pts 1-3 received CTL119 for CD19+ relapse after prior murine CD19 CAR T cells. Pt 1 had 1.2% CD19+ residual disease despite expansion with detectable CTL119 by D28 and received PEM at 2mo for progressive disease with decreasing circulating CTL119. CTL119 became detectable at 0.2% of CD3+ cells by flow cytometry, but disease progressed. Pt 2 had no response after initial CTL119 expansion with a rapid disappearance by D28. After CTL119 reinfusion with PEM added 14d later, circulating CAR T cells remained detectable at 4.4% by D28, but disease progressed with decreased CD19 expression. In Pt 3, prior treatment with both CTL019 and CTL119 produced CR with poor CAR T cell persistence followed by CD19+ relapse. CTL119 reinfusion combined with PEM at D14 resulted in CR with prolonged CTL119 persistence (detectable at D50 compared to loss by D36 after 1st CTL119 infusion). Pt 4 received PEM for widespread extramedullary (EM) involvement at D28 post CTL019 infusion despite marrow remission. Initial CTL019 expansion peaked at 63% at D10 and fell to 20% at D28. Resurgence of CTL019 expansion, with a 2nd peak of 70% 11d after PEM, was associated with dramatic reduction in PET-avid disease by 3mo post CTL019. **Conclusions:** PEM was safely combined with CAR T cells and increased or prolonged CAR T cell detection, with objective responses seen. Immune checkpoint pathways may impact response to CAR T cell treatments and warrant further investigation. Clinical trial information: NCT02374333, NCT02906371.

104 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Preliminary results of a phase I/IIa study of BMS-986156 (glucocorticoid-induced tumor necrosis factor receptor–related gene [GITR] agonist), alone and in combination with nivolumab in pts with advanced solid tumors. *First Author: Lillian L. Siu, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: BMS-986156 is a fully human IgG1 agonist mAb that binds GITR and promotes T effector cell activation and possible reduction/inactivation of T regulatory cells. Preclinical data show enhanced antitumor T-cell activity with anti-GITR + anti–programmed death-1 (PD-1). Here we describe preliminary dose escalation data from a phase I/IIa study of BMS-986156 ± nivolumab (anti–PD-1 mAb) in pts with advanced solid tumors (NCT02598960). **Methods:** During dose escalation, pts received BMS-986156 (10–800 mg) or BMS-986156 (30–800 mg) + nivolumab (240 mg) every 2 weeks. Objectives included safety (primary), immunogenicity, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy. **Results:** As of Dec 12, 2016, 66 pts were treated with BMS-986156 (n = 29) or BMS-986156 + nivolumab (n = 37).No dose-limiting toxicities (DLTs) were reported during dose escalation. The most common treatment-related adverse events reported with BMS-986156/BMS-986156 + nivolumab included pyrexia (21%/30%), chills (10%/16%), and fatigue (14%/14%); events were G1/2 in all pts except for 4 pts (6%) treated with the combination (G3 lipase [n = 1], G3 lung infection [n = 1], G3 fatigue [n = 1], and G3 aspartate aminotransferase with G4 creatine phosphokinase [n = 1; leading to discontinuation of treatment]). Preliminary data indicate that the incidence of immunogenicity to BMS-986156 was low when BMS-986156 ± nivolumab was administered. Preliminary data also indicate that BMS-986156 ± nivolumab exhibits linear PK with dose proportionality after a single dose, and BMS-986156 ± nivolumab is biologically active in PD analyses in peripheral blood. Initial antitumor activity has been observed in several pts treated with the combination; these data will be reported. **Conclusions:** This is the first report of clinical data with an anti-GITR mAb ± a PD-1 inhibitor.BMS-986156 ± nivolumab was well tolerated, with no DLTs and low immunogenicity. Antitumor activity was observed with BMS-986156 + nivolumab at doses predicted to be biologically active. Further evaluation of this combination in pts with advanced solid tumors is ongoing. Clinical trial information: NCT02598960.

105 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

A phase Ib dose escalation study of combined inhibition of IDO1 (GDC-0919) and PD-L1 (atezolizumab) in patients (pts) with locally advanced or metastatic solid tumors. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Nashville, TN*

Background: GDC-0919, a small molecule inhibitor of indoleamine-2,3-dioxygenase 1 (IDO1), reduces tryptophan catabolism and kynurenine production within the tumor microenvironment that may promote normal effector T cell activity and an immunogenic state. IDO1 inhibition may complement targeting of PD-L1 with atezolizumab. **Methods:** A Phase Ib, open-label, study assessed safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity (RECIST v1.1) of GDC-0919 and atezolizumab in pts with locally advanced or metastatic solid tumors. Pts were given escalating doses of GDC-0919 (50-1000 mg orally twice daily, for 21 days) and atezolizumab (1200 mg IV, every 3 weeks) using a standard 3 +3 design. **Results:** As of 14Dec2016, 52 pts were treated in 6 cohorts of GDC-0919 plus atezolizumab. The median number of prior systemic therapies was 3 (range 1-9); 2 pts received prior immunotherapy. Pts received a median of 4 cycles of GDC-0919 and atezolizumab (range 1-17). No MTD was identified. Across all dose levels, 1 DLT was observed (Grade [G] 3 sepsis syndrome at GDC-0919 200 mg); no G4/5 AEs were attributed to study treatment. G3+ AEs, regardless of causality were reported in 34 (65%) pts. Related G3 AEs were reported in 7 (13%) pts, included nausea, rash, sepsis syndrome, fatigue, and pneumonitis. Two pts (4%) had AEs leading to treatment discontinuation, related in 1/2 (G3 pneumonitis). Combination PK was consistent with single agent observations and supports BID dosing of GDC-0919. Peripheral PD showed dose-dependent decreases in plasma kynurenine, consistent with systemic modulation of IDO1. Preliminary efficacy data from 45 pts with ≥ 1 on-treatment tumor assessments included 4 patients (9%) with partial response and 11 (24%) pts with stable disease. **Conclusions:** The combination of GDC-0919 and atezolizumab was generally well-tolerated and demonstrated peripheral IDO1 modulation and preliminary efficacy in a heterogeneous patient population during dose escalation. The study is currently enrolling pts with select tumor types in expansion cohorts to assess tumor PD and combination efficacy. Clinical trial information: NCT02471846.

106 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

A phase I study of enfortumab vedotin (ASG-22CE; ASG-22ME): Updated analysis of patients with metastatic urothelial cancer. *First Author: Daniel Peter Petrylak, Yale School of Medicine, New Haven, CT*

Background: Enfortumab vedotin, an antibody–drug conjugate, delivers monomethyl auristatin E to tumors expressing Nectin-4, which is overexpressed in metastatic urothelial cancer (mUC). **Methods:** This Phase I study (NCT02091999) enrolled patients (pts) with solid tumors, including pts with mUC, treated with ≥1 prior chemotherapy regimen. All pts received different dose levels of IV enfortumab vedotin (0.5, 0.75, 1, 1.25 mg/kg) once weekly for 3 out of 4 wks. Nectin-4 expression was determined by IHC on archival tumor specimens and quantified by histochemical scoring (H-score). Primary endpoint was tolerability; secondary endpoint was antitumor activity assessed every 8 wks per RECIST v1.1. **Results:** As of 3 Jan 2017, 68 pts with mUC (46 M/22 F; median age, 67 yr [range: 41–84]) had been treated. Of these, 62% received ≥2 prior therapies in the metastatic setting and 40% had prior immune checkpoint inhibitor (CPI) therapy. In these pts, Nectin-4 expression was high and prevalent (median H-score, 280 [range: 32–300]). Treatment-related adverse events (TRAEs) were reported in 58 pts (85%); diarrhea, fatigue, nausea, and pruritus were TRAEs reported in ≥25% of pts. Most TRAEs were grade ≤2 in severity; 19 pts (28%) experienced a TRAE of grade ≥3. The most common grade ≥3 AEs (occurring in ≥5 pts), regardless of attribution to treatment, were urinary tract infection (10%) and hypophosphatemia (9%). No treatment-related deaths have occurred. Sixty pts had ≥1 post-baseline assessment. Antitumor activity was observed across the dose range; overall response rate (ORR) was 40% (95% CI: 27.6–53.5) for all evaluable pts (n = 60), 46% (95% CI: 25.6–67.2) in pts with prior CPI exposure (n = 24), and 44% (95% CI: 19.8–70.1) in pts with metastasis to the liver (n = 16). Complete responses were noted in 3 pts at doses ≥1 mg/kg. Median treatment duration was 26 wks (range: 5.1–64.6), median duration of response was 18 wks (95% CI: 8.4–40.1), and median progression-free survival was 17 wks (95% CI: 15.1–23.3). Study enrollment is ongoing. **Conclusions:** Enfortumab vedotin demonstrated a favorable tolerability profile with encouraging antitumor activity in heavily pretreated mUC, including pts for whom CPIs have failed. Clinical trial information: NCT02091999.

108 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Single agent activity of DS-8201a, a HER2-targeting antibody-drug conjugate, in heavily pretreated HER2 expressing solid tumors. *First Author: Toshihiko Doi, Department of Experimental Therapeutics, National Cancer Center Hospital, Chiba, Japan*

Background: Human epidermal growth factor 2 (HER2) is a potential strong tumor driver for breast (BC) and gastric cancer (GC) as well as other HER2 expressing tumors. Antibody-drug conjugates (ADC) provide wider therapeutic window by more efficient and specific drug delivery. DS-8201a is a HER2 targeting ADC of high drug to antibody ratio (7 to 8) with a novel topoisomerase I inhibitor. In preclinical studies, DS-8201a showed a broader antitumor spectrum than T-DM1, including efficacy against low HER2 expressing tumors. Current trial includes dose escalation (Part 1) and expansion (Part 2) focusing on HER2 expressing solid tumors (NCT02564900). **Methods:** Part 1 used a modified continuous reassessment method to identify the expansion dose in patients (pts) with BC or GC. Part 2 was designed to evaluate the safety and efficacy in 4 expansion cohorts: T-DM1 treated HER2+ BC, trastuzumab treated HER2+ GC, BC with low HER2 expressing and other HER2 expressing solid tumors. Adverse events (AEs), objective response rate (ORR) and durability of responses were assessed. **Results:** 89 pts were administered in total: 24 pts in Part 1 and 65 pts (BC, GC, colorectal, salivary and non-small cell lung cancer) in Part 2 with median prior therapies of 4. DS-8201a was administered up to 8.0 mg/kg in Part 1, and dose levels of 6.4 and 5.4 mg/kg IV every 3 weeks were chosen for Part 2. There was no dose limiting toxicity, and maximum tolerated dose was not reached in Part 1. The most common AEs in Part 1 and Part 2 were nausea (62%), anorexia (56%) and platelet count decreased (28%). 29% pts experienced ≥ Gr3 AEs (Gr3: 25% Gr4: 4%). The ORR and disease control rate (DCR: CR + PR + SD) are shown in the table. ORR and DCR were 40% and 90%, respectively in evaluable 73 pts including 14 low HER2 expression. One T-DM1 treated BC pt achieved CR. 4 PRs were achieved in pts with low HER2 expression. 63 pts in total are currently being treated. Median duration of treatment was ≥27 weeks in Part 1 and not reached in Part 2. **Conclusions:** DS-8201a was well tolerated and is remarkably active in heavily pretreated HER2 expressing cancers. Clinical trial information: NCT02564900.

	ORR	DCR
Total	40% (29/73)	90% (66/73)
Part 1	43% (10/23)	91% (21/23)
Part 2	38% (19/50)	90% (45/50)
Low HER2	29% (4/14)	93% (13/14)

109 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

A phase II study of glembatumumab vedotin (GV), an antibody-drug conjugate (ADC) targeting gpNMB, in advanced melanoma. *First Author: Patrick Alexander Ott, Dana-Farber Cancer Institute, Boston, MA*

Background: gpNMB is an internalizable transmembrane glycoprotein expressed in melanoma and multiple other tumor types. The ADC GV (CDX-011) delivers the potent cytotoxin MMAE to gpNMB+ cells. GV has shown promising activity in advanced melanoma and breast cancer. **Methods:** This Phase II study (CDX011-05) assessed the efficacy and safety of GV monotherapy (1.9 mg/kg q3w) for patients (pts) with advanced melanoma progressive after ≤1 chemotherapy, ≥1 checkpoint inhibitor (CPI) and if $BRAF^{V600}$mutated, ≥1 BRAF/MEK inhibitor. Central IHC determined gpNMB expression in archival and/or pre-treatment tumor. Primary endpoint was objective response rate (ORR) (RECIST 1.1) with ≥6 responders out of 52 evaluable pts as threshold for antitumor activity. Additional endpoints: progression free survival (PFS), overall survival (OS), duration of response (DOR), safety, PK/PD and correlation of tumor gpNMB expression with efficacy. **Results:** 62 pts enrolled (all evaluable) had median age of 67 years; 55% male; 21% $BRAF^{V600}$mutated; 63% with ≥3 lines prior therapy; 100% had prior CPI; 100% Stage IV; 89% M1c. One confirmed complete response (CR) and 6 confirmed partial responses (PR, including 1 unconfirmed CR) were seen (confirmed ORR = 11%, p = 0.035 comparing to reference ORR 5%); 33 pts had stable disease including 3 unconfirmed PR. Median DOR = 6.0 (range: 4.1, 14+) months (mos), median PFS = 4.3 mos and median OS = 9.8 mos; 26 pts continue to be followed for survival. All pts with available tissue (60/60) had gpNMB+ tumors; 47/60 had 100% gpNMB+ epithelial cells; no clear correlation with outcome was seen in this population with consistent high expression. Toxicities included alopecia, neuropathy, rash, fatigue and neutropenia. Treatment-related rash in cycle 1 was associated with improved ORR (rash = 22%; no rash = 7%), PFS (p = 0.007) and OS (p = 0.035). **Conclusions:** GV has promising activity (primary endpoint of ORR was met) with a manageable safety profile in heavily pre-treated melanoma pts. Additional cohorts evaluating GV with either varlilumab, an activating anti-CD27 monoclonal antibody, or PD-1 inhibitors are open to accrual to provide further insights into the synergy of ADC and immunotherapy. Clinical trial information: NCT02302339.

LBA500 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

APHINITY trial (BIG 4-11): A randomized comparison of chemotherapy (C) plus trastuzumab (T) plus placebo (Pla) versus chemotherapy plus trastuzumab (T) plus pertuzumab (P) as adjuvant therapy in patients (pts) with HER2-positive early breast cancer (EBC). *First Author: Gunter Von Minckwitz, German Breast Group (GBG), Neu-Isenburg, Germany*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 5, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

501 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

9 weeks vs 1 year adjuvant trastuzumab in combination with chemotherapy: Results of the phase III multicentric Italian study Short-HER. *First Author: Pier Franco Conte, Department of Surgery, Oncology and Gastroenterology, University of Padua, Medical Oncology 2, Instituto Oncologico Veneto IRCCS, Padova, Italy*

Background: 1-year trastuzumab with chemotherapy is the standard adjuvant treatment for HER2+ breast cancer patients (pts). The efficacy of less extended trastuzumab exposure is still under investigation. The Short-HER study is an independent, non-profit study aimed to test the non-inferiority of 9 weeks vs 1 year of adjuvant trastuzumab. **Methods:** This is a phase III, multicenter, Italian trial where pts with HER2+ breast cancer were randomly assigned to: Arm A (Long) AC or ECx4 followed by 4 courses of 3-weekly docetaxel in combination with trastuzumab, followed by 14 additional courses of 3-weekly trastuzumab; or Arm B (Short) 3 courses of 3-weekly docetaxel plus weekly trastuzumab for 9 doses followed by FEC x3. When indicated, radiation therapy was administered after the completion of chemotherapy. Hormonal therapy started at the completion of chemotherapy for pts with hormone receptor positive tumors. This is a non-inferiority trial with disease-free survival (DFS) as primary end-point.Overall survival (OS) is evaluated as second primary analysis outcome. The sample size of 1250 pts has been estimated based on a hazard ratio <1.29 for the short arm to be non-inferior. The definitive analysis will take place after 198 DFS events. Secondary aims include 2-yrs failure rate, cardiac toxicity, correlative biomarkers analyses. Hazard ratio for DFS and OS (90% CI) will be estimated according to the Cox model. Data will also be analyzed by the Bayesian approach. **Results:** from Dec-2007 to Oct-2013, 1254 pts from 82 centers have been randomized. Pts characteristics are the following: median age 55 yrs (25-78), stage I 37.3%, IIA 40%, IIB 20.6%, III 2.1%. 30% of the pts had 1-3 positive nodes, 16% $>=4$. Sixty-eight% of the pts had ER+ tumors. Characteristics were balanced between the two arms. At the time of this writing, 95% of the planned DFS events have been reported. 105 Grade ≥ 2 cardiac events have been reported, 78 in arm A (long) and 27 in arm B (short). Grade 3-4 cardiac events were 20 in arm A and 11 in arm B. **Conclusions:** Shorter trastuzumab administration almost halves the rate of severe cardiac toxicity**.** Final DFS data will be available at the time of the meeting. Clinical trial information: NCT00629278.

502 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Updated results from the phase III ALTTO trial (BIG 2-06; NCCTG (Alliance) N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L+T) in the adjuvant treatment of HER2-positive early breast cancer. *First Author: Alvaro Moreno-Aspitia, Mayo Clinic, Jacksonville, FL*

Background: Pre-specified 5-year analyses of the phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) Trial defined in Amendments 11&12. **Methods:** From June 2007 to July 2011, 8381 patients (pts) were randomised from 946 sites in 44 countries to receive either L+T, T→L, L, or T. In 2011, due to futility the L arm was closed and is not included in this analysis. The primary end point is disease-free survival (DFS). Secondary objectives include treatment comparisons with respect to overall survival (OS), time to recurrence (TTR), time to distant recurrence (TDR), cardiac and overall safety and tolerability. Primary analysis results of the study were published in JCO 2015 34:1034-1042. This updated analysis occurs at a 6.9 yrs median follow up (MFU). **Results:** All patients have reached 5-years of follow-up. 705 DFS events for L+T vs T have been observed. HR for DFS was 0.86 (95% CI, 0.74-1.00; 6-yr DFS%=85% vs 82%) for L+T vs T and 0.93 (95% CI, 0.81-1.08; 6-yr DFS%=84% vs 82%) for T→L vs. T. The 6-year OS was 93%, 92%, and 91% for L+T, T→L, and T, respectively. HR for OS was 0.86 (95% CI, 0.70-1.06) for L+T vs. T and 0.88 (95% CI, 0.71-1.08) for T→L vs. T. DFS differences for L+T vs. T were slightly higher for the hormone-receptor(ER)-negative [HR 0.80 (95% CI, 0.64-1.00; 6-yr DFS%=84% vs. 80%)] and the sequential chemotherapy [HR 0.83 (95% CI, 0.69-1.00; 6-yr DFS%=83% vs.79%)] subgroups. There were no differences in sites of first DFS events according to treatment arm for CNS, locoregional, or distant recurrences. There were more AEs related to study treatment (L+T 93% vs T 64%). The incidence of primary cardiac end points was low: 1% for L+T, 0.5% for T→L and 0.9% for T. **Conclusions:** The HRs for this updated analysis are similar to those from the Primary Analysis and the event rate remains lower than anticipated (705 vs 850 planned). Cardiac toxicity remains low. This analysis suggests that HER2+/ER- tumors may have a different biology than HER2+/ER+ and may benefit more from dual HER2 blockade. Long-term follow up continues. Clinical trial information: NCT00490139.

503 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

SOLE (Study of Letrozole Extension): A phase III randomized clinical trial of continuous vs intermittent letrozole in postmenopausal women who have received 4-6 years of adjuvant endocrine therapy for lymph node-positive, early breast cancer (BC). *First Author: Marco Colleoni, IBCSG and SOLE Investigators, Bern, Switzerland*

Background: In animal models of hormone receptor positive (HR+) breast cancer, acquired resistance to continued letrozole was shown to be reversed by estrogen-induced apoptosis. Sensitization to reintroduction of estrogen withdrawal by letrozole was hypothesized to improve treatment outcome. SOLE tested the hypothesis that 3 mos treatment-free intervals during extended adjuvant therapy will improve disease-free survival (DFS). **Methods:** SOLE enrolled 4884 postmenopausal women with HR+ lymph node-positive BC who had completed 4-6 yrs of adjuvant endocrine therapy (19% SERM, 43% AI, 38% both; stratification factor). Pts were randomly assigned to an additional 5 yrs continuous letrozole (2.5 mg daily; n = 2441) vs 5 yrs intermittent letrozole (taken for the first 9 mos of yrs 1-4, and 12 mos in yr 5; n = 2443). The primary endpoint was DFS (randomization until invasive local, regional, distant recurrence or contralateral BC; 2nd malignancy; death). Final analysis was at 665 DFS events, after 2 interim analyses. SOLE required 4800 pts for 80% power to detect a 20% DFS hazard reduction with 2-sided $\alpha = 0.05$ using a stratified log rank test. Analysis is by intention-to-treat. **Results:** At 60 mos median follow-up, 5 yr DFS from randomization was 85.8% vs 87.5% for patients assigned intermittent vs continuous letrozole (HR = 1.08; 95% CI 0.93-1.26; P = 0.31). Similar outcome was observed for breast cancer-free interval (HR = 0.98; 95% CI 0.81-1.19), distant recurrence-free interval (HR = 0.88; 95% CI 0.71-1.09), and overall survival (HR = 0.85; 95% CI 0.68-1.07). AEs of grade $>$ 3 were reported for 43.5% vs 41.6% of pts assigned intermittent vs continuous letrozole. Overall 24% pts discontinued letrozole early in both groups. **Conclusions:** Among postmenopausal women with HR+ BC, extended intermittent letrozole did not improve DFS vs continuous letrozole. The similar observed outcomes and incidence of AEs provides clinically relevant information on the intermittent administration of extended letrozole for patients who could benefit from temporary treatment breaks. Clinical trial information: NCT00553410.

504 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Prospective WSG phase III PlanB trial: Final analysis of adjuvant 4xEC→4x doc vs. 6x docetaxel/cyclophosphamide in patients with high clinical risk and intermediate-to-high genomic risk HER2-negative, early breast cancer. *First Author: Nadia Harbeck, Brustzentrum der Universität München (LMU), Munich, Germany*

Background: Optimal chemotherapy in HER2-negative, particularly HR-positive, early breast cancer (EBC), especially the survival impact of anthracyclines, is still a matter of debate. Retrospective analyses saw most benefit of 6xCEF vs. 6xCMF in HER2+ EBC. Prospective trials have shown conflicting results; no predictive molecular factors have been validated so far, particularly for HR+ EBC. The WSG PlanB trial is the first trial that randomized only patients with high clinical risk or with Recurrence Score >11 in the HR+/HER2- subgroup (pN0-1). Patients with RS<11 (pN0-1) had an excellent prognosis (five-year DFS of 94%) with endocrine therapy alone (Gluz et al. ASCO 2016). **Methods:** The WSG PlanB trial was originally planned as a non-inferiority study for comparison of 6 cycles of anthracycline-free TC (Arm A) vs. standard anthracycline-taxane based chemotherapy (4xEC→4xDoc) (Arm B) in patients with high-risk pN0 (T2-4, G2-3, <35 years, or high uPA/PAI-1) or pN+ HER2- EBC. Following an early amendment, Oncotype DX was performed in all HR+ tumors, and omission of chemotherapy (CT) was recommended in RS≤11 HR+ pN0-1 disease. Primary endpoint was DFS, defined as time to any recurrence, secondary cancer or death. Final analysis for the CT randomization was planned after completed 5-year follow-up in all patients. **Results:** From 2009 to 2011, PlanB enrolled 3198 patients (n=3073 with central pathology review). In 348 patients (15.3%), CT was omitted based on RS≤11. 2449 patients were randomized to 6xTC (n=1222) and 4xEC→4xDoc (n=1227). Within this cohort, 41% were pN+, 42% had G3 tumors and 18% HR-negative tumors by central pathology. After median follow-up of 61 months, very similar five-year DFS of 89.9% [88.1%-91.7%] vs. 90.2% [88.4%-92.0%] and five-year OS of 94.7% [93.4%-96.1%] vs. 94.6% [93.2%-96.0%] were observed in Arms A vs. B. Five treatment-related deaths were observed in Arm A (TC) vs. one in Arm B (EC-Doc) (0.4% vs. 0.1%), despite a trend to more SAE's in Arm B vs. Arm A (n=397 vs. 358). Although recurrence score is a strong prognostic factor, it was not predictive for anthracycline efficacy; no efficacy differences between the study arms were observed in (locally) triple-negative patients or in those with >4 involved lymph nodes, despite the prognostic impact of these factors. **Conclusion:** In the WSG PlanB trial, patients with early HER2-negative BC seem to be sufficiently treated by six cycles of docetaxel/cyclophosphamide compared to four cycles of EC followed by four cycles of docetaxel – no efficacy differences are evident in high-risk subgroups defined by triple-negative status, nodal status, or high Recurrence Score. Further prospective studies are urgently needed before final conclusions for impact of anthracyclines in HER2-negative BC can be drawn. Clinical trial information: NCT01049425.

505 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Targeted sequencing in a phase III trial of luminal breast cancer: Identification of novel targets. *First Author: John Bartlett, Ontario Institute for Cancer Research, Toronto, ON, Canada*

Background: The International Cancer Genome Consortium and The Cancer Genome Atlas have had a global transformative impact on our understanding of cancer. These programs have mapped the genomic landscape of common and rare tumors setting the scene for a comprehensive change in the approach to cancer diagnosis and treatment. However, the task remains incomplete until these mutational events are linked to clinical outcomes in the context of current therapeutic intervention to drive future stratified medicine approaches. **Methods:** We performed targeted sequencing in patients from the Tamoxifen Exemestane Adjuvant Multicentre trial. DNA was extracted and a 101 gene panel analysed using a novel mutation calling pipeline. Both a priori and machine learning analyses were performed using distant recurrence free survival as the primary endpoint. **Results:** In 1,491 successfully analyzed samples 1,070 (71.76%) samples exhibited at least one single nucleotide mutation (range 0-94, 1.828+/-0.133, mean+/-s.e.). 98/101 genes were mutated in at least one patient. Only variants in *PIK3CA*, *TP53*, *MLL3*, *CDH1* were detected in 5% or more of samples. Twenty genes were associated with increased risk of recurrence in multivariate analyses corrected for clinic-pathological variables, 50% of these genes were involved in transcriptional regulation or RNA/protein processing. In a multivariate analysis, two combined signalling modules were independently prognostic for residual risk following hormone therapy (HRvalidation 3.10 95%CI 1.78-5.40 and HRvalidation 2.70 95%CI 1.57-4.64). **Conclusions:** We successfully performed a signalling pathway-based targeted sequencing analysis within predefined signalling modules. In supervised and unsupervised analyses we identified multiple signalling cassettes linked to poor outcome in patients with ER+ve breast cancers treated with modern endocrine therapy in the context of a phase III clinical trial. These results identify novel candidates as targets to treat endocrine refractory breast cancers.

506 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2. *First Author: Rita Nanda, The University of Chicago, Chicago, IL*

Background: Pembro is an anti-PD-1 antibody with single agent activity in HER2– metastatic BC. I-SPY 2 is a multicenter, phase 2 platform trial which evaluates novel neoadjuvant therapies; the primary endpoint is pathological complete response (pCR, ypT0/Tis ypN0). We report current efficacy results, with final results at ASCO. **Methods:** Patients (pts) with invasive BC ≥2.5 cm by exam or ≥2 cm by imaging are assigned weekly paclitaxel x 12 (control) +/- an experimental agent, followed by doxorubicin/cyclophosphamide x 4. Combinations of hormone-receptor (HR), HER2, & MammaPrint (MP) status define the 8 signatures studied. MP low HR+ BC is excluded. Adaptive randomization is based on each arm's Bayesian probability of superiority over control. Graduation by signature is based on an arm's Bayesian predictive probability of a successful 1:1 randomized phase 3 trial with a pCR endpoint. We provide raw & Bayesian estimated pCR rates adjusted for covariates, time effects over the course of the trial, & serial MRI modeling for pts not yet assessed for pCR surgically. **Results:** 69 pts were randomized to pembro (HER2- subsets only) from Dec 2015 until it graduated in Nov 2016. 46 pts have undergone surgery (table); the other 23 have on-therapy MRI assessments. In 29 HR–/HER2– (TNBC) pts, pembro increased raw & estimated pCR rates by >50% & 40%, respectively; in 40 HR+/HER– pts, it did so by 13% and 21%. 5 pts had immune-related grade 3 adverse events (AEs); 1 hypophysitis & 4 adrenal insufficiency. 4 pts presented after completion of AC (149-179 d after starting pembro); 1 presented prior to AC (37 d after starting pembro). 7 pts had grade 1-2 thyroid abnormalities. **Conclusion:** Pembro added to standard therapy improved pCR rates in all HER2- BCs that meet I-SPY 2 eligibility, especially in TNBC. Immune-mediated AEs were observed; pt follow up is ongoing. Clinical trial information: NCT01042379.

	Current raw data: pCR/n [total assigned]		Estimated pCR rate (95% prob interval) [equivalent n]		Prob pembro superior	Pred prob of success in phase III
Signature	Pembro	Control	Pembro	Control		
HR+/HER2–	7/25 (28.0%) [40]	13/88 (14.8%) [99]	34.2% (17-51%) [29.4]	13.6% (6-21%) [72.4]	99.0%	86.8%
TNBC	15/21 (71.4%) [29]	16/83 (19.3%) [89]	62.4% (45-80%) [28.6]	22.3% (12-33%) [58.4]	>99.9%	99.3%

507 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

A phase III trial of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2-blockade for HER2+ breast cancer: The TRAIN-2 study (BOOG 2012-03). *First Author: Mette S. Van Ramshorst, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Neoadjuvant chemotherapy with dual HER2 blockade boosts pathologic complete response (pCR) rates in HER2+ breast cancer. The optimal chemotherapy backbone in this setting is unknown. We conducted a multicenter phase III trial to study whether anthracyclines would improve outcome compared to a carboplatin-taxane regimen (NCT01996267). **Methods:** We randomly assigned (1:1) patients with stage II-III HER2+ breast cancer to receive 9 cycles paclitaxel (80mg/m^2 day 1 and 8) and carboplatin (AUC = 6mg/ml·min) (arm A) or 3 cycles 5-fluoruoracil (500mg/m^2), epirubicin (90mg/m^2), and cyclophosphamide (500mg/m^2) followed by 6 cycles paclitaxel and carboplatin (arm B). Both arms received trastuzumab (6mg/kg, loading dose 8mg/kg) and pertuzumab (420mg, loading dose 840mg) concurrent with all chemotherapy cycles, and cycles were repeated every 3 weeks. The primary endpoint was pCR in breast and axilla (ypT0/is,ypN0). **Results:** 438 patients were included and 418 (arm A 206 vs arm B 212) were evaluable for the primary endpoint. The pCR rate did not differ between arms (arm A 68% [95% CI 61-74] vs arm B 67% [95% CI 60-73], p = 0.75). Hormone receptor (HR) negative tumors had significantly higher pCR rates (87% vs 54%, p < 0.0001), but we found no evidence for treatment-by-HR interaction (p = 0.23). Common adverse events grade ≥3 were neutropenia (arm A 53% vs arm B 57%, p = 0.34), febrile neutropenia (arm A 2% vs arm B 11%, p = 0.0001), and diarrhea (arm A 17% vs arm B 12%, p = 0.14). Neuropathy grade ≥2 was common in both arms (arm A 31% vs arm B 29%, p = 0.83), while left ventricular ejection fraction (LVEF) decline grade ≥2 (defined as ≥10% decline from baseline or LVEF < 50%) was more common in arm B (arm A 18% vs arm B 29%, p = 0.007). Symptomatic left ventricular systolic dysfunction was rare (< 1%) in both arms. **Conclusions:** Anthracyclines increase the incidence of febrile neutropenia and grade ≥2 LVEF decline, but do not improve pCR rate in the contemporary neoadjuvant treatment of HER2+ breast cancer with dual HER2 blockade. Therefore, we currently favor a carboplatin-taxane based regimen. Follow-up is required to confirm these results with regard to long-term outcome. Clinical trial information: NCT01996267.

508 Oral Abstract Session, Mon, 9:45 AM-12:45 PM

Mastectomy rates in relation to adoption of a margin guideline. *First Author: Monica Morrow, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Surgery after initial lumpectomy to obtain a bigger negative margin is common and may lead to mastectomy. The impact of a 2014 consensus statement endorsing a minimal negative margin for invasive breast cancer on surgeon attitudes, re-excision rates, and final surgical procedure is uncertain. **Methods:** Women with stage I and II breast cancer diagnosed between 7/13–8/15 and reported to the Los Angeles and Detroit SEER registries were surveyed about 2 months post diagnosis, and 70% responded; 3729 comprise the analytic sample. All attending surgeons identified by the patients (n=489) were sent a questionnaire at the end of the patient survey period, and 376 (77%) responded. Pathology reports were reviewed for margin status. Multinomial regression models were used to assess trends. **Results:** The 67% initial lumpectomy rate was unchanged during the study. The final lumpectomy rate increased by 13% (to 65% from 52%) from 2013–2015, accompanied by a decrease in unilateral (to 18% from 27%) and bilateral (to 16% from 21%) mastectomy (p=0.002). Surgery after lumpectomy, both re-excision and mastectomy, declined by 16% ($p<0.001$). Pathology review showed no association between date of treatment and positive margins. Patient report of surgeon-recommended mastectomy after initial lumpectomy declined to 8% from 20% ($p<0.001$). 69% of surgeons endorsed a margin of no ink on tumor to avoid re-excision in ER+PR+ cancer and 63% for ER-PR- cancer. Surgeons treating >50 breast cancers annually were more likely to accept this margin than those treating <20 cases ($p<0.001$). **Conclusions:** Additional surgery after initial lumpectomy markedly decreased between 2013–2015 after publication of a margin guideline endorsinga minimal negative margin. This resulted in a substantial increase in lumpectomy as the definitive surgical procedure, which illustrates that guidelines can be an effective, low-cost approach to addressing clinical controversies.

509 Poster Discussion Session; Displayed in Poster Session (Board #109), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

A randomized, double-blind, phase III study comparing SB3 (trastuzumab biosimilar) with originator trastuzumab in patients treated by neoadjuvant therapy for HER2-positive early breast cancer. *First Author: Xavier B. Pivot, University Hospital Jean Minjoz, Besançon, France*

Background: SB3, a proposed biosimilar to the originator trastuzumab (TRZ), demonstrated similarity to its originator in terms of biological activities and pharmacokinetic (PK) equivalence. This study compared SB3 to TRZ in terms of efficacy, safety, PK, and immunogenicity in patients treated by neoadjuvant therapy for HER2 positive early breast cancer (NCT02149524). **Methods:** Phase III, randomized, double blind, multicenter study compared neoadjuvant SB3 or TRZ for 8 cycles concurrently given with chemotherapy (docetaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide). Then patients underwent surgery followed by 10 cycles of SB3 or TRZ. The primary endpoint was breast pathologic complete response (bpCR) rate. Equivalence was declared if the 90% confidence interval (CI) of the ratio or the 95% CI of the difference of the bpCR rates in the per-protocol set (PPS) were contained within the pre-defined equivalence margins (0.785, 1.546) and (-13%, 13%), respectively. Secondary endpoints were total pathologic complete response (tpCR), overall response rate (ORR), event-free survival, PK, immunogenicity, and safety. **Results:** 800 patients were included in PPS. The bpCR rates were 51.7% for SB3 and 42.0% for TRZ. The ratio of bpCR rate was 1.259 and its 90% CI was 1.112-1.426, within the pre-defined equivalence margin. The difference of bpCR rate was 10.70% and its 95% CI was 4.13-17.26; the lower margin was contained within, the upper margin was outside the pre-defined equivalence margin. Secondary endpoints were comparable between SB3 vs TRZ: tpCR rate (45.8% vs 35.8%); ORR (96.3% vs 91.2%). Safety was comparable between SB3 vs TRZ during neoadjuvant period: incidence of treatment-emergent adverse events (96.6% vs 95.2%), most commonly neutropenia, alopecia, and nausea; incidence of serious adverse events (10.5% vs 10.7%). PK equivalence was demonstrated and immunogenicity between SB3 vs TRZ was comparable (0.7% vs 0.0%). **Conclusions:** Equivalence was demonstrated between SB3 and TRZ based on the ratio of bpCR rates. Safety, PK, and immunogenicity were similar. Complete safety and survival data will follow. Clinical trial information: NCT02149524.

510 Poster Discussion Session; Displayed in Poster Session (Board #110), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Double-blind, randomized phase III study to compare the efficacy and safety of CT-P6, trastuzumab biosimilar candidate versus trastuzumab as neoadjuvant treatment in HER2 positive early breast cancer (EBC). *First Author: Justin Stebbing, Imperial College Healthcare NHS Trust, London, United Kingdom*

Background: CT-P6 (C) is a proposed biosimilar to trastuzumab. This trial (NCT02162667) evaluated the similarity of C and trastuzumab in efficacy and safety for HER2+ EBC. **Methods:** 549 patients with HER2+ EBC were randomized to receive C (n=271) or trastuzumab (n=278) in combination with docetaxel (Cycles 1-4) and 5-fluorouracil, epirubicin, and cyclophosphamide (Cycles 5-8). C or trastuzumab was administered at 8 mg/kg (Cycle 1 only) followed by 6 mg/kg every 3 weeks. The primary endpoint was pathological complete response (pCR) rate at surgery. Secondary endpoints were overall response rate (ORR), PK, PD and safety. After surgery, patients received adjuvant C or trastuzumab to complete a total of 1-year treatment. **Results:** The pCR rate was 46.8% for C and 50.4% for trastuzumab. The 95% CIs for the risk ratio estimate were within the equivalence margin (0.74, 1.35) in PPS and ITT analyses. Other efficacy endpoints were similar between C and trastuzumab. The proportion of patients with at least 1 treatment-emergent SAE was 6.6% for C and 7.6% for trastuzumab. Only 1 patient in each group withdrew treatment due to significant LVEF decrease. Infusion-related reaction was reported for 8.5% of patients in C and 9.0% of patients in trastuzumab. **Conclusions:** This study demonstrated the similarity of efficacy in terms of pCR between CT-P6 and trastuzumab in EBC patients. Secondary efficacy endpoints also supported the similarity between CT-P6 and trastuzumab. CT-P6 was well tolerated with a similar safety profile to that of trastuzumab during the neoadjuvant period. Clinical trial information: NCT02162667.

Summary of efficacy endpoints.

	PPS		ITT	
	CT-P6 n=248	trastuzumab n=256	CT-P6 n=271	trastuzumab n=278
pCR rate (ypT0/is ypN0)				
pCR rate (95% CI)	46.8 (40.4 – 53.2)	50.4 (44.1 – 56.7)	43.5 (37.6 – 49.7)	47.1 (41.1 – 53.2)
Risk ratio estimate (95% CI)	0.9282 (0.7753 – 1.1113)		0.9240 (0.7687 – 1.1108)	
pCR rate (ypT0 ypN0)				
pCR rate (95% CI)	39.9 (33.8 – 46.3)	41.4 (35.3 – 47.7)	37.3 (31.5 – 43.3)	38.8 (33.1 – 44.9)
Risk ratio estimate (95% CI)	0.9641 (0.7806 – 1.1906)		0.9593 (0.7749 – 1.1877)	
ORR (independent review)				
ORR (95% CI)	87.1 (82.3 – 91.0)	86.3 (81.5 – 90.3)	84.9 (80.0 – 88.9)	84.2 (79.3 – 88.3)
Risk ratio estimate (95% CI)	1.0089 (0.9423 – 1.0803)		1.0083 (0.9386 – 1.0831)	

511 Poster Discussion Session; Displayed in Poster Session (Board #111), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). *First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Boston, MA*

Background: Retrospective data suggest that patients (pts) with small HER2+ cancers have more than just minimal risk of disease recurrence. The APT trial was designed to address treatment for such pts. We have previously reported 3-yr disease-free survival (DFS) and here we provide an updated analysis with 7-yr DFS. **Methods:** APT is a single arm multicenter, phase II study of TH. Pts with HER2+ BC (IHC 3+ and/or FISH ratio > 2.0) with negative nodes (a single axillary lymph node micrometastasis was allowed) and tumor size < 3 cm were eligible. Pts received T (80 mg/m^2) with H x 12 weekly (w), followed by H (weekly or q3w) x 39w. The primary endpoint was DFS. Recurrence Free Interval (RFI), Breast Cancer Specific Survival (BCSS), and overall survival (OS) were also analyzed. Intrinsic subtyping by PAM50 was performed on the nCounter Analysis system on archival tissue. **Results:** 410 pts were enrolled from September 2007 to September 2010 and 406 began protocol therapy. 67% had hormone-receptor (HR)+ tumors. Distribution by tumor size: 2% T1mi; 17% T1a; 30% T1b; 42% T1c, and 9% T2 ≤ 3 cm. 6 pts had a nodal micrometastasis. With a median follow-up of 6.5 yrs, there were 23 DFS events observed: 4 (1.0%) distant recurrences, 5 local/regional recurrences (1.2%), 6 new contralateral BC (1.5%), and 8 deaths without documented recurrence (2.0%). The 7-yr DFS was 93.3% (95% CI 90.4-96.2); 7-yr DFS for HR+ pts was 94.6% (95% CI 91.8-97.5) and for HR- pts was 90.7% (95% CI 84.6-97.2). 7-yr RFI was 97.5% (95% CI 95.9-99.1); 7-year BCSS is 98.6% (95% CI 97.0-100); and 7-yr OS was 95.0% (95% CI 92.4-97.7). Ongoing PAM50 testing (n = 227 pts) identified 142 (63%) HER2-enriched; 22 (10%) luminal A, 26 (11%) luminal B, and 20 (9%) basal-like; 17 samples had a poor quality assay. Additional testing and associations with clinical outcomes will be presented at the meeting. **Conclusions:** These data suggest that TH as adjuvant therapy for node-negative HER2+ BC is associated with few recurrences and only 4 distant recurrences with longer follow-up. Based on these data, if chemotherapy/trastuzumab is given to a pt with stage I HER2+ breast cancer, the TH regimen should be considered a standard treatment. Clinical trial information: NCT00542451.

512 Poster Discussion Session; Displayed in Poster Session (Board #112), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Survival outcomes of the NeoALTTO study: Updated results of a randomized multicenter phase III neoadjuvant trial. *First Author: Jens Bodo Huober, University of Ulm, Ulm, Germany*

Background: In the neoadjuvant NeoALTTO trial dual HER2 blockade with lapatinib (L) plus trastuzumab (T) combined with weekly paclitaxel significantly increased the pathologic complete response rate (pCR) compared with either anti-HER2 agent alone plus paclitaxel. At first analysis pts with pCR had a better event free survival (EFS) and overall survival (OS) after median follow-up of 3.84 yrs. **Methods:** 455 pts with operable HER2-positive breast cancer were randomized to receive either L (n=154) 1500mg/day, T 4mg/kg loading dose followed by 2mg/kg/wk (n=149) or L 1000mg/day plus T (n=152) for 6 weeks followed by the assigned anti-HER2 treatment combined with paclitaxel weekly x 12. Following surgery pts received 3 cycles fluorouracil, epirubicin and cyclophosphamide q 3 weeks. The assigned anti-HER2 treatment was continued for 34 weeks thereafter. Primary endpoint was pCR (ypT0/is), secondary endpoints were EFS and OS and the association between pCR and OS analyzed by landmark analysis 30 weeks after randomization. Median follow-up was 6.7 years. **Results:** 6-yrs EFS rate was 67%/ 67%/74% with L/T/TL, respectively (L vs T HR 0.98 [95% CI 0.64–1.51] p=0.93; TL vs T HR 0.81 [95% CI 0.52–1.26] p=0.35). In the hormone receptor negative group 6- yrs EFS rate was 61%/ 63%/74% for the 3 groups, respectively (L vs T HR 1.09 [95% CI 0.61–1.95] p=0.76; TL vs T HR 0.81 [95% CI 0.44–1.51] p=0.52). OS at 6 yrs was 82%/79%/ 85% for L, T and TL, respectively (L vs T: HR 0.85 [95% CI 0.49-1.46] p=0.56; TL vs T HR 0.72 [95% CI 0.41-1.27] p=0.26). In landmark analyses, pts with a pCR had significantly higher 6-yrs EFS (77% /65%) and OS (89% /77%) compared to those without pCR, both overall and for the hormone receptor negative cohort. **Conclusions:** The updated results of the NeoALTTO study confirm the sustained survival benefits for pts who achieve a pCR. EFS and OS after 6 yrs did not differ significantly between the 3 treatment groups. The combination of T and L showed numerically higher EFS compared to T, especially in the hormone-receptor negative group. Clinical trial information: NCT00553358.

pCR vs no pCR	Hazard Ratio	95% CI	p-value
EFS			
all	0.54	0.34-0.82	0.005
HR-	0.47	0.27-0.81	0.008
HR+	0.69	0.32-1.35	0.30
OS			
All	0.43	0.23-0.75	0.005
HR -	0.35	0.16-0.70	0.005
HR+	0.67	0.22-1.69	0.44

513 Poster Discussion Session; Displayed in Poster Session (Board #113), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Chemotherapy (CT) for isolated locoregional recurrence (ILRR) of breast cancer in ER-positive (ER+) and ER-negative (ER-) cohorts: Final analysis of the CALOR trial. *First Author: Irene Wapnir, International Breast Cancer Study Group, NSABP/NRG Oncology, Breast International Group, Bern, Switzerland*

Background: ILRR is associated with a high risk of developing breast cancer distant metastases and death. The CALOR trial (NCT00074152) investigated the effectiveness of CT following local therapy for ILRR. Previously reported results at 5-yrs median follow-up (MFU) showed significant benefit of CT for ER- ILRR, but further follow-up was required in ER+ ILRR. This report presents results at 8.8 yrs MFU within ER status cohorts. **Methods:** CALOR is an open-label, randomized trial for patients with completely excised ILRR after unilateral breast cancer. Eligible patients were randomized to CT (selected by the investigator; multidrug for at least 3 months recommended) or No-CT, and stratified by prior CT, hormone-receptor (ER, PR) status, and location of ILRR. Patients with ER and/or PR positive ILRR received adjuvant endocrine therapy. Radiation therapy was mandated for patients with microscopically involved margins, and anti-HER2 therapy was optional. Endpoints are disease-free survival (DFS), overall survival (OS) and breast cancer-free interval (BCFI). **Results:** From August 2003 to January 2010, 162 patients were enrolled: 104 ER+ and 58 ER-. The results at 8.8 years MFU in ER status cohorts are summarized in the Table (40 and 27 DFS events, respectively). The reduction in the hazard of an event associated with CT for the ER- ILRR cohort was sustained, but no benefit was observed for the ER+ cohort; interactions were significant for DFS and BCFI. The reduction in the hazard of an event seen in the ER- cohort was not apparent in ER+, with significant interactions for DFS and BCFI. Results for the 3 endpoints were consistent in multi-variable analyses adjusting for location of ILRR, prior chemotherapy, and interval from primary surgery. **Conclusions:** The final analysis of CALOR confirms that CT benefits patients with resected ER- ILRR. Long-term CALOR trial results do not support the use of CT for ER+ ILRR. Clinical trial information: NCT00074152.

		CT 10-yr %	No-CT 10-yr %	HR	95% CI	P-int
DFS	ER+	50	59	1.07	0.57-2.00	0.013
	ER-	70	34	0.29	0.13-0.66	
OS	ER+	76	66	0.70	0.32-1.55	0.53
	ER-	73	53	0.48	0.19-1.20	
BCFI	ER+	58	62	0.94	0.47-1.85	0.034
	ER-	70	34	0.29	0.13-0.67	

514 Poster Discussion Session; Displayed in Poster Session (Board #114), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Breast conservation after neoadjuvant chemotherapy for triple-negative breast cancer: Surgical results from an international randomized trial (BrighTNess). *First Author: Mehra Golshan, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA*

Background: Neoadjuvant systemic therapy (NST) increases the frequency of breast-conserving therapy (BCT) in stage II-III breast cancer, but there is little data on how often it converts patients (pts) from BCT-ineligible (BCT-I) to BCT-eligible (BCT-E) and on the impact of other factors on surgical choices. We collected surgical assessment and management data from an international randomized trial of NST in triple-negative breast cancer (TNBC). **Methods:** Women with operable TNBC were randomized to veliparib (V) with carboplatin (C) and paclitaxel (P), placebo with C and P or placebo with P followed by doxorubicin and cyclophosphamide. The surgeons assessed BCT candidacy by clinico-radiographic criteria before and after NST; surgical management was at surgeon and patient discretion. We assessed interactions between BCT eligibility pre- and post-NST, germline BRCA mutation (*gBRCA)* status, continent of treatment and achievement of pathologic complete response(pCR) and percentage of pts who underwent BCT versus mastectomy. **Results:** Pre- and post-NST surgical assessments were available for 604 pts who underwent surgery. BCT rates are listed in the Table. The BCT rate was 68% among pts deemed BCT-E after NST. pCR rates were identical between BCT-E pts who chose BCT (55%) vs. mastectomy (53%). Of 141 pts deemed BCT-I at baseline, 75 (53%) converted to BCT-E but only 42 (56%) of these opted for BCT. pCR rates were 49% in BCT-E converts vs. 36% in those remained BCT-I. *gBRCA* pts (n = 84) were less likely to choose BCT even if they were BCT-E. Pts treated in North America (NA) were less likely to choose BCT (55% vs. 80% for Europe and Asia P<0.0001) even among non-*gBRCA* considered BCT-E post-NST (61% vs. 85% P<0.0001). **Conclusions:** This largest prospective analysis of the impact of NST in TNBC demonstrates a conversion rate from BCT-I to BCT-E of 53%. BCT rates were lower in pts with *gBRCA*; the much higher mastectomy rate among BCT-E pts in NA merits investigation. Clinical trial information: NCT02032277.

	All pts		Post-NST BCT-E	
Category	**N**	**BCT**	**N**	**BCT**
All	604	57%	507	68%
Non-*gBRCA*	520	62%	439	74%
gBRCA	84	26%	68	32%
North America	281	47%	238	55%
NA non-*gBRCA*	246	52%	209	61%
Europe/Asia	323	67%	269	80%
E/A non-*gBRCA*	274	72%	230	85%

515 Poster Discussion Session; Displayed in Poster Session (Board #115), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Phase 3 randomized study of adjuvant anastrozole (A), exemestane (E), or letrozole (L) with or without tamoxifen (T) in postmenopausal women with hormone-responsive (HR) breast cancer: The FATA-GIM3 trial. *First Author: Francesco Perrone, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G. Pascale"- IRCCS, Naples, Italy*

Background: Uncertainty still exists regarding the optimal schedule of adjuvant treatment of breast cancer with aromatase inhibitors (AI) and no trial has ever compared all the three AI. **Methods:** FATA-GIM3 is a multicenter, open label, 2x3 factorial phase 3 randomized study of adjuvant A, E and L upfront (UP - for 5 years) or sequentially (SEQ - for 3 years after 2 years of T) in postmenopausal HR breast cancer pts. Two comparisons were planned: UP vs SEQ and A vs E vs L. DFS (including local or distant relapse, second breast or non-breast cancer, DCIS and death, whichever came first) was the primary end-point; 2% at 5 yrs (corresponding to a HR of 0.79) was defined as the minimum difference required to declare superiority of UP vs SEQ. With two-tailed alfa 0.05, power 80%, 669 events and the enrolment of 3600 patients were planned. Following Data Monitoring Committee advice, final analysis was performed after 5yrs median follow-up. For each comparison a Cox regression model was applied adjusted by stratification factors and stratified by the other treatment factor. Analyses were based on intention-to-treat. **Results:** from 3/2007 to 7/2012, 3697 patients were enrolled at 76 centres. Median age 64, pT1 69.7% , pN0 64.3%, ER and PgR positive 88.9%, HER2 positive 8.9%, previous chemotherapy 38.3%. At 60 months median follow-up, 401 events were reported. 5yrs DFS was 89.8 with UP and 88.5 with SEQ (delta 1.32%, 95% CI -0.90-3.54; HR 0.89, 95% CI 0.73-1.08; P=0.23). 5yrs DFS was 90.0 with A, 88.0 with E and 89.4 with L (P=0.19). **Conclusions:** in the FATA-GIM3 trial there is a small non statistically significant DFS advantage for UP vs SEQ. No significant difference is evident among the three AI. Supported by the FARM5K3MEE AIFA grant from the Italian Drug Agency. Clinical trial information: NCT00541086.

516 Poster Discussion Session; Displayed in Poster Session (Board #116), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Standard anthracycline-based vs. docetaxel-capecitabine in early breast cancer: Results from the chemotherapy randomization (R-C) of EORTC 10041/ BIG 3-04 MINDACT phase III trial. *First Author: Fatima Cardoso, Breast Unit, Champalimaud Clinical Centre, Champalimaud Foundation, Lisbon, Portugal*

Background: The MINDACT trial demonstrated that 46% of breast cancer patients (pts) at high clinical (C) but low genomic (G) risk based on MammaPrint (70-gene signature), might safely forego adjuvant CT *(Cardoso NEJM 2016).* A second 1:1 randomization (R-C) was optional in all pts for whom CT was decided, between standard anthracycline-based regimens (AT) and experimental docetaxel 75 mg/m² IV + oral capecitabine 825 mg/m² bid x 14 days (DC), q3wks for 6 cycles after surgery. **Methods:** MINDACT included 6693 pts, of whom 2895 received CT. C-low/G-low pts were allocated to no CT, C-high/G-high to CT and those with discordant G/C results were randomized to use either G or C risk to decide use of CT. Primary endpoint for R-C was disease-free survival (DFS). Secondary endpoints included OS and safety. Statistical hypothesis: HR-0.76 in favour of DC. **Results:** A total of 1301 pts (45%), of whom 787 (61%) were C-high/G-high, 351 (27%) C-high/G-low, 137 (11%) C-low/G-high, and 26 (2%) C-low/G-low, were randomized to AT or DC. Main reason for not inclusion in R-C was CT given outside the trial. Compliance rates for R-C were 97% overall. At 5-years median follow-up, DFS was not significantly different between AT (649 pts) and DC (652 pts) [HR = 0.83 (0.60- 1.15, p = 0.263], and OS was similar in both arms (HR 0.91, 95% CI, 0.54- 1.53). For the relevant C-high/G-high group, DFS was also not different (5-years DFS 86.1 vs 88.1%; HR 0.83, 95% CI, 0.58-1.21). Of note, number of events is still small (AT: 30; DC: 27). Commonest adverse events in DC were grade 2 hand/foot syndrome (28.5% vs 3.3%), grade 2 diarrhea (13.7% vs 5.8%) and grade 1 peripheral neuropathy (27.1% vs 11.2%). Grade 2 anemia (14.2% vs 5.1%) and grade 4 neutropenia (24.6% vs 20.5%) were higher in AT. Cardiac events occurred in 9 pts overall, including 1 cardiac failure (AT), while 53 pts developed secondary cancers (AT: 32; DC: 21; leukemia: 2 in AT vs. 1 in DC). Four deaths occurred (AT:1 and DC:3) while on therapy. **Conclusions:** Docetaxel-capecitabine did not improve DFS or OS, compared with standard anthracycline-based CT, including for the C-high/G-high group. Safety profile of both regimens was as expected. Clinical trial information: NCT00433589.

517 Poster Discussion Session; Displayed in Poster Session (Board #117), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

A phase III, open label, prospective, randomized, multicenter, neoadjuvant study of chemotherapy versus endocrine therapy in premenopausal patient with hormone responsive, HER2 negative, breast cancer (KBCSG 012). *First Author: hee Jeong Kim, Department of Surgery, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, South Korea*

Background: Neoadjuvant endocrine therapy has shown efficacy in hormone-responsive postmenopausal breast cancer patients. We aimed to assess the efficacy and safety of cytotoxic chemotherapy versus endocrine therapy for hormone-responsive lymph node-positive premenopausal breast cancer patients in a neoadjuvant setting. (NCT01622361). **Methods:** In this phase 3, randomized, double blind, parallel group, multicenter study, we enrolled premenopausal women with estrogen receptor (ER)-positive, HER2-negative, and lymph node-positive premenopausal breast cancer patients. Patients were randomized to either 24 weeks of neoadjuvant chemotherapy with adriamycin plus cyclophosphamide (AC) followed by taxane (T) or neoadjuvant endocrine therapy with zoladex and tamoxifen. **Results:** 187 patients were randomly assigned to chemotherapy (n=95) or endocrine therapy (n=92), and 174 patients completed the 24 week neoadjuvant treatment period (n=87, both). More patients in the chemotherapy group had a complete or partial response than did those in endocrine therapy arm on both caliper (chemotherapy 83.9% vs endocrine therapy 71.3%, OR 0.476 95% CI 0.228 to 0.994) and MRI (chemotherapy 83.7% vs endocrine therapy 52.9%, OR 0.219, 95% CI 0.107 to 0.447). Three patient on chemotherapy group (3.4%) and 1 patients (1.15%) on endocrine treatment group showed complete pathologic response. In the patients who had breast cancer with low Ki 67 expression (<20%) on initial biopsy, clinical response on caliper were shown similar on both treatment group (HR 0.958, 95%CI 0.296 to 3.101). Five patients who had no tumor on the breast or lymph node after 24 week neoadjuvant endocrine therapy had higher ER score (all allred score >6), all low grade (1or 2) low Ki 67(≤20%) expression (4/5 patients) on initial biopsy specimen. **Conclusions:** In premenopausal breast cancer patients, 24 weeks neoadjuvant chemotherapy showed better clinical response than endocrine therapy. Low Ki 67 expression could be a parameter of the endocrine treatment. Clinical trial information: NCT01622361.

518 Poster Discussion Session; Displayed in Poster Session (Board #118), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

A randomised phase III trial comparing two dose-dense, dose-intensified approaches (EPC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto). *First Author: Andreas Schneeweiss, University of Heidelberg, Heidelberg, Germany*

Background: The sequential use of intense does-dense (idd) epirubicin, paclitaxel, cyclophosphamide (EPC) and weekly paclitaxel/liposomal doxorubicin (+/- carboplatin (Cb) in triple negative breast cancer (TNBC) (PM(Cb)) are considered highly efficient regimens for high-risk early stage breast cancer (BC). **Methods:** GeparOcto (NCT02125344) patients (pts) received 18 weeks (wks) either EPC (3x E 150mg/m² q2w followed by 3x P225 mg/m² q2w followed by 3x C 2000mg/m² q2) or PM(Cb) (12x P 80mg/m² plus M 20 mg/m² q1w, plus Cb AUC 1.5 q1w in TNBC). For HER2+ BC trastuzumab 6 (8) mg/kg q3w and pertuzumab 420 (840) mg q3w cycles were given concomitantly with P and C. Pts with histologically confirmed, cT1c - cT4a-d BC and central receptor assessment were included. Pts with HER2+ or TNBC were eligible irrespective of nodal status, luminal B-like tumours only if pN+. Primary objective compared pathologic complete response (pCR) rates (ypT0/is ypN0). Sample size calculations assumed a pCR rate of 50% for EPC and 60% for PM(Cb), requiring 950 pts to show superiority of PM(Cb). Secondary objectives compared pCR rates within the stratified subgroups (BC subtype, HER2+ vs HER2- HR+ vs HER2- HR-), amongst others. **Results:** 961 pts were recruited between 12/2014 and 05/2016, 945 started treatment. Median age was 48 years, 4% T3, 2% T4d, 46% N+, 82% ductal invasive, 66% G3 tumors; 40% were HER2+, 43% TNBC. 347 pts reported SAEs (176 EPC/171 PM(Cb)) and 2 pts died. 35 pneumonias (2 EPC vs 33 PM(Cb)) and 18 pneumonitis (3 EPC vs 15 PM(Cb)) were reported. 16.4% pts with EPC and 33.8% with PM(Cb) discontinued treatment (p<0.001), mainly due to AEs (47 EPC vs 113 PM (Cb)). Mean treatment duration was 17 wks with EPC and 16 wks with PM (Cb). pCR rate was 48.3% with EPC and 47.6% with PM(Cb)(OR 0.97 (95%CI 0.75-1.25), p=0.876). pCR rate in TNBC was 48.5% with EPC and 51.7% with PM(Cb); in HER2+ 62.0% vs 57.4% and in Luminal B 14.1% vs 14.6%. **Conclusions:** In high-risk early stage breast cancer pts pCR rates of idd EPC compared to weekly PM(Cb) were not significantly different. PM(Cb) appeared to be less feasible. Clinical trial information: NCT02125344.

519 Poster Discussion Session; Displayed in Poster Session (Board #119), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Effects of neoadjuvant chemotherapy (NAC) on tumor infiltrating lymphocytes (TIL) and PD-L1 expression in the SWOG S0800 clinical trial. *First Author: Vasiliki Pelekanou, Yale School of Medicine, New Haven, CT*

Background: Higher baseline TILs and PD-L1 expression are associated with greater pathologic complete response (pCR) rates, but how chemotherapy affects these immune parameters is unknown. The goal of this study was to examine TIL and PD-L1 expression in pre- and post-NAC tumor specimens from the S0800 clinical trial that compared weekly nab-paclitaxel/bevacizumab + dose-dense doxorubicin and cyclophosphamide (AC) with nab-paclitaxel + AC as NAC for HER2-negative cases. Association between immune parameters, pCR and NAC-induced changes were tested using ER and NAC-arm adjusted logistic regression. **Methods:** TILs were assessed on H&E stained full sections of 120 pre- and 62 post-NAC tissues (tumor bed of pCR) including 59 matched samples. PD-L1 immunohistochemistry was performed using the FDA cleared 22C3 assay and results were available for 121 baseline and 43 matched post-NAC samples. **Results:** At baseline, the mean TIL count was 18%; 16% had no TILs and 9% had > 50% TILs. Higher baseline TILs were associated with higher pCR rate (p = 0.043, trend test p = 0.014) but there was no interaction with NAC arm. Post-NAC, the mean TIL counts was 11%; 5% had no TILs and 1.6% had > 50% TILs. In the matching post-NAC samples, the mean change was 15% decrease in TILs, but in 32% of cases TILs increased. Cases with residual disease (n=44) had lesser average decrease (p=0.029) than cases with pCR (n=15). The post-NAC decrease in TILs was also observed after excluding cases with pCR. At baseline, PD-L1 expression either in the stroma or on epithelial cells or in both was detected in 52 (43%) of 121 cases (5 tumor only, 29 stroma only, 18 tumor + stroma). Those with baseline PD-L1 expression had higher pCR (63% vs. 37%; p=0.008). Post-NAC, PD-L1 expression was seen in 14 of 43 (33%) cases (7 stroma only, 7 tumor + stroma). In the 39 matching pre- and post-NAC samples, PD-L1 expression was negative in both in 20, positive in both in 10 cases and 6 patients had PD-L1 expression at baseline but not in the post-NAC sample. **Conclusions:** TIL counts and PD-L1 expression generallydecreased, but in a minority of cases increased after NAC. The decrease in TIL was significantly greater in cases achieving pCR. Clinical trial information: NCT00856492.

520 Poster Discussion Session; Displayed in Poster Session (Board #120), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Phase 3 study evaluating efficacy and safety of veliparib (V) plus carboplatin (Cb) or Cb in combination with standard neoadjuvant chemotherapy (NAC) in patients (pts) with early stage triple-negative breast cancer (TNBC). *First Author: Charles E. Geyer, Virginia Commonwealth University Massey Cancer Center, Richmond, VA*

Background: Clinical studies suggest that TNBC is sensitive to DNA-damaging agents, including Cb. V is a potent PARP inhibitor that may enhance the antitumor activity of such agents. We present primary response data from a phase 3 randomized, placebo-controlled study (NCT02032277) evaluating the addition of V + Cb or Cb to neoadjuvant paclitaxel (P) followed by doxorubicin + cyclophosphamide (AC). **Methods:** Pts with histologically confirmed, invasive TNBC (T2–T4 N0–2 or T1 N1–2) amenable to surgical resection were randomized 2:1:1 to (Arm A) P 80 mg/m^2 weekly + Cb AUC 6 mg/mL/min q3 weeks + V 50 mg PO BID; (Arm B) P + Cb + PO placebo; or (Arm C) P + IV placebo + PO placebo, for 12 weeks followed by AC (60 mg/m^2 or 600 mg/m^2 q2 or 3 weeks) $\times$ 4. Primary endpoint was pathologic complete response (pCR) in breast and nodes with $>$ 80% power at 2-sided α of 0.05 using pair-wise comparisons for A vs B and A vs C to detect significant treatment effects using X^2 test; secondary endpoint was rate of conversion to eligibility for breast conservation surgery (BCS). Adverse events (AEs) were assessed with NCI CTCAE V4.0. **Results:** Six hundred thirty-four pts (median age 50 years; range 22–79) were randomized to Arms A (n = 316), B (n = 160), or C (n = 158). Baseline characteristics were well balanced. No pCR difference was observed between Arms A and B (53.2% vs 57.5% p = 0.36), but pCR in Arm A was higher than Arm C (53.2% vs 31.0% p $<$ 0.001). In non-prespecified analysis, pCR in Arm B was also higher than Arm C (57.5% vs 31.0% p $<$ 0.001). Among pts ineligible for BCS at screening (n = 141), 62% were eligible after NAC in Arm A vs 44% each in Arms B (p = 0.13) and C (p = 0.14). Grade 3–4 AEs (Arms A/B/C, 86%/85%/45%) and serious AEs (30%/27%/14%) neutropenia, thrombocytopenia, anemia, nausea, and vomiting were increased with the addition of Cb; V did not impact toxicity. Median cycles of NAC were not reduced with V + Cb + P or Cb + P vs P. **Conclusions:** Addition of V to neoadjuvant Cb + P followed by AC did not increase pCR rate in breast and nodes in stage II–III TNBC, while addition of V + Cb or Cb alone to P followed by AC did. Cb (+/– V) increased toxicity but did not impact delivery of NAC. Clinical trial information: NCT02032277.

521 Poster Session (Board #121), Sun, 8:00 AM-11:30 AM

SWOG S0221 updated: Randomized comparison of chemotherapy schedules in breast cancer adjuvant therapy. *First Author: G. Thomas Budd, Cleveland Clinic, Cleveland, OH*

Background: S0221 investigated weekly vs q 2 week dosing of doxorubicin/cyclophosphamide (AC) and paclitaxel (P) in patients (pts) with high risk early breast cancer as previously reported (JCO 33:58-64, 2015). After enrollment of 2716 pts randomization to the two AC arms was stopped for futility and an additional 578 pts received 4 cycles of q 2 week AC and were randomized to P weekly (Pw) or P q 2 weeks (P2). We report updated results of the original trial design and the first report of the 578 pts treated with AC x 4 and Pw x 12 or P2 x 6. **Methods:** Between December 2003 and November 2010, 2716 pts were randomized in a 2x2 factorial design to 1) 15 weeks of weekly AC (A 24 mg/m2/week and C 60 mg/m2/day po) vs 6 cycles of q 2 week AC (A 60 mg/m2 and C 600 mg/m2) and 2) Pw (paclitaxel 80 mg/m2/week x 12) vs P2 (paclitaxel 175 mg/m2 q 2 weeks x 6), with growth factor support as previously described. After study amendment 578 patients received 4 cycles of q 2 week AC followed by Pw or P2. Updated survival was assessed using log-rank tests and Cox regression models. **Results:** At a median follow-up of 8.5 years, among the pts treated in the original protocol, there were no significant differences among the four treatments for DFS (p=0.21) or OS (p=0.08). The triple-negative subset had worse DFS (P$<$0.001) than the HER2-positive or ER/PR+/HER2- subsets, with 5 year DFS of 75% vs 83% and 84%, respectively. While we previously found in the triple negative subset that the arm using q 2 weeks for both AC and paclitaxel was marginally superior, the differences among the arms are no longer significant for DFS (p=0.12) or OS (p=0.11). Among the 578 pts assigned ACx4 and randomized to Pw v P2 there were no overall differences in DFS (p=0.70) or OS (p=0.63) after 4.4 years median follow-up. **Conclusions:** There were no significant differences in DFS or OS between any of the schedules with extended follow-up in the original cohort and no difference in outcome by paclitaxel schedule for the 578 additional patients in the revised protocol. Either paclitaxel schedule may be recommended, with selection based on toxicity, cost, or patient preference rather than efficacy. Support: NCI grants CA32102, CA38926, CA21115, CA21076, CA77597, CA25224, CA77202, CCSRI15469, and Amgen, Inc. Clinical trial information: NCT00070564.

522 Poster Session (Board #122), Sun, 8:00 AM-11:30 AM

Multi-institutional comparison of breast cancer risk stratification by 70-gene signature and 21-gene assay. *First Author: David J. Dabbs, Department of Pathology Magee Women's Hospital, Pittsburgh, PA*

Background: Breast cancer risk stratification with the 70-gene signature (70-GS) provides a binary low risk (LR) or high risk (HR) result; by contrast the 21-gene assay (21-GA) provides LR, intermediate (IR), and HR results. Results from these two assays were compared for 769 patients from 5 institutions. **Methods:** The study included patients from McGill University (n = 86), UPMC (n = 437), USF (n = 135), Morton Plant North Bay Hospital (n = 79), and Cleveland Clinic (n = 32, all 21-GA IR). **Results:** With the 70-GS, 487 (63%) patients had a LR and 282 (37%) patients had a HR result. Excluding 32 cases selected for 21-GA IR results (n = 737), the 21-GA gave 369 (50%), 250 (34%), and 118 (16%) patients with LR, IR, and HR scores, respectively. Using the TAILORx cutoff, there were 134 (18%), 432 (59%), and 171 (23%) patients with LR, IR, and HR scores, respectively. There were 329 (45%) and 486 (66%) patients who were not classified in the same risk category by both assays using the clinical and TAILORx cutoffs for IR, respectively. **Conclusions:** In a large multi-institutional study the 70-GS and 21-GA results were discordant in 45-66% of patients, and the proportion of patients with a 21-GA score in the IR range varied from 34-59%. The 70-GS provided clinically actionable results for all patients.

		All Patients			Full RS Range		
21-GA	**RS**	**70-GS-LR**	**70-GS-HR**	**Total**	**70-GS-LR**	**70-GS-HR**	**Total**
Clinical-LR	0-17	304	65	369	304	65	369
Clinical-IR	18-30	169	113	282	147	103	250
Clinical-HR	31-80	14	104	118	14	104	118
Trial-LR	0-10	115	19	134	115	19	134
Trial-IR	11-25	335	125	460	315	117	432
Trial-HR	26-80	37	138	175	35	136	171
Total		487(63%)	282(37%)	769	465(63%)	272(37%)	737

523 Poster Session (Board #123), Sun, 8:00 AM-11:30 AM

Anastrozole after tamoxifen in early breast cancer patients with chemotherapy-induced ovarian function failure. *First Author: Vivianne C. Tjan-Heijnen, Maastricht University Medical Centre, Maastricht, Netherlands*

Background: The DATA study compared 6 and 3 years of anastrozole therapy in postmenopausal women with hormone-receptor positive early breast cancer previously treated with 2-3 years tamoxifen (oral presentation SABCS 2016 #S01-03). The study included postmenopausal women, allowing those with chemotherapy-induced ovarian function failure (CIOFF). However, these may be at risk of ovarian function recovery (OFR). The current analysis compared the survival of women with CIOFF with definite postmenopausal women and examined the influence of OFR on survival. **Methods:** We selected patients from the DATA study aged 45-57 years at randomization who had received (neo-)adjuvant chemotherapy. They were classified by menopausal status at randomization (definite postmenopausal before chemotherapy or by ovariectomy, versus CIOFF). The latter were monitored by estradiol measurements for OFR during anastrozole. Endpoints: Disease-free Survival (DFS), Distant Recurrence-free Survival (DRFS), and Overall Survival (OS), corrected for tumor size, nodal status, grade, and hormone-receptor status. We used the landmark method to calculate residual 5-year survival rates. **Results:** In total, 261 patients were definite postmenopausal and 395 had CIOFF, of whom 39 experienced OFR while 290 did not (66 were excluded from the landmark analysis because follow-up estradiol levels were lacking). When comparing the CIOFF with the definite postmenopausal women, the 5-year survival rates were not significantly different. Within the group with CIOFF, experiencing OFR was associated with a trend for worse outcome (DFS-event HR 1.33 (95% CI 0.61-2.90), P=0.48; DRFS-event HR 2.11 (95% CI 0.89-5.02), P=0.09; and OS-event HR 2.24 (95% CI 0.92-5.45), P=0.07). Patients who experienced OFR in the first year had a residual 5-year rate for DFS of 73.1% compared with 87.4% in those who did not. For DRFS these rates were 76.9% vs. 92.1%, and for OS 80.8% vs. 94.4% respectively. **Conclusions:** These results suggest that women with CIOFF undergoing anastrozole treatment may be at increased risk of disease recurrence if experiencing OFR despite close monitoring of estradiol levels and adjusting endocrine treatment. Clinical trial information: NCT00301457.

524 Poster Session (Board #124), Sun, 8:00 AM-11:30 AM

Copy-number and targeted sequencing analyses to identify distinct prognostic groups: Implications for patient selection to targeted therapies amongst anti-endocrine therapy resistant early breast cancers. *First Author: Jane Bayani, Ontario Institute for Cancer Research, Toronto, ON, Canada*

Background: Hormone receptor positive breast cancer is a therapeutic challenge. Despite optimal anti-endocrine therapies, most breast cancer deaths follow a diagnosis of early luminal cancer. To understand the impact of multiple aberrations in the context of current therapy, we assessed the prognostic ability of genomic signatures as a putative stratification tool to targeted therapies. **Methods:** This *a priori* study is based on molecular pathways which might predict response to targeted therapies. DNA from 420 patients from the phase III TEAM pathology cohort were used. Patients with a distant recurrence within 5 years were matched by clinical variables to those disease-free at follow up. Copy number analysis was performed using the Affymetrix Oncoscan Assay. Targeted sequencing was performed in a subset of samples for genes based on signaling cassettes mined from the ICGC. Pathways were identified as aberrant if there were copy number variations (CNVs) and/or mutations in any of the pre-determined pathway genes: 1) CCND1/CCND2/CCND3/CDK4/CDK6; 2) FGFR1/FGFR2/FGFR2/FGFR4; and 3) AKT1/AKT2/PIK3CA/PTEN. Kaplan-Meier and log-rank analyses were used for DFS between groups. Hazard ratios were calculated using the Cox proportional hazard models adjusted for age, tumour size, grade, lymph node and HER2 status. **Results:** 390/420 samples passed informatics QC filters. For the CCND/CDK pathway, patients with no CNV changes experienced a better DFS (HR = 1.7, 95% CI 1.3-2.3, $p < 0.001$). For the FGFR/FGF pathway, a similar outcome is seen among patients without CNVs (HR = 1.5, 95% CI 1.1-2.0; p = 0.005). For AKT/PIK3CA, a decrease in DFS was seen in those with aberrations (HR = 1.4, 95% CI 1.0-1.8, p = 0.03). **Conclusions:** We demonstrated that CNVs of genes within CDK4/CCND, PIK3CA/AKT and FGFR pathways are independently linked to high risk of relapse following endocrine treatment, with implications for identifying those patients who are at high-risk for recurrence despite optimal anti-endocrine therapy and linking molecular features driving these cancers to targeted therapies.

525 Poster Session (Board #125), Sun, 8:00 AM-11:30 AM

COOLHAIR: A prospective randomized trial to investigate the efficacy and tolerability of scalp cooling in patients undergoing neoadjuvant chemotherapy for early breast cancer. *First Author: Katharina Smetanay, National Center for Tumor Diseases (NCT) and Women's University Hospital Heidelberg, Heidelberg, Germany*

Background: Chemotherapy induced alopecia (CIA) is a distressing side effect for women with breast cancer (BC) undergoing chemotherapy (CT). Scalp cooling is a method aiming to prevent CIA, but its efficacy is not well defined. Observational studies show a positive effect of scalp cooling to reduce hair loss, but randomized trials until recently have been lacking. **Methods:** In our monocentric prospective randomized trial patients with early BC undergoing (neo)adjuvant CT were 1:1 randomized to either scalp cooling (CAP) or not (noCAP). All patients received 18 to 24 weeks of anthracycline (A) and/or taxane (T)-based CT. The DigniCap System was used for scalp cooling. The primary endpoint was patient reported rate of alopecia according to the Dean Scale (Grade 0: no hair loss, grade 1: > 0 - 25%; grade 2: > 25 - 50%; grade 3: > 50 - 75%; grade 4: > 75%). Hair preservation was defined as hair loss £ grade 2. Secondary endpoints were rate of alopecia determined by nursing staff and an independent and blinded evaluator, rate of wig/scarf use as well as quality of life. **Results:** From August 2014 until January 2016 seventy-nine patients were included (41 CAP and 38 noCAP). The drop-out rate was 32% in the CAP arm and 34% in the noCAP arm. Main reasons for drop out were hair loss, adverse events (CAP) and randomization into control arm. At the time of this analysis all patients had completed CT. Hair preservation was observed in 39% of patients in the CAP arm versus 0% in the No CAP arm ($p < 0.001$). There was a strong concordance between patients and staff evaluation (weighted Cohen's Kappa = 0.92). Wig/scarf use was significantly less frequent in the CAP group (36% vs 92% at home, $p < 0.001$; 64% vs 91% outside, $p < 0.001$). We did not observe any differences in hair preservation between A-based and non A-based regimens. **Conclusions:** Our prospective randomized trial shows that scalp cooling is effective in preventing CIA in a relevant number of patients. This option should be made available for patients undergoing T+/-A-based (neo)adjuvant chemotherapy for EBC.

526 Poster Session (Board #126), Sun, 8:00 AM-11:30 AM

Non-adherence behaviors among young women on adjuvant endocrine therapy for breast cancer. *First Author: Johanna Wassermann, Dana-Farber Cancer Institute, Boston, MA*

Background: Young age at diagnosis (dx) is a predictor of worse prognosis in patients (pts) with luminal breast cancer (BC). Poorer adherence to endocrine therapy (ET) among younger women may contribute to this disparity. Aim: To assess non-adherent behaviors and associated factors among young women with stage 1-3 hormone receptor (HR)+ BC taking ET. **Methods:** This study is a part of a multicenter, prospective cohort of pts with dx of BC at or under age 40. On a survey 30 months after dx, among pts reporting taking ET, adherence was measured using a 3-item Likert-type scale (Do you ever forget to take your ET? If you feel worse when you take your ET, do you stop taking it? Did you take your ET exactly as directed by your doctor?). Pts reporting any non-adherent behavior during the last 3 months were classified as non-adherers. Variables with a *p*-value <0.20 were included in a multivariate logistic model. **Results:** Among361 pts eligible for this analysis, 174 (48%) reported some non-adherent behaviors in the last 3 months; 56 (16%) moderate or greater non-adherent behaviors. None of the studied variables was associated with non-adherent behaviors (table). **Conclusions:** Non-adherent behaviors to ET are present in almost half of the young women with HR+ BC. Further analyses of explanatory factors and impact of non-adherence are required to understand and potentially improve this problem.

		Univariable			Multivariable		
	med. (range)	OR	95% CI	p	OR	CI95%	p
Age at dx	36.0 (17-40)	0.98	0.93-1.03	0.42			
	n (%)						
White	330 (91)	1.35	0.61-3.00	0.46			
College-educated	316 (88)	0.71	0.38-1.34	0.29			
Married/Living as married	283 (78)	0.67	0.41-1.12	0.12	0.67	0.40-1.14	0.14
Children pre-dx	218 (60)	0.95	0.62-1.45	0.82			
Full Employment	173 (48)	1.03	0.68-1.55	0.88			
Financial comfort	194 (54)	1.17	0.77-1.77	0.46			
Stage (ref=3)							
1	149 (41)	1.61	0.84-3.10	0.15	1.44	0.70-2.99	0.33
2	162 (45)	1.63	0.85-3.12	0.14	1.53	0.77-3.06	0.23
HER2+	97 (27)	0.89	0.56-1.42	0.63			
Complete mastectomy	201 (56)	1.42	0.93-2.16	0.10	1.41	0.86-2.34	0.18
Radiotherapy	217 (60)	0.67	0.44-1.02	0.06	0.82	0.49-1.39	0.47
Chemotherapy	249 (69)	1.09	0.70-1.71	0.70			
Tamoxifen (vs. AI)	350 (97)	0.52	0.15-1.81	0.31			
Fertility concerns	150 (42)	1.07	0.70-1.63	0.75			
Fear of recurrence	56 (16)	0.81	0.46-1.44	0.48			

527 Poster Session (Board #127), Sun, 8:00 AM-11:30 AM

Yoga in women undergoing treatment for breast cancer: Impact on quality of life in a randomized controlled trial. *First Author: Nita S. Nair, Department of Surgical Oncology, Breast Disease Management Group, Tata Memorial Centre (TMC), Mumbai, India*

Background: Yoga has been tested in multiple small-randomized studies for its impact on quality of life (QOL) on breast cancer (BC). We propose to study the effect of yoga on disease free survival as the primary endpoint in women with operable breast cancer. (Study methodology details refer to NCT02161900). **Methods:** Women with non-metastatic BC were randomized to yoga and conventional exercise (YCE) versus conventional exercise only (CE) in addition to standard therapy. Over and above documentation of recurrence and death, QOL was assessed in these women using the EORTC QLQC30, BR23, Brief fatigue inventory (BFI), Visual pain scores (VPS) and a spirituality questionnaire (SQ). EORTC QLQ was assessed at baseline (BL), 6-9 months (mo), 18-21 mo. BFI and VPS at BL, 6-8 mo and 12-15 mo and SQ at BL and 12-15 mo. We report the first interim analysis of QOL in 605 patients randomized to the study with atleast 1 year of follow up. The groups were balanced in both arms with respect to clinico-pathological factors. **Results:** At 6-9 mo (completion of adjuvant therapy), there was no significant difference in global QOL scores (p = 0.08), however 52% women on YCE showed an improvement from baseline compared to 42% in CE. At 18-21 mo emotional function scores were better in YCE (p = 0.002); with lesser systemic side effects in YCE arm (44% vs 56% p = NS). The median score of fatigue after adjuvant therapy measured by QLQ C30 was lower in YCE (17.37vs22.22, p = 0.003) which was similar to that observed by BFI at 12-15 mo (1.6vs 2, p = 0.04). Also in YCE there was lower reporting of detriment in general activity (41%vs 59%) and mood (34%vs66%) (p = NS). In VPS at 12-15mo, the median scores for pain intensity (p = 0.042), pain on movement (p = 0.038), pain on mobilization (p = 0.008) were lower in YCE. Lastly SQ assessed spirituality and showed no difference, but less deterioration compared to baseline scores in YCE. **Conclusions:** Yoga did not show a significant difference in global QOL but had a major benefit reaching statistical significance in fatigue, emotional score and pain. Yoga is a low-risk, low-cost complementary therapy that may improve compliance to therapy by improving parameters that can affect day-to-day activity in women with breast cancer. Clinical trial information: NCT02161900.

528 Poster Session (Board #128), Sun, 8:00 AM-11:30 AM

Refined estimates of local recurrence risks and the impact of the DCIS score adjusting for clinico-pathological features: Meta-analysis of E5194 and Ontario DCIS cohort studies. *First Author: Eileen Rakovitch, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Better tools are needed to estimate the risk of local recurrence (LR; DCIS or invasive) after breast-conserving surgery (BCS) for DCIS to inform treatment decisions. The DCIS Score (DS) was validated as a predictor of LR in E5194 and Ontario DCIS Cohort (ODC) after BCS without radiation (Solin,2013; Rakovitch,2015). We performed a meta-analysis (MA) combining data from E5194 and ODC with additional follow-up from E5194 adjusting for pertinent clinico-pathologic factors to provide refined prediction estimates of LR risk after BCS alone. **Methods:** The MA used data from E5194 and ODC. Patients with positive margins and multifocality were excluded. Identical Cox regression models were fit including age at diagnosis (<50, ≥ 50 yr), tumor size (1cm, >1cm), DCIS Score and year of surgery (before vs after 2000). Grade was not significant. MA was used to calculate precision-weighted estimates of 10 year LR risk by DS. **Results:** Combined cohort includes 773 pts (tamoxifen used in 20% E5194, 17% of ODC $>$ 65 yr). The DS and the clinico-pathologic variables age, tumor size and year provided independent prognostic information on 10 yr LR risk ($p \leq .009$). Hazard ratios from E5194 and ODC cohorts were similar for tumor size ≤ 1 vs. >1cm (1.45, 1.47), age ≥ 50 vs. <50 yr (0.61, 0.84) and surgery year after 2000 (0.67, 0.49). 10 yr LR risks by combinations of age, tumor size, and DS are detailed in Table. For patients ≥ 50 yr with tumors ≤ 1cm and low risk DS, the 10 yr LR risks range from 5.3-10.0%. A high risk DS is associated with a higher 10 yr predicted risk of LR in all subsets. 10 yr risk of contralateral BC was 5.4%. **Conclusions:** This MA provides refined estimates of 10 yr LR risk after BCS alone for DCIS. Adding clinico-pathologic factors to the DCIS Score provides enhanced prognostic LR risk estimates to guide individualized treatment decision-making.

		10 yr LR risk (Range) (%)		
Tumor Size (cm)	Age (yr)	Low Risk DS	Intermediate Risk DS	High Risk DS
≤1	≥50	7.2 (5.3-10.0)	11.3 (10.2-12.7)	14.6 (12.9-23.1)
	< 50	10.2 (7.4-13.9)	15.8 (14.1-17.4)	19.6 (17.7-30.7)
1.1-2.5	≥50	10.1 (7.3-12.6)	13.9 (12.8-15.6)	19.5 (15.8-28.7)
	< 50	14.5 (10.1-17.2)	18.9 (17.4-21.1)	23.2 (21.4-37.2)

529 Poster Session (Board #129), Sun, 8:00 AM-11:30 AM

Impact of DNA repair deficiency signature on outcomes in triple negative breast cancer (TNBC) patients treated with AC chemotherapy (SWOG S9313). *First Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS*

Background: Biomarkers of response and resistance to adjuvant chemotherapy for TNBC are needed. Deficiency in DNA damage response (DDR) and repair pathways have been reported in TNBC and may impact response to chemotherapy. Aims: To investigate DNA damage response deficiency (DDRD) molecular signature, *BRCA1*mRNA expression and Tumor Infiltrating Lymphocytes (TILs) as prognostic markers in TNBC patients treated with adjuvant AC on S9313. **Methods:** S9313 accrued 3125 early stage BC patients to two alternative schedules of AC with no difference in outcomes between the two arms. We identified 425 (14%) patients with centrally determined TNBC with tissue availability. DDRD signature (44 gene signature, Almac Inc.) and *BRCA1*expression (NanoString nCounter) were performed on RNA isolated from pre-treatment FFPE tumor tissue. DDRD score was classified in quartiles. TILs evaluation was performed using previously described criteria. Markers were tested for prognostic effect on DFS and OS using Cox regression model with adjustment for randomized treatment assignment. **Results:** For 425 TNBC patients median age: 45 yrs, and 5 year DFS and OS = 74% and 82%, respectively. DDRD signature was successfully evaluated in 89.6% (381/425) but only 267 (62.8%) met 60% tumor content criterion for inclusion. DDRD score quartiles were associated with DFS (5 year DFS 59% & 82% in the lowest & highest quartiles respectively, $p = 0.0005$) and OS (5 year OS 74% and 86% in lowest and highest quartiles respectively, $p = 0.008$). *BRCA1* expression and TILs were successfully determined in 78% and 99% samples, respectively. *BRCA1*expression was not associated with DFS. TILs were associated with DFS (10% increase HR = 0.88; 95% CI 0.79-0.97; $p = 0.016$) and OS (HR = 0.84; 95% CI 0.74-0.94; $p = 0.0005$). DDRD score and TILs were highly correlated (Pearson = 0.62). In multivariate model of DFS including TILs and DDRD quartiles, only DDRD remains significant ($p = 0.018$). **Conclusions:** DDRD signature was prognostic in TNBC patients treated with AC chemotherapy and has the potential to be used as a selection criterion to identify TNBC patients whose prognosis is sufficiently poor to justify evaluation of alternative treatment.

530 Poster Session (Board #130), Sun, 8:00 AM-11:30 AM

Effects of age, immune landscape, and response to trastuzumab (H) in HER-2 positive (HER2+) breast cancer in NCCTG (Alliance)-N9831. *First Author: Aixa Elena Soyano, Mayo Clinic Florida, Jacksonville, FL*

Background: Therapeutic efficacy of H involves activation of the immune system.Age-dependent progressive deterioration of the immune response is referred as immunosenescence. In HER2+ breast cancer, the effects of aging and the ability of H to activate endogenous anti-tumor immunity is unknown. A previous report from HERA trial showed no significant increase in risk of early recurrence with age ($\leq$ or $>$ 40). We evaluated the long-term outcome of HER2+ patients (pt) related to age and immune landscape. **Methods:** 1,392 pt from N9831 trial were evaluated. Stromal tumor infiltrating lymphocytes (sTIL) were evaluated in H&E slides. Lymphocyte predominant breast cancer (LPBC) was defined as sTIL $\geq$ 50%. Molecular TIL (mTIL) and immune subset signatures were evaluated using NanoString research CodeSets. Cox proportional hazard ratio (HR) was used for analysis. **Results:** There were 1,111 (79.8%) pt $>$ 40 years old (yo) and 281 (20.2%) pt $\leq$ 40 yo. Younger age was significantly associated with hormone receptor positivity (p 0.00011) and luminal B subtype (p 0.011). With a median follow up of 10.6 years, there was no significant difference in long-term outcome among pt $\leq$ 40 vs. $>$ 40 yo who received H (HR = 0.88 (0.62-1.24), p = 0.45). Similar findings were observed when age was dichotomized at 50 and 60 yo. While there was no association between sTIL and age, a small but significant increase in mTIL CD45 expression with age (p 0.003) was observed. Similar small increases in cytotoxic cell (p 0.007) and T cell (p 0.015) immune scores were also observed with increasing age. Among pt who received chemotherapy alone, pt $>$ 40 yo with LPBC (n 55) had excellent outcome with 92.4% recurrence free survival (RFS) at 10 years. However, there was no significant difference in RFS among pt $\leq$ 40 yo with or without LPBC. **Conclusions:** Among pt treated with H, there was no significant difference in outcome related to age. In contrast to a decline expected from immunosenescence, we observed small but significant increases in mTIL signatures for total lymphocytes, cytotoxic, and T cell subsets. Among patients who received chemotherapy alone, our data suggested that pt $>$ 40 yo with LPBC had excellent prognosis, compared to pt $>$ 40 yo without LPBC.

531 Poster Session (Board #131), Sun, 8:00 AM-11:30 AM

Endocrine therapy non-persistence in young women with early-stage breast cancer. *First Author: Shoshana M. Rosenberg, Dana-Farber Cancer Institute, Boston, MA*

Background: The greatest age disparity in early stage breast cancer (BC) outcomes is in young women with hormone receptor positive (HR+) BC. While differences in biology may play a role, understanding the role of non-persistence (early discontinuation) with endocrine therapy (ET) is critical given the demonstrated efficacy of ET in this population. **Methods:** As part of a prospective cohort that enrolled women with BC diagnosed (dx) at age $\leq$40 between 2006-2016, we identified women with HR+, Stage I-III BC. Socio-demographic and treatment information, fertility concerns and confidence with the ET treatment decision were assessed by survey within 1 yr of dx. Medical record review was used to ascertain stage and HR status. Women who initiated ET but did not report taking tamoxifen or an aromatase inhibitor at 3 yrs post-diagnosis (or last follow-up if $<$3 yrs) were classified as non-persistent. Chi-square tests were used to compare categorical variables between persisters and non-persisters and stepwise multivariable regression to evaluate predictors of non-persistence. **Results:** In 538 women who initiated ET, median age at dx was 36; 10% were non-persistent. Discontinuation of ET was more likely in those who were less confident with their ET decision compared to those who were more confident (25/179, 14% vs 18/263, 7%, p=0.01). A greater proportion of women concerned about fertility discontinued vs. women not concerned (29/213,14% vs 25/319, 8%, p=0.03), and fertility concerns were associated with non-persistence in multivariable analyses (OR: 1.85, 95% CI 1.05-3.26, p=0.03). Age at dx, race, education, employment, financial comfort, marital status, parity, stage, chemotherapy and local therapy were not associated with non-persistence. **Conclusions:** A significant minority of women with HR+ BC discontinued ET within 3 yrs. The association between fertility concerns expressed soon after dx and non-persistence underscores a need to address psychosocial issues that can impact treatment decisions in young women. Strategies to reduce decisional conflict and increasing confidence with the choice to take ET, may influence persistence. Future work will evaluate the contribution of other factors (eg symptom burden) to non-persistence.

532 Poster Session (Board #132), Sun, 8:00 AM-11:30 AM

A population-based analysis of treatment and outcomes in 2,500 metaplastic breast cancer patients. *First Author: Cecilia Tuongquang Ong, Department of Surgery, Duke University Medical Center, Durham, NC*

Background: Metaplastic breast cancer (MBC) is a rare, aggressive variant that is often triple negative (TN). Current guidelines recommend use of standard receptor-based treatment for MBC despite evidence of chemoresistance. We sought to compare treatment patterns and outcomes of MBC and non-MBC. **Methods:** Women age > 18 with stage I-III MBC and non-MBC histology diagnosed from 2010-2013 were identified in the National Cancer Database. Kaplan Meier and multivariate Cox proportional hazards models were used to estimate MBC association with overall survival (OS). Subgroup analyses were conducted for (1) MBC patients only and (2) TN MBC and TN non-MBC patients. **Results:** 2451 MBC and 568,057 non-MBC patients were included. 70.3% of MBC were TN vs 11.3% of non-MBC ($p < 0.001$). 19.2% of MBC were luminal (i.e., ER+ and/or PR+, and HER2-). MBC presented with higher clinical T stage (cT4: 5.4% vs 1.8%) and grade (grade 3: 72.1% vs 29.7%) but was less frequently node-positive (19.1% vs 29.7%, all $p < 0.001$). A higher proportion of MBC patients were treated with mastectomy (59.0% vs 44.9%), axillary dissection (ALND, 35.2% vs 32.2%), and chemotherapy (74.1% vs 43.1%, all $p \leq 0.001$). 5-year OS was reduced among MBC vs non-MBC patients for both the entire cohort (72.7% vs 87.5%) and the TN-only analysis (71.1% vs 77.8%, both log-rank $p < 0.001$). Among MBC cases, TN subtype was not associated with worse OS than the luminal subtype (HR 1.16, $p = 0.28$). Chemotherapy (HR 0.69, $p = 0.004$) and/or radiotherapy (HR 0.52, $p < 0.001$) improved OS in MBC, and the proportional benefit of chemotherapy did not vary with pathological T or N stage (interaction $p > 0.05$ for both). Among TN patients, a higher proportion of TN MBC patients underwent mastectomy (58.4% vs 49.5%, $p < 0.001$), but in contrast to the full cohort, a lower proportion of TN MBC patients received chemotherapy (76.6% vs. 78.7%, $p = 0.008$) and ALND (35.2% vs. 38.2%, $p = 0.01$) vs TN non-MBC patients. **Conclusions:** MBC had worse OS vs non-MBC, and unlike other histologies, outcome was not driven by receptor status. Multimodal therapy improved outcomes. Further investigation into MBC tumor biology and the development of MBC-specific guidelines could potentially improve treatment standardization and outcomes.

533 Poster Session (Board #133), Sun, 8:00 AM-11:30 AM

Prognostic value of histopathology, stromal tumor infiltrating lymphocytes (sTILs) and adjuvant chemotherapy (AdjCT) in early stage triple negative breast cancer (TNBC). *First Author: Roberto Antonio Leon-Ferre, Mayo Clinic, Rochester, MN*

Background: Current guidelines define TNBC as complete absence of estrogen (ER) and progesterone receptor (PR), without HER2 amplification. However, the prognostic impact of clinical and histopathological factors, sTILs, and AdjCT in TNBC meeting these strict criteria is unknown. **Methods:** From a cohort of 9985 women who underwent upfront surgery for M0 breast cancer (BC) at Mayo Clinic Rochester from 1985-2012, 1159 pts with ER negative or low (≤10%) BC were identified for central ER/PR/HER2 staining and HER2 FISH (IHC2+ only) to select those with TNBC by modern definitions. Cox proportional hazards models were used to assess the impact of clinicopathological variables on invasive disease-free (IDFS) and overall survival (OS). **Results:** Tumors from 605 pts (median age 56.3 yrs) met criteria for TNBC (ER < 1%, PR < 1% and HER2 0, 1 or 2+ and FISH negative). 51% were T1, 65% N0, 88% grade 3, and 75% had Ki67 > 15%. Histologically, 39% were anaplastic, 26% invasive ductal, 16% medullary, 8% metaplastic, 6% apocrine and 5% others. Median sTILs was 20% (0-90%). 55% pts received AdjCT [21% anthracycline (A), 19% A + taxane, and 15% other]. Median follow-up for IDFS and OS were 7.4 and 10.6 yrs, respectively. Multivariate analyses demonstrated that higher N stage ($p < 0.01$), lower sTILs ($p = 0.01$) and no AdjCT ($p < 0.01$) were independently associated with worse IDFS and OS. Histology (medullary subtype) was associated with better IDFS in univariate (HR 0.56, 95% CI, 0.35-0.89) but not in multivariate analyses, once sTILs were accounted for. Among systemically untreated pts ($n = 182$), higher N ($p < 0.01$) and lower sTILs ($p = 0.04$) were associated with worse IDFS. For systemically untreated T1N0 pts ($n = 111$), the 5-yr IDFS was 70% (95% CI, 61-81) [T1a: 83% (95% CI, 63-100), T1b: 68% (95% CI, 52-88) and T1c: 67% (95% CI, 55-83)], compared to 78% (95% CI, 68-84) for T1N0 pts treated with AdjCT. **Conclusions:** In TNBC pts, N stage, sTILs and receipt of AdjCT were independently prognostic for IDFS and OS. sTILs remained prognostic for IDFS in systemically untreated TNBC. In N0 TNBC, the risk of recurrence or death was substantial in the absence of chemotherapy, even for those with T1 tumors.

534 Poster Session (Board #134), Sun, 8:00 AM-11:30 AM

Prospective study of magnetic resonance imaging (MRI) and multiparameter gene expression assay in ductal carcinoma in situ (DCIS): A trial of the ECOG-ACRIN Cancer Research Group (E4112). *First Author: Seema Ahsan Khan, Northwestern Memorial Hospital, Chicago, IL*

Background: Prior retrospective studies have evaluated breast MRI in DCIS, and prospective-retrospective biomarker studies have shown that the DCIS Score is prognostic for recurrence after BCS alone. E4112 is a prospective cohort study designed to assess the combined impact of breast MRI and DCIS Score on surgical and RT management. **Methods:** Women diagnosed with screen-detected DCIS on core biopsy, if BCS eligible, underwent breast MRI. Those remaining so following MRI and related biopsies, with no invasive disease, underwent BCS. If final surgical margins were ≥2 mm, the DCIS lesion was submitted for DCIS Score assay. Women with low DCIS Score (≤39, LS) were advised that RT could be avoided; RT was recommended to those with high/intermediate (H/I) scores. The primary objective was to estimate the fraction converting to mastectomy (Mx) following MRI. Secondary objectives included estimation of re-operation rates after first BCS, and DCIS Score distribution.A sample size of 333 evaluable women would allow estimation of Mx rate of 12% with 95% confidence interval 9-16%. **Results:** 334 enrolled women had completed surgery; the first surgical procedure was Mx in 54 (16.2%) and BCS in 280 (83.8%), of whom 62 (22.1%) required at least one re-excision, and 11 (3.9%) converted to Mx. DCIS Scores were obtained on 171 patients who completed BCS, of whom 82 were LS and 89 were H/I. Demographics were similar between the two groups, other features will be reported. Only 7/82 (8.5%) of the LS group received RT, whereas 82/89 (92.1%) of the H/I group received RT. Of the 98 BCS patients who did not qualify for DCIS Score-based therapy, 23 had invasive disease, 34 had final surgical margins < 2 mm, and 13 had both. There was insufficient tissue for DCIS Score in 11, and 17 did not complete follow-up. **Conclusions:** In this study, among DCIS patients who were BCS-eligible following MRI, total mastectomy rate was 19.5%; re-excision rate was 22.1% for women who had BCS. Approximately half had low DCIS Scores, and RT recommendations based on the DCIS Score were acceptable to most women. Clinical trial information: E4112.

535 Poster Session (Board #135), Sun, 8:00 AM-11:30 AM

Long-term outcome of breast cancer patients diagnosed ≤40 years according to breast cancer subtype in the absence of adjuvant systemic therapy: The PARADIGM initiative. *First Author: Gwen Dackus, Division of Molecular Pathology, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Background: Young age at breast cancer diagnosis is considered a poor prognostic factor. As a result, many treatment guidelines advice adjuvant systemic treatment for young patients. Answering prognostic questions on young patients has therefore become a challenge. The PARADIGM (PAtients with bReast cAncer DIaGnosed preMenopausally) project aims to assess the long-term outcome of women diagnosed with breast cancer ≤40 years in the absence of adjuvant systemic therapy, using real world data from the nationwide Netherlands Cancer Registry (NCR) coupled with tissue biobanking. **Methods:** All women ≤40 years, diagnosed in the Netherlands between 1989-2000 with a primary invasive, histologically proven, $T_{any}N_0M_0$ breast cancer, without adjuvant systemic treatment were identified through the NCR. Back then N_0 patients were considered low risk and did not receive adjuvant systemic treatment. Tissue specimens were revised by a team of dedicated breast pathologists. Cox regression was performed to estimate hazard ratios for recurrence-free (RFS) and overall survival (OS) according to immunohistochemical (IHC) subtype. Analyses were adjusted for grade, pathological T-stage, histological subtype and radiotherapy. **Results:** We included 2310 patients with a mean follow-up of 15.4 years (range 0-25 years). OS for the whole cohort was 68% and RFS 58.4% at 25 years. In total 740 deaths and 1043 recurrences were observed. Hormone receptor (HR)+/HER2+ patients had a significantly worse OS when compared to HR-HER2+ patients (adjusted Hazard Ratio 1.58; 95% confidence interval 1.05-2.38; p=0.029). No difference was observed between HR-HER2+ and the triple negative and HR+/HER2- subgroups at 25-years. RFS was similar for all IHC subtypes. **Conclusions:** In this large cohort of non-adjuvant systemically treated young breast cancer patients with long-term follow-up HR+/HER2+ patients have a significantly worse survival when compared to triple negative, HR-/HER2+ and HR+/HER2- patients. The latter three subtypes have similar OS at 25 years. Future molecular studies have been planned to distinguish the favorable from the unfavorable prognostic patients.

536 Poster Session (Board #136), Sun, 8:00 AM-11:30 AM

Independent validation of stromal uPA in archived tumor samples from the prospectively randomized ABCSG8 trial to provide level 1b evidence for a prognostic value of uPA immunohistochemistry in endocrine-treated postmenopausal breast cancer patients. *First Author: Christian F. Singer, Medical University of Vienna, Department of Obstetrics and Gynecology, Comprehensive Cancer Center, Vienna, Austria*

Background: We have recently demonstrated that urokinase Plasminogen Activator (uPA), together with its inhibitor PAI-1, have prognostic value in hormone-receptor positive early breast cancer, and can be measured in FFPE archived tumor samples. We have now aimed to validate the prognostic role of uPA protein expression in FFPE archived tumor samples in an independent cohort of endocrine-treated breast cancer patients. **Methods:** 303 post-menopausal women with hormone receptor–positive, early breast cancer who had received 5 years of endocrine therapy in the prospectively designed ABCSG-08 trial, and in whom FFPE tumor tissue was available, were included in this analysis. Stromal uPA and PAI-1 protein expression was evaluated by immunohistochemistry and correlated with distant recurrence-free survival (DRFS) and overall survival (OS). **Results:** Stromal uPA was detected in 132 of 297 tumors (44.4%), and 74 out of 269 samples (27.5%) exhibited stromal PAI-1, while co-expression of both proteins was found in 48 of 294 (16.3%) samples. Neither uPA nor PAI-1 expression were associated with tumor size, age, nodal status, grading, or receptor status. Patients whose tumor stroma expressed uPA protein were more likely to have a shorter DRFS (adjusted HR for relapse: 2.78; 95% CI 1.31-5.93; p=0.008 Cox regression analysis) and OS (adjusted HR for death: 1.29; 95% CI 0.86-12.50; p=0.161) than women without uPA expression. No such association was observed for PAI-1 and for the uPA/PAI1 ratio. After a median follow-up of 5.6 years women with uPA-positive tumors experienced a significantly shorter DRFS (93.3% vs 84.8%; p<0.013 log rank test) and tended to have a worse OS (83.0.4% vs 77.3%; p=0.106) compared to women with uPA negative tumors. **Conclusions:** By confirming the clinical utility of stromal uPA IHC in archived breast cancer samples from an independent prospective randomized trial, we now provide level 1b evidence for a prognostic role of stromal uPA in women with endocrine-responsive early breast cancer.

537 Poster Session (Board #137), Sun, 8:00 AM-11:30 AM

The performance of the 21-gene assay standard cutpoints of 18 and 31 in HR+, HER2- invasive breast cancer (BC), while waiting for TAILORx mid-range recurrence score results. *First Author: Dave P. Miller, Genomic Health, Redwood City, CA*

Background: The Recurrence Score (RS) was shown in NSABP B-20 to predict chemotherapy (CT) benefit for RS ≥31 and no CT benefit for RS <18. The TAILORx results for RS <11 (NEJM 2015) reported excellent outcomes with no opportunity for CT to add additional benefit. As we await TAILORx results for RS 11-25, we characterized BC specific mortality (BCSM) for RS groups (cutoffs of 11, 18, 25, and 31) in the population-based SEER study of pts treated based on RS. **Methods:** RS results were provided to SEER registries per their methods (npj Breast Cancer 2016). Pts diagnosed (Jan 2004 - Dec 2012) with NO HR+ HER2- negative BC, and no prior malignancy were eligible. BCSM estimates by CT use were computed using standard cutpoints of 18 and 31 and TAILORx cutpoints of 11 and 25. **Results:** Among 49,681 with a RS, 9,486 (19%) had RS <11, 17,988 (36%) had RS 11-17, 14,541 (29%) had RS 18-25, 3,805 (8%) had RS 26-30, and 3,861 (8%) had RS ≥31. Reported CT use and 5-y BCSM increased with increasing RS. For pts with both RS <11 and RS 11-17, CT use was uncommon and 5-y BCSM was low regardless of CT use. For pts with RS 18-25, CT use was more common and the 5-y BCSM was about 1% regardless of CT use. For pts with RS of 26-30 or ≥31, CT was common, and lower 5-y BCSM was observed with CT reported yes than with CT reported no or unknown. **Conclusions:** Pts in real-world clinical practice with RS <11, consistent with TAILORx, and pts with RS 11-17 have low 5-y BCSM with limited CT use, supporting hormonal therapy alone for pts with RS <18. The high end of the TAILORx mid-range (18-25) also showed good 5-y BCSM both with and without CT, highlighting the importance of the randomized results of TAILORx.

	CT Reported No or Unknown		CT Reported Yes	
RS	**N (%)**	**5-y BCSM (95% CI)**	**N (%)**	**5-y BCSM (95% CI)**
< 11	9167 (97%)	0.4 (0.3%, 0.6%)	319 (3%)	0.4% (0.1%, 2.5%)
11-17	16520 (92%)	0.4% (0.3%, 0.6%)	1468 (8%)	0.6% (0.3%, 1.4%)
18-25	10278 (71%)	1.0% (0.8%, 1.3%)	4263 (29%)	1.1% (0.7%, 1.6%)
26-30	1741 (46%)	3.1% (2.1%, 4.5%)	2064 (54%)	1.8% (1.1%, 2.7%)
≥31	1146 (30%)	6.8% (5.1%, 9.1%)	2715 (70%)	3.8% (2.9%, 4.8%)

538 Poster Session (Board #138), Sun, 8:00 AM-11:30 AM

Which patient characteristics drive treatment decisions in elderly patients with early stage hormone receptor–positive breast cancer? *First Author: Sacha Satram-Hoang, Q.D. Research, Inc., Granite Bay, CA*

Background: Hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) is the most common biologic subtype of breast cancer (BC). We examined treatment patterns and outcomes associated with adjuvant or neoadjuvant therapy among elderly patients (pts) in the US. **Methods:** The analysis included 18,470 first primary HR+HER2- BC pts from the linked SEER-Medicare database. Pts were diagnosed with Stage I-III disease between 1/1/2007-12/31/2011, ≥66 years, continuously enrolled in Medicare Parts A/B in the year prior to diagnosis, enrolled in Part D in the year after diagnosis, and underwent BC surgery ≤6 months after diagnosis. Time-varying Cox proportional hazards regression assessed overall survival adjusting for pt characteristics. Date of last follow-up was 12/31/2013. **Results:** There were 13,670 (74%) pts treated with hormonal therapy +/- chemotherapy and 4,800 (26%) untreated. Compared to treated pts, untreated pts were older, had earlier stage, lower grade, smaller tumors, poorer performance, higher comorbidity, and less genomic testing for risk of recurrence (p<0.0001). In a multivariate analysis, increasing age, stage, tumor size, tumor grade, comorbidity score and poor performance were significantly associated with higher mortality risks, while use of genomic testing was associated with a lower risk of death. The Cox model showed a 48% higher risk of death in untreated compared to treated pts (HR=1.48; 95% CI=1.35-1.61). Even in a subset of 8,967 pts with stage I disease, tumor size <2.0cm and grade 1/2; untreated pts had a 22% higher risk of death compared to treated pts (HR=1.22; 95% CI=1.05-1.41). **Conclusions:** Patients who are older with favorable disease characteristics (earlier stage, smaller tumor, lower grade) are less likely to be treated and have a higher risk of death compared to pts who received adjuvant or neoadjuvant therapy. The unmet need among elderly BC pts remains, suggesting that age should not deter guideline-based therapy.

	Treated N=13670	Untreated N=4800
Mean Age* (95% CI)	74.7 (74.6-74.8)	78.0 (77.8-78.2)
Stage*, (%)		
1	56	70
2	34	25
3	9	5
Grade*, (%)		
1	29	35
2	49	47
3/4	18	14
Tumor Size <2.0cm*, (%)	63	72

*p-value <0.001

539 Poster Session (Board #139), Sun, 8:00 AM-11:30 AM

A propensity score analysis exploring the impact of adjuvant chemotherapy (aCT) in a multi-center series of resected early stage pure invasive lobular breast carcinoma (ILC). *First Author: Luisa Carbognin, University of Verona, Verona, Italy*

Background: Patients (pts) resected for early breast cancer are assigned to receive aCT according to international guidelines based upon immunophenotype and clinical/pathological features, regardless of the histotype, given the lack of prospective data for ILC. Thus, the magnitude of the benefit of aCT for ILC is still not sizable. The aim of this analysis was to investigate the effect of aCT in a multi-center series of early stage pure ILC. **Methods:** Clinical-pathological data of consecutive pts affected by pure ILC, undergone surgery at 3 Italian institutes, were correlated with disease-free and overall survival (DFS/OS) using a Cox model. A propensity score analysis was performed to evaluate the prognostic impact of aCT. Kaplan-Meier curves were compared with Log-Rank analysis. **Results:** Data from 739 pts were gathered (median age 57 years (yrs); Luminal/Triple-Negative/HER2 pos.: 98%/1.6%/0.4%). At median follow-up of 78 months, 5-/10-yrs DFS and OS were 79.4%/66.0% and 91.4%/76.5%, respectively. Tumor-size according to TNM (T, HR 1.34, 95% CI 1.04-1.72, *p=0.025*) and lymph-node (N) status (HR 2.39, 95% CI 1.47-3.89, *p<0.0001*) were independent predictors for DFS at multivariate analysis. T (HR 1.87, 95% CI 0.99-3.54, *p=0.05*), N status (HR 3.24, 95% CI 1.69-6.22, *p<0.0001*), Ki67 (HR 2.48, 95% CI 0.95-6.42, *p=0.06*), and age (HR 2.23, 95% CI 1.16-4.30, *p=0.016*) were predictors for OS. A significant prognostic effect of aCT upon OS was found after adjusting for independent factors with the propensity score method, as shown in the table below. Particularly, aCT significantly prolongs OS and DFS in pts with T >1, with an absolute difference of 17%/35% and 15%/13% at 5 and 10 yrs, respectively (*p=0.003* and *p=0.04*). OS was longer for pts with positive N (*p=0.02*), Ki67 >4% (*p=0.01*) and grading >1 (*p=0.01*). **Conclusions:** Despite the retrospective nature of this analysis, the propensity score analysis indicates that pts with ILC may significantly benefit from aCT in terms of long-term survival, particularly for larger and more aggressive tumors.

Outcome	**Category**	**5-yrs (%)**	**10-yrs (%)**	***Log-Rank***
DFS	aCT	84.3	75.6	*p=0.33*
	No aCT	84.7	64.0	
OS	aCT	94.3	87.4	*p=0.002*
	No aCT	88.7	64.5	

540 Poster Session (Board #140), Sun, 8:00 AM-11:30 AM

Longer follow-up on cardiac safety and distant disease free survival of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab in patients with early-stage HER2-positive breast cancer. *First Author: Rui Wang, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: We previously reported the cardiac safety results and distant disease-free survival (DDFS) on a phase 2 trial of dose-dense (dd) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) and trastuzumab (H) in patients with early stage, human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The incidence of congestive heart failure (CHF) was 1.4% both at a median follow-up of 2 and 7 years. Here, we report updated CHF and DDFS rates with longer follow-up. **Methods:** Patients were enrolled with HER2 overexpressed (immunohistochemistry 3+) or amplified (fluorescent in situ hybridization ratio $>$ 2.0) disease, regardless of size or nodal status, and baseline left ventricular ejection fraction (LVEF) of $>$ 55%. Patients (pts) received dd AC (60/600 mg/m2) q 2 weeks (w) x 4 $\rightarrow$T (175 mg/m2) q 2 w x 4 with H (loading dose 4 mg/kg $\rightarrow$ 2 mg/kg q w during T $\rightarrow$ 6 mg/kg q 3 w for rest of 1 year); pegfilgrastim was administered after each chemotherapy cycle. LVEF monitoring with multigated acquisition scan occurred at baseline, months 2 (after AC), 6, 9, and 18 (after therapy completion). **Results:** From January 2005 to November 2005, 70 pts were enrolled; 2 (3%) and 68 (97%) were treated in neoadjuvant and adjuvant settings, respectively. In 68 pts treated in adjuvant setting, 40 (60%) and 27 (40%) had node-positive and node-negative disease, respectively. The median age was 49 years old (range 27-72); 55 (79%) had hormone-receptor positive disease, 11 (16%) had hypertension, and 21 (30%) had left sided radiation. The median baseline LVEF was 68% [range, 55%-81%]). With a median follow-up of 10.9 yrs, there was no additional CHF event. Therefore, the cumulative incidence of CHF remains to be 1.4% (95% confidence interval [95% CI], 1.36%- 7.7%). The 9 and 10 year DDFS rates were 89% (95% CI, 78%-94%) and 87% (95% CI 75%-93%), respectively. **Conclusions:** Longer follow-up of this study has demonstrated that ddAC $\rightarrow$TH is associated with a low risk of CHF and promising DDFS in patients with early-stage HER2-positive breast cancer.

541 Poster Session (Board #141), Sun, 8:00 AM-11:30 AM

Recent time trends in chemotherapy use and oncologists' chemotherapy recommendations for early-stage, hormone receptor-positive breast cancer. *First Author: Allison W. Kurian, Stanford School of Medicine, Stanford, CA*

Background: Advances in tumor genomic profiling enable increasingly precise estimates of the benefit of adjuvant chemotherapy in early-stage breast cancer. However, little is known about how chemotherapy use, medical oncologists' (MO) perspectives and recommendations have changed in recent years, particularly in key clinical subgroups such as node-negative and node-positive. **Methods:** We surveyed 5,080 women (70% response rate), newly diagnosed with breast cancer in 2013-2015 and accrued through two population-based SEER registries (Georgia and Los Angeles), about their MOs' chemotherapy recommendations and whether they received chemotherapy. Using patient report, we identified 470 attending MOs and surveyed them (n=310, 66% response) about approaches to chemotherapy recommendation, using node-negative and node-positive case scenarios. We evaluated factors associated with chemotherapy receipt over time using multi-level logistic regression. **Results:** The analytic sample was 2,926 patients with stages I-II, estrogen receptor-positive, HER2-negative breast cancer. Chemotherapy use declined to 21% from 34% during the study period (2013-2015, p$<$.001). For node-positive patients, chemotherapy use declined to 64% from 81% and for node-negative/micrometastasis patients to 14% from 27%. Based on patient report, MOs' recommendations for chemotherapy declined during the study period to 32% from 45% (p$<$.001). Recommendations reported by MOs were generally guideline-concordant. MOs were much more likely to order tumor genomic profiling when patient preferences were discordant with recommendations [67%, standard error (SE) 3% versus 18% (SE 2%) without discordance], and they adjusted chemotherapy recommendations based on patient preferences and genomic profiling results. **Conclusions:** For both node-negative/micrometastasis and node-positive patients, chemotherapy receipt and oncologists' recommendations for chemotherapy declined markedly in recent years. The results of ongoing clinical trials of genomic profiling will be essential to confirm the quality of this approach to breast cancer care. Funded by NCI P01CA163233.

543 Poster Session (Board #143), Sun, 8:00 AM-11:30 AM

Clinical outcomes in ER+ HER2-negative breast cancer (BC) where treatment decisions incorporated the 21-gene recurrence score (RS): Elderly (≥70 yrs) vs younger patients (Pts). *First Author: Salomon M. Stemmer, Davidoff Cancer Center, Tel Aviv, Israel*

Background: Elderly BC pts are generally undertreated, despite evidence suggesting that they may benefit from adjuvant chemotherapy (CT). We compared treatments/clinical outcomes in elderly vs younger Clalit Health Services (CHS) pts undergoing RS testing. **Methods:** This exploratory analysis of the CHS registry included BC pts with N0/N1mi/N1 disease who were RS-tested from 1/2006 (CHS approval of the test) through 12/2010 (N0) or 12/2011 (N1mi/N1). Medical records were reviewed to verify treatments/recurrences/survival. **Results:** The analysis included 458 elderly and 2052 younger pts, with a median (range) follow-up of 5.7 (0.9-9.6) and 6.1 (0.1-10.3) yrs, respectively. In the elderly/younger pts, median age was 73/58 yrs, 48%/52% had grade 2 tumors, median tumor size was 1.6/1.5 cm, 70%/72% were N0 and 30%/28% were N1mi/N1. RS distribution ($<$18, 18-30, ≥31) among elderly pts was 56%, 33%, and 11%, respectively, compared to 49%, 41%, and 10%, respectively, in younger pts. In pts with RS 18-30 and RS≥31, CT use was significantly lower in the elderly (*P*$<$.001). Kaplan-Meier estimates for 5-yr distant recurrence and BC death risk are presented (Table). **Conclusions:** In elderly pts, the proportion of those with RS≥31 was very similar to younger pts; however, overall CT use was significantly lower. Within each RS group, there was no statistically significant difference in clinical outcomes between the age groups; though, numerically, in RS 18-30 pts, outcomes were worse in the elderly. In pts with RS$<$18, outcomes were excellent regardless of age and despite very low rates of CT use.

	RS<18			RS: 18-30			RS≥31			
Age	N	CT use, %	5-yr distant recurrence risk (95% CI)/ 5-yr BC death risk (95% CI)	N	CT use, %	5-yr distant recurrence risk (95% CI)/ 5-yr BC death risk (95% CI)	N	CT use, %	5-yr distant recurrence risk (95% CI)/ 5-yr BC death risk (95% CI)	P*
<70	1001	3	1.4 (0.8-2.4) 0.1 (0.0-0.7)	841	31	3.5 (2.4-5.0) 1.2 (0.6-2.2)	210	91	11.6 (8.0-16.9) 6.5 (3.8-10.9)	<.001 <.001
≥70	258	2	2.0 (0.8-4.7) 0.4 (0.1-2.8)	150	11	6.0 (3.2-11.3) 3.5 (1.5-8.3)	50	68	8.0 (3.1-19.9) 4.2 (1.1-15.6)	.006 <.001

* Distant recurrence risk/BC death across RS groups were compared using log-rank test.

544 Poster Session (Board #144), Sun, 8:00 AM-11:30 AM

An NCDB analysis of trends in male breast cancer from 2004-2009 and 2010-2014. *First Author: Esther Dubrovsky, NYU Langone Medical Center, New York, NY*

Background: To examine the trends in clinicopathologic features, treatment, and survival of male breast cancer (MBC), utilizing the National Cancer Data Base (NCDB). **Methods:** MBC patients entered in the NCDB from 2004-2009 were compared with those from 2010-2014 for demographics, stage at diagnosis, tumor characteristics, treatment type, and overall survival (OS). Male patients were also compared to female patients from the same time periods. Statistical analysis included Pearson's chi-square test. **Results:** Of 2,047,868 breast cancer cases, a total of 19,409 (0.95%) men were available for analysis. The group of MBC patients from 2004 to 2009 included 9,790 men with a median age of 65. The group from 2010 to 2014 included 9,619 men with a median age of 66. In the later group there was a decreased rate of DCIS, increased rate of invasive ductal carcinoma, and increased rate of hormone positive tumors. Among the earlier and later MBC groups, 24% vs. 27% of patients underwent lumpectomy. Of these, 61% vs 68% received post-lumpectomy radiation, respectively. Patients in the later group (2010-2014) were more likely to receive adjuvant hormonal therapy (61% vs. 84%, p $<$ 0.0001). MBC patients were older than female patients (65 vs. 61 years, p $<$ 0.0001), had larger tumors (20mm vs. 16mm, p $<$ 0.0001), slightly later stage at diagnosis, and more likely to undergo mastectomy (74 vs. 42%, p $<$ 0.0001). MBC patients also had higher rates of hormone positive tumors, but lower rates of adjuvant hormonal therapy (55% vs. 58%, p $<$ 0.0001). The OS for male vs. female patients in the 2004-2009 groups was 66% vs. 77% (median follow-up 73.9m vs 80.4m) respectively. Similarly, in the 2010-2014 groups, survival was 84% vs. 90% (median follow-up 33.85m vs 35.91m), respectively. **Conclusions:** Although men have higher rates of hormone positive tumors, they are less likely to receive adjuvant hormonal therapy. There was a significant trend over time towards more standard therapies in men, such as post-lumpectomy radiation and hormonal therapy use. There has been an improvement of OS in men which mirrors that in women. The disparities in outcomes between male and female patients, however, still require further investigation.

546 Poster Session (Board #146), Sun, 8:00 AM-11:30 AM

Breast Cancer Index (BCI) prognostic and predictive classification in older versus younger patients with early-stage HR+ breast cancer (BC) and correlation with clinical risk factors. *First Author: Yuan Yuan, City of Hope, Duarte, CA*

Background: Older patients with HR+ BC may present distinct challenges for treatment decision-making. BCI is a validated gene expression assay for pts with early stage HR+ BC that provides 2 results: BCI Predictive, based on HoxB13/IL17BR (H/I ratio), reports a prediction of likelihood of benefit from extended endocrine therapy (EET); BCI Prognostic, based on the combination of H/I and proliferation-based genes, reports individualized risk of late distant recurrence (DR). Here, the predictive and prognostic value of BCI results across the aging spectrum (< 64y, 65-74y, ≥75y) and correlation with clinical risk factors were examined. **Methods:** The BCI Clinical Database for Correlative Studies is an IRB-approved de-identified database that contains > 50 clinicopathologic and molecular variables from cases submitted for BCI in clinical practice (N = 14,463). Clinicopathologic variables were abstracted from pathology reports, and were available for a subset of cases. Chi-squared tests were used to compare BCI results between age groups and clinical subsets. **Results:** Analyses included LN- pts (N = 3,395): median age 59.1y; 5.5% ≥75y (N = 188), 24.0% 65-74y (N = 814), 70.5% ≤64y (N = 2,393). BCI Prognostic had a wide distribution of individual risk assessments in all age groups. The proportion of pts classified as high risk was similar between age groups (48.4%, 48.4% and 49.8% in ≥75y, 65-74y and ≤64y; p = 0.76). The proportion of pts with high risk results increased with increasing tumor size and grade in all age groups (P < 0.05 for all). Notably, in pts ≥75y, BCI identified 31.9% of T1a/b and 21.1% of Grade 1 tumors as high risk of late DR. BCI Predictive (H/I) also identified similar proportions as High H/I across age groups (42.0%, 41.8%, and 40.6% in ≥75y, 65-74y, and ≤64y; p = 0.81). Similar proportions of pts ≥75y were identified as high H/I across size and grade subsets (P = 0.702, P = 0.193, respectively). **Conclusions:** BCI identifies pts with high risk disease and who may benefit from EET across the aging spectrum. Individualized decisions for EET also must include life expectancy, competing comorbidities and potential toxicities from therapy.

547 Poster Session (Board #147), Sun, 8:00 AM-11:30 AM

Adjustments in relative dose intensity (RDI) for FECD chemotherapy in breast cancer: A population analysis. *First Author: Zachary William Neil Veitch, Tom Baker Cancer Centre, Calgary, AB, Canada*

Background: Reductions in RDI of adjuvant chemotherapy for breast cancer (BC) has been associated with inferior survival. However, earlier studies may be confounded by uncharacterized BC subtype(s) (TNBC, HER2+) and non-taxane chemotherapy regimens (CMF, AC). This retrospective study evaluates survival (DFS/OS) outcomes for patients receiving RDI reductions for FECD adjuvant chemotherapy in Alberta, Canada. **Methods:** Patients with stage I-III, ER +/-, HER2- BC receiving adjuvant FECD chemotherapy from 2007-2014 were identified using the Alberta Cancer Registry. RDI of individual chemotherapeutics (cycle 1-6) were recorded. Average RDI was stratified by <85% vs ≥85% of total dose. Subgroup analysis for early (cycle 1-3) versus late (cycle 4-6) RDI reductions were evaluated. Events (recurrence/death) from any cause were identified. **Results:** FECD patients (n=1304) receiving an average RDI <85% (range 25-84%) compared to ≥85% demonstrated a significant decline in DFS (79% vs 85%; p<0.01) and OS (82% vs 89%; p<0.01). Early reductions (any) compared to no reduction in RDI were correlated with inferior DFS (77% vs 86%; p<0.01) and OS (79% vs 90%; p<0.01). Late reductions in RDI did not affect DFS/OS. Proportions of TNBC were non-significant for comparative cohorts. Significantly more N0 and N1-3 patients were seen in the any and no early reduction cohort respectively. **Conclusions:** In high risk BC patients, average RDI <85% is correlated with reduced DFS/OS for FECD. Early (FEC) compared with late (docetaxel) reductions in RDI are correlated with inferior survival. This data suggests that where possible, total (<85%) and early (FEC) dose reductions should be avoided in patients receiving adjuvant FEC-D chemotherapy.

Baseline patient characteristics.

	FECD				Early (FEC)				Late (Docetaxel)			
	<85% (n=202)		≥85% (n=1101)		Yes (n=238)		No (n=1065)		Yes (n=688)		No (n=1065)	
Patient Characteristics	n	%	n	%	n	%	n	%	n	%	n	%
Age	56	-	54	-	55	-	54	-	55	-	53	-
HR+	166	82.2	943	85.6	195	81.9	914	85.8	597	86.8	512	83.3
TNBC	36	17.8	158	14.4	43	18.1	151	14.2	91	13.2	103	16.7
Nodes												
N0	19	9.4	93	8.4	30	12.6**	82	7.7	57	8.3	55	8.9
N1-3	129	63.9	701	91.6	136	57.1	694	65.2*	432	62.8	398	64.7
N>4	54	26.8	307	27.9	72	30.3	289	27.2	199	28.9	162	26.3

*p=0.02; **p=0.015

548 Poster Session (Board #148), Sun, 8:00 AM-11:30 AM

An estimation model for Oncotype Dx score using routine clinical and pathological parameters. *First Author: Rossana Esther Ruiz Mendoza, Scientific & Academic Direction, Oncosalud - AUNA, Lima, Peru*

Background: Oncotype Dx(ODX) prognosticates the risk of recurrence and predicts the benefit of adjuvant chemotherapy in estrogen-receptor-positive breast cancer (BC). However, its cost makes it prohibitive for many health care systems. Our objective is to develop a model using routine clinical and pathological parameters to estimate ODX high risk category to guide adjuvant chemotherapy decisions. **Methods:** We retrospectively reviewed ODX and pathology reports from 190 early BC patients (2014 to 2016) in a specialized cancer center. Variables were selected through a multiple linear regression model. Coefficients of statistically significant variables were used to build an equation. Its results were divided into 2 estimated risk categories. ODX RS was also divided into 2 categories; above or below 25 (cut-off in TAILORx and RxPONDER). The final locked model was independently validated in 57 patients. **Results:** Among the tested variables, tumor size (pT), progesterone receptor (PR), Ki67 and Elston-Ellis grade were significantly associated with ODX RS (Table 1). The linear predictor is: (0.2544 x pT) – (0.0739 x PR) + (0.0861 x Ki67) + (5.4232 x Elston grade). The threshold score for this equation was set on 13 (median value) to discriminate low and high estimated risks. The correct classification rate (CCR) for the training and validation sets was 60% and 56%, respectively. CCR for high risk was 72% and 87% in the training and validation sets, respectively. **Conclusions:** An equation based on readily available variables correctly classified more than half of cases. Although the overall CCR is modest, our equation is remarkably useful for high risk cases requiring chemotherapy. With further validation, our model could provide a clinically useful estimation of high risk at lower cost.

Variable	Coefficient	S.E.	t-value	p-value
(Intercept)	1.9486	6.1387	0.317	0.751
Age	0.0677	0.0531	1.275	0.204
pT	0.2544	0.0896	2.84	0.005
ER	-0.0252	0.0411	-0.613	0.541
PR	-0.0739	0.0178	-4.141	<0.001
Ki67	0.0861	0.0435	1.98	0.049
Elston grade	5.4232	1.6364	3.314	0.001

549 Poster Session (Board #149), Sun, 8:00 AM-11:30 AM

Toxicity of extended adjuvant aromatase inhibitors therapy in postmenopausal breast cancer patients: A systematic review and meta-analysis. *First Author: Hadar Goldvaser, Rabin Medical Center, Beilinson Hospital, Davidoff Center, Toronto, ON, Canada*

Background: Aromatase inhibitors (AI) are a gold standard adjuvant endocrine therapy for postmenopausal women with breast cancer. A number of randomized trials (RCTs) have reported modest improvements in breast cancer outcomes from extending treatment with AI beyond the initial 5 years after diagnosis. However, less in known about the toxicity of extended AI compared with no therapy. **Methods:** We conducted a systematic review of MEDLINE to identify RCTs that compared extended AI to placebo or no treatment. The search was supplemented by a review of abstracts from the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium meetings between 2013 and 2016. Odds ratios (ORs), 95% confidence intervals (CI), absolute risks, and the number needed to harm (NNH) associated with one adverse event were computed for prespecified safety and tolerability outcomes including cardiovascular disease, bone fractures, second cancers (excluding new breast cancer), treatment discontinuation due to adverse events and death without recurrence. **Results:** Seven trials comprising 16349 patients met the inclusion criteria. Longer treatment with AI was associated with increased odds of cardiovascular disease (OR = 1.18, 95% CI 1.00-1.40, P=0.05; NNH = 122) and bone fractures (OR = 1.34, 95% CI 1.16 - 1.55, P < 0.001; NNH = 72). Compared to control, longer AI therapy was associated with a higher odds of treatment discontinuation due to adverse events (OR = 1.45, 95% CI 1.25 - 1.68, P < 0.001; NNH = 20). Longer AI therapy did not influence the odds of second cancers (OR = 0.93, 95% CI 0.73-1.18, P = 0.56). There was a numerical excess of death without recurrence with longer AI therapy, but this was not statistically significant (OR = 1.11, 95% CI 0.9 - 1.36, P = 0.34). **Conclusions:** Longer durations of AI use are associated with increased cardiovascular events and bone fracture. There is a numerical, but non-statistically significant excess of deaths without breast cancer recurrence among patients receiving longer AI therapy. These data should be taken into account when considering extended adjuvant AI therapy for breast cancer patients.

550 Poster Session (Board #150), Sun, 8:00 AM-11:30 AM

Disparities in multigene signature testing and its impact on adjuvant therapy in early stage breast cancer. *First Author: Maris S. Jones, John Wayne Cancer Institute, Santa Monica, CA*

Background: Commercially available prognostic multigene signature tests (PMT) have been available for over a decade to guide adjuvant therapy in early stage breast cancer. This study explores persistent disparities in the availability of PMT and how results influence the use of adjuvant therapy. **Methods:** Females > 18 years of age with newly diagnosed, primary, Stage I-III, ER positive, HER2-neu negative breast cancer that did not receive neoadjuvant therapy between 2006-2014 were captured from the National Cancer Database (NCDB) participant user file. Univariate and multivariate analyses identified factors associated with utilization of PMT as well as receipt of adjuvant chemotherapy for patients with PMT risk stratification. **Results:** Of 574,921 eligible females, 130,297 (22.66%) received PMT. Almost all patients that had PMT had pathologically negative (pN0 = 83%) or 1-3 positive LNs (pN1 = 16%). Controlling for tumor features, patients least likely to have PMT were of lower socioeconomic status, uninsured, not White non-Hispanic, < 40 or > 70 years of age, and treated at community hospitals or in the Western region (all $p < 0.001$). Very few patients with PMT results actually received adjuvant chemotherapy (0.64% of 92,235). Of this small group, younger patients (ages 18-49) those with less education (OR = 1.37, 95%CI:1.07-1.76), positive lymph nodes, and larger tumors (OR = 1.62, 95%CI:1.37-1.91) were more likely to receive adjuvant chemotherapy whereas patients with PR positive tumors (OR = 0.33, 95%CI:0.18-0.60) and those treated at academic facilities (OR = 0.81, 95%CI:0.68-0.96) were less likely to receive adjuvant chemotherapy after controlling for competing factors. Intermediate (OR = 5.34, 95%CI: 4.42-6.45) or high risk (OR = 32.65, 95%CI: 25.74-41.43) PMT scores had the greatest impact on receipt of adjuvant chemotherapy regardless of nodal status. **Conclusions:** Common socioeconomic and racial/ethnic disparities exist for PMT testing, though inappropriate use (high T or N stage) was minimal. Since PMT results strongly influenced recommendation of adjuvant therapy, decreasing disparities and making PMT available to all patients that are deciding on adjuvant therapy should be a priority.

551 Poster Session (Board #151), Sun, 8:00 AM-11:30 AM

Clinical utilization of Breast Cancer Index (BCI) for late recurrence risk assessment and prediction of extended endocrine therapy (EET) benefit in early stage HR+ breast cancer. *First Author: Reshma L. Mahtani, Sylvester Comprehensive Cancer Center University of Miami Health System, Deerfield Beach, FL*

Background: Randomized trials demonstrated a modest (3-5%) absolute benefit from EET in patients (pts) with early stage HR+ breast cancer (BC), but also a risk of toxicities. BCI is a validated gene expression-based assay that provides 2 results: BCI Prognostic, based on the algorithmic combination of HoxB13/IL17BR (H/I ratio) and a set of proliferation-based genes, reports individualized risk of late distant recurrence (DR); BCI Predictive, based on H/I alone, reports a prediction of high vs low likelihood of benefit from EET. The objective of this study was to assess clinical and pathologic patient characteristics, prognostic and predictive assay results, and physician testing patterns in >14,000 clinical cases. **Methods:** The BCI Clinical Database for Correlative Studies is a de-identified database developed under an IRB approved protocol that contains >50 clinicopathologic and molecular variables from cases submitted for BCI in clinical practice. Clinicopathologic variables were abstracted from pathology reports, and were available for a subset of cases. **Results:** Across all pts (N=14,463), median age was 58.2y (range: 23-92y; 73.9% ≥50y). The majority were Stage I (47.3% IA, 3.5% IB, 29.1% IIA, 14.1% IIB, 6% III). Cases were 29%, 51%, and 20% Grade 1, 2, and 3, respectively. Most pts were ER+/PR+ (87.7%) or ER+/PR- (11.3%); 11.3% were HER2+. The majority of cases (55.7%) were ordered 4-6y postdiagnosis, with 23.1% >6y, 14.4% between 1-4y, and 6.8% <1y postdiagnosis. In LN- pts (n=3395), BCI Prognostic identified 50.6% as low risk for late DR vs 49.4% as high risk, while BCI Predictive (H/I) classified 41.0% as high vs 59.0% as low likelihood of benefit. In LN+ pts tested with the BCIN+ Prognostic algorithm (BCI + size/grade, n=818), 77.3% were classified as high risk vs 22.7% as low risk, while BCI Predictive (H/I) classified 44.6% and 55.4% as high vs low likelihood of benefit. **Conclusions:** Findings from this large cohort characterize utilization of BCI in clinical practice for pts with early-stage, HR+ BC. BCI stratification of pts with high risk and high likelihood of benefit from EET may facilitate selection of pts for prolonged regimens.

552 Poster Session (Board #152), Sun, 8:00 AM-11:30 AM

Effect of denosumab on bone mineral density (T-score classification of −1.0 to −2.5) in postmenopausal Japanese women receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *First Author: Katsuhiko Nakatsukasa, Department of Endocrine and Breast Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan*

Background: Adjuvant aromatase inhibitor (AI) therapy is well established in postmenopausal women with hormone receptor-positive breast cancer, but such therapy is associated with bone loss and increased fracture risk. Denosumab, a fully human monoclonal antibody against receptor of nuclear-κB ligand, was previously proven to protect against AI-induced bone loss. In Japan, however, the efficacy of denosumab in the treatment of AI-associated bone loss has not been proven in a prospective study. **Methods:** This non-randomized prospective study was conducted at four institutions in Japan. we prospectively evaluated the bone mineral density (BMD) of the lumbar spine and bilateral femoral neck in hormone-receptor positive clinical stageI–IIIA, postoperative postmenopausal breast cancer patients who were scheduled for treatment with AI as adjuvant endocrine therapy or during AI adjuvant therapy. They received supplemental calcium, vitamin D and subcutaneous denosumab 60mg (n=103) every six months. At enrollment, all patients were required to have evidence of low bone mass, excluding osteoporosis. The primary endpoint was percentage change in lumbar spine BMD from baseline to month 12. The secondary endpoint was percentage change in bilateral femoral neck BMD from baseline to month 12. This is the first trial where the right and left femoral neck BMD are measured separately. **Results:** We enrolled 103 patients between November, 2014 to October, 2016. At 12 months, lumber spine BMD increased by 4.7 %. The patients who were administered prior AI therapy (n=60) had a 4.8 % increase, and the patients without prior AI therapy (n=40) had a 4.6 % increase. At 12 months, the right and left femoral neck BMD increased by 2.9 % and 2.0 %, respectively. Hypocalcemia ≥ grade2, osteonecrosis of the jaw (ONJ) and non-traumatic clinical fracture were absent in this study. **Conclusions:** Twice-yearly treatment with denosumab was associated with consistently greater gains in BMD among Japanese women receiving adjuvant AI therapy, regardless of whether prior AI therapy was administered. Clinical trial information: UMIN000013863.

553 Poster Session (Board #153), Sun, 8:00 AM-11:30 AM

Long term cardiac outcomes and anthracycline exposure in breast cancer survivors: A retrospective cohort data linkage and competing risks analysis. *First Author: Kelly Rust, NHS Lothian, Edinburgh, United Kingdom*

Background: Anthracycline chemotherapy is used frequently in adjuvant breast cancer treatment but there is clinical trial evidence of cardiac toxicity. Attempts to quantify this risk in routine care have been limited by follow up time & confounding factors. The aim of this project was to exploit rich Scottish NHS datasets for this purpose. **Methods:** Patients treated surgically for stage I-III invasive breast cancer between 2000 & 2010 were identified from a local cancer database (Edinburgh Cancer Centre). Outcomes were captured by linkage to the Scottish Morbidity & death Records. Follow-up was until March 2016. The primary outcome was a cardiac event or cardiac death, identified from coding. Analysis used the Latouche approach (estimating cause-specific hazards & sub-distribution hazards) for the primary outcome & the competing risks of death from breast cancer & death from other causes. Results were adjusted for age, deprivation (SIMD), co-morbidity (Charlson), year of diagnosis, side of radiotherapy, cancer stage, grade, ER & HER 2 status. **Results:** 4080 patients were identified, 1658 received an anthracycline containing regime, 297 received non-anthracycline chemotherapy & 2125 received no chemotherapy. A total of 33946 women years were analysed. During median follow up of 8.2 years there were 448 cardiac events & 559 breast cancer deaths. After adjustments there was no association between anthracycline use & cardiac outcomes (HR 0.9, 95% CI 0.67-1.21). There was an increased risk of breast cancer death (HR 1.66, 95% CI 1.28-2.16).Age & Charlson score were associated with an increased cardiac risk. Stage & grade were statistically associated with breast cancer death. **Conclusions:** No increased risk of cardiac events was seen in women treated with anthracyclines, they can be safely used in carefully selected patients. This data suggests selection may be over-cautious, a lower threshold for treatment may lead to improved breast cancer outcomes. Rich routine health datasets & appropriate analysis methods make outcomes monitoring feasible in Scotland. Oncologists are skilled at assessing both cardiac risk factors & breast cancer risk.

554 Poster Session (Board #154), Sun, 8:00 AM-11:30 AM

Role of axillary node dissection after mastectomy with positive sentinel nodes. *First Author: Tristen Sinae Park, Duke University, Durham, NC*

Background: The ACOSOG Z11 trial demonstrated that sentinel lymph node biopsy (SLNB) alone was safe for women with early stage node positive cancer undergoing breast conservation therapy with radiation. Little data exists regarding management of this population undergoing mastectomy. The purpose of our study is to determine the benefit of axillary lymph node dissection (ALND) or SLNB with adjuvant radiation in patients with 1-3 positive SLN after mastectomy. **Methods:** Using data from the National Cancer Database (2004-2014), we performed a retrospective review of patients who underwent mastectomy and were clinically node negative at presentation, but were found to have 1-3 positive nodes on pathology. Patients were categorized as undergoing SLNB alone (1-5 nodes examined) or ALND (≥8 nodes examined). Patients who received SLNB without ALND were further categorized by receipt of radiation treatment (RT). Patients with either neoadjuvant chemotherapy or stage IV disease were excluded. **Results:** Of 42,371 patients, 10.0% had SLNB+RT, 22.4% had SLNB alone, and 67.5% had ALND. Median age of the cohort was 58 years and median tumor size 2.3 cm. Median follow up was 4.1 years. After adjustment for covariates including age at diagnosis, tumor size, chemotherapy, endocrine therapy and receptor status, SLNB+RT had comparable overall survival to ALND (HR = 1.06, p = 0.52), but SLNB alone was found to be associated with a 25% increase in hazard of death compared to ALND (HR = 1.25, 95% CI 1.11-1.41, $p < 0.001$). **Conclusions:** In clinically node negative patients with 1-3 positive sentinel nodes treated with mastectomy, SLNB alone was associated with a significantly increased risk of all-cause mortality compared to ALND or SLNB+RT. These results suggests that ALND may be avoided in these patients in the setting of adjuvant radiation, possibly avoiding the morbidity associated with axillary lymphadenectomy.

555 Poster Session (Board #155), Sun, 8:00 AM-11:30 AM

Randomized surgical multicenter trial to evaluate the usefulness of lymphoscintigraphy (LSG) prior to sentinel node biopsy (SLNB) in early breast cancer: SenSzi (GBG80) trial. *First Author: Sherko Kummel, Breast Unit, Kliniken Essen-Mitte, Essen, Germany*

Background: It is not clear whether SLNB performed with LSG is necessary to reliably detect sentinel lymph nodes (SLN) in breast cancer. The omission of LSG might offer an accelerated preoperative workflow, cost reduction, and the opportunity for developing innovative, safe detection strategies. **Methods:** Patients with cN0 early breast cancer or extensive/high grade DCIS received standard radiolabeled colloid LSG and SLNB. Patients were randomized 1:1 to either conducting SLNB with the performing surgeon knowing the preoperative LSG pictures and results or without knowledge of the LSG results. Since the false negative rate (FNR) of SLNB correlates with the number of harvested SLN, our primary endpoint was the average number of histologically detected SLN per patient in both treatment arms in a non-inferiority design. An average number of 2.7 SLN with a standard deviation of 1.8 was assumed. LSG of all patients were collected postoperatively for central review. **Results:** Between May 2014 and October 2015 n = 1198 patients were randomized in 23 participating breast centers. Baseline characteristics were well-balanced between the treatment arms. Modified intention-to-treat analysis (n = 1163) confirmed the omission of LSG. The average number of histologically detected SLN was 2.207 with LSG and 2.258 without. The range for the one-sided 95% CI for the difference between the arms was (-0.18, +infinity), i.e. above the pre-specified non-inferiority margin of -0.27. Secondary endpoints were analyzed to rule out differences in reliable detection of nodal metastases. Rates of nodal positive disease as identified by SLNB (Odds ratio (OR) 1.005, 95%CI (0.759, 1.33), p = 0.972) and rates of completion axillary dissection (OR 0.984, 95% CI (0.567, 1.71), p = 0.954) in the two treatment arms and in specific subgroups showed no statistically significant differences. **Conclusions:** Our results support the hypothesis that SLNB is equally effective irrespective of the knowledge of preoperative LSG results. We therefore suggest performing SLNB without LSG to accelerate the preoperative workflow, reduce costs, and improve the comfort for the patients. Clinical trial information: NCT02481128.

556 Poster Session (Board #156), Sun, 8:00 AM-11:30 AM

Pembrolizumab (pembro) + chemotherapy (chemo) as neoadjuvant treatment for triple negative breast cancer (TNBC): Preliminary results from KEYNOTE-173. *First Author: Peter Schmid, Barts Cancer Institute, London, United Kingdom*

Background: Pembro has shown efficacy and acceptable safety in pts with previously treated metastatic TNBC. The phase Ib KEYNOTE-173 study (NCT02622074) evaluated pembro + chemo as neoadjuvant therapy for locally advanced TNBC. We present cohorts A and B. **Methods:** Women aged ≥18 y with locally advanced, nonmetastatic TNBC; ECOG PS 0/1; and no prior chemo, targeted therapy, or immunotherapy within 12 mo were eligible. Dosing in A was single-dose pembro followed by 4 cycles of pembro Q3W + nab-paclitaxel (Np) weekly followed by 4 cycles of pembro + doxorubicin + cyclophosphamide Q3W. Dosing in B was the same as in A but with carboplatin Q3W added to pembro + Np. Concentrations were pembro 200 mg; doxorubicin 60 mg/m^2; cyclophosphamide 600 mg/m^2; Np 125 mg/m^2 in A, 100 mg/m^2 in B; and carboplatin AUC 6 (1 cycle = 21 d). DLTs were assessed at cycles 1-3 and 6-7. Dose levels were deemed toxic if ≥3 of the first 6 pts or ≥4 of 10 pts had DLTs. Surgery was 3-6 wk after treatment completion/discontinuation. Primary end points were safety and recommended phase 2 dose of pembro combined with chemo. Key efficacy end points were pathological CR (pCR) rate, defined as ypT0/Tis, ypN0, and ypT0 ypN0, and ORR (RECIST v1.1, investigator). pCR analyses included all pts. **Results:** By Jan 6, 2017, 10 pts were in each cohort. Median age was 53 y (range 32-71); most pts had invasive ductal histology (90%), primary tumor stage ≥T2 (90%), and nodal involvement (75%). DLTs (myelosuppression) occurred in 7 pts (3 in A, 4 in B) and were unrelated to pembro. Gr 3-4 treatment-related AEs (TRAEs) occurred in 8 pts in A and 10 pts in B; none were fatal. One pt in A and 2 pts in B discontinued for a TRAE (2 ALT elevations with pembro; 1 DVT with chemo). Overall ORR (CR+PR) before surgery was 80% (90% CI, 49-96) in A and 100% (90% CI, 74-100) in B. ypT0/Tis pCR rate was 70% (90% CI, 39-91) in A and 100% (90% CI, 74-100) in B; ypT0 ypN0 pCR rate was 50% (90% CI, 22-78) in A and 90% (90% CI, 61-100) in B; and yT0/Tis ypN0 pCR rate was 60% (90% CI, 30-85) in A and 90% (90% CI, 61-100) in B. **Conclusions:** Preliminary data suggest that pembro + chemo as neoadjuvant therapy for TNBC results in manageable toxicity and promising antitumor activity. Clinical trial information: NCT02622074.

557 Poster Session (Board #157), Sun, 8:00 AM-11:30 AM

Primary operation in synchroneous metastasized invasive breast cancer patients: First oncologic outcomes of the prospective randomized phase III ABCSG 28 POSYTIVE trial. *First Author: Florian Fitzal, Medical University Vienna, Vienna, Austria*

Background: The ABCSG 28 Posytive trial compared primary surgery versus primary systemic therapy without surgery in stage IV breast cancer patients. The primary aim was to investigate whether immediate resection of the primary tumor followed by standard systemic therapy improves median survival compared with no surgical resection (NCT01015625). The trial had to be stopped early due insufficient recruitment. **Methods:** Untreated stage IV breast cancer patients with the primary in situ were randomly assigned to either surgery of the primary versus no surgery followed by systemic therapy between 2011 and 2015 in 15 breast health centers in Austria. Systemic therapy included endocrine therapy or chemotherapy. Patients were routinely followed every 3-6 months. Primary endpoint was median survival. **Results:** 90 patients (45 with surgery, 45 with primary systemic therapy without surgery) were randomized. Stratification criteria were age, endocrine responsiveness, her2 expression, planned first line therapy and bone only versus other metastases. Patients in the surgery arm had more cT3 breast cancer (22% versus 7%) and more cN2 staging (16% versus 4%) as well as more her2 positive breast cancer cases (27% versus 18%). The median follow up was 37.5 months and immunohistochemical subtype analysis showed 9% basal like, 22% her2 positive, 51% luminal A and 13% luminal B cancers. Both groups were well balanced regarding first line treatment (endocrine versus chemotherapy) however, there were more taxane treated patients in the no surgery group (24.4 versus 15.6%). The median survival in the surgery arm was 34.6 months versus 54.8 months in the no surgery arm without statistical significance (HR 0.691 CI 0.358 – 1.333; p=0.267). Time to distant progression was insignificantly longer in the no surgery arm (surgery arm 13.9 versus no surgery arm 29.0 months). **Conclusions:** This first analysis of the prospective randomized phase III trial POSYTIVE-ABCSG-28 demonstrated no benefit in overall survival for immediate surgery of the primary in de novo stage IV breast cancer patients. Clinical trial information: NCT01015625.

559 Poster Session (Board #159), Sun, 8:00 AM-11:30 AM

Contemporary breast conservation patient outcomes for ductal carcinoma in situ and margins < 2 mm. *First Author: Audree Tadros, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Recent national consensus guidelines regarding optimal margin width for the management of DCIS have been published; however, controversy remains for managing margins <2mm. The relationship between margin width and locoregional recurrence (LRR) was determined in a contemporary cohort of patients. **Methods:** 1504 patients with DCIS undergoing definitive breast conserving surgery from 1996 to 2010 were analyzed for clinical and pathologic characteristics from a prospectively managed comprehensive academic cancer center database. Cox proportional hazard models were used to examine the relationship between margin width (<2mm or ≥2mm) and LRR by adjuvant radiation therapy (RT). Patients with positive margins (n=11) were excluded. **Results:** Overall, 3.4% of patients had a LRR at a median follow-up of 8.7 years. Univariate analysis of age, family history, grade, tumor size, comedonecrosis, RT, adjuvant hormonal therapy, ER status, and margin width found younger age (< 40 yr, p=0.02), no RT (n=299, p=0.005), and margin width <2mm (n=138, p=0.005) to be associated with LRR. The association between margin width and LRR differed by adjuvant radiation therapy status (p=0.02 for the interaction). There was no statistical significant difference in LRR for patients with margins <2mm vs ≥2 mm who received RT, (10-year LRR 6.0% vs 3.2%, respectively; HR 1.5, 95% CI 0.5-4.2, p=0.48). For patients who did not receive RT (n=299), those with margins < 2 mm were significantly more likely to develop a LRR than those with margins ≥2mm (10-year LRR 35.7% vs. 4.6%, respectively; HR 7.2, 95%CI 2.6-19.4, p=0.0001). **Conclusions:** In patients with <2mm margins receiving adjuvant radiation therapy, there is no difference in locoregional recurrence when compared to patients with ≥2mm margins. Additional surgery for wider margins of resection are not routinely justified in this group of patients but should be obtained for patients with <2mm margins who forego radiotherapy.

560 Poster Session (Board #160), Sun, 8:00 AM-11:30 AM

Systematic analysis of parameters predicting pathological axillary status (ypN0 vs. ypN+) in patients converting from cN+ to ycN0 through primary systemic therapy (PST). *First Author: Cornelia Liedtke, University of Schleswig-Holstein Campus Luebeck, Lübeck, Germany*

Background: Optimization of axillary staging in patients converting from cN+ to ycN0 through PST is needed. The aim of this analysis was to develop a nomogram predicting the probability of ypN+ after PST based on clinical/pathological parameters. **Methods:** Patients converting from cN+ to ycN0 through PST from a prospective study (SENTINA arm C) were included. Univariate/multivariate analyses were carried out for 14 clinical/pathological parameters to predict ypN+ using logistic regression models. Odds ratios and 95% confidence intervals were reported. Model performance was assessed by leave-one-out cross-validation (LOOCV at .5 cut-offs) and ROC analyses. Calculations were performed using the SAS Software (Version 9.4). **Results:** 553 patients were assessed. Stepwise backward variable selection based on a multivariate analysis of all significant parameters resulted in a model (5M, Table, N = 369 evaluable) including ER (3.81; 2.25-6.44), multifocality (2.22; 1.26-3.92), LVI (9.16; 4.68-17.90), detection of SLN after PST (.50; .26-.95) and ycT (1.03; 1.01-1.06). In LOOCV, this model had an area under the curve of .81. Multivariate analysis of parameters available preoperatively showed an association between ypN0/ypN+, ER and ycT. Full subset selection resulted in a model (2M, N = 414) containing only ER (4.36; 2.80, 6.81) and ycT (1.04; 1.02, 1.07). **Conclusions:** A prediction model including parameters evaluable before/after definitive surgery resulted in a nomogram with acceptable accuracy. Limitation to parameters evaluable before surgery (i.e. ER, ycT) showed reduced accuracy that was comparable/superior to accuracy of using individual parameters. Since tumor biology was the strongest parameter in our models, we hypothesize that modern tumor biologic parameters such as gene expression profiling might optimize prediction of axillary status after PST improving patient counseling.

	Accuracy (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
5M (N = 369)	72.6	73.4	71.8	75.0	70.0
2M (N = 414)	67.9	81.4	52.6	66.1	71.3
ER (N = 414)	67.9	80.5	53.6	66.3	70.7
ycT (N = 414)	58.2	64.5	51.0	60.0	55.9

561 Poster Session (Board #161), Sun, 8:00 AM-11:30 AM

Axillary management in early breast cancer: Surgeon attitudes in a population-based study. *First Author: Monica Morrow, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The ACOSOG Z0011 trial established the safety of omitting axillary dissection (ALND) for patients with 1–2 sentinel node (SN) metastases having breast-conserving therapy (BCT) to reduce treatment-related morbidity. Little is known about surgeon uptake of this practice. **Methods:** Women with stage I and II breast cancer diagnosed between 7/13–8/15 (n=3729) reported to the Los Angeles and Georgia SEER registries were surveyed about 2 months after diagnosis. All attending surgeons identified by the patients (n=489) were sent a questionnaire and 77% (n=377) responded. Pathology reports for SN positive patients are under review. **Results:** Mean surgeon age was 54 years, 25% were female, and median years in practice was 21. 49% and 63% endorsed ALND for Z0011 eligible patients with 1 or 2 SN macrometastases, respectively. Surgeons were classified as low (n=92), selective (n=178), or high (n=91) users of ALND based on responses to case scenarios with SN involvement ranging from isolated tumor cells in 1 SN (12% would do ALND) to macrometastasis in 3 SNs (92% would do ALND). 93% of high-use surgeons would perform ALND for any SN macrometastasis vs 40% of selective surgeons and 1% of low-use surgeons (p<.001). High-use surgeons were older, male, saw fewer breast cancer patients, and were less likely to discuss cases in tumor board (Table). High-ALND users were substantially less likely to endorse BCT margins of no ink on tumor (40%) than selective (63%) or low users (83%; p<.001). **Conclusions:** Wide variation exists in acceptance of Z011 results with one-quarter of surgeons endorsing routine ALND. Surgeons favoring ALND also endorse wider margins for BCT, suggesting an overall more aggressive surgical approach. Lower breast volume and lack of tumor board participation identify surgeons who should be targeted for educational interventions.

Surgeon characteristics.

	Low ALND	Selective ALND	High ALND	p-value
Number	92	178	91	
Mean age (yrs)	52	53	56	.06
% Female	33	25	16	.02
% Practice breast ca	38	21	14	.0000
% Cases in tumor board				.0001
None	10	12	30	
>50	60	39	29	

562 Poster Session (Board #162), Sun, 8:00 AM-11:30 AM

What drives overtreatment? Surgeon and radiation oncologist views on omission of adjuvant radiotherapy for elderly women with early stage breast cancer. *First Author: Dean Alden Shumway, University of Michigan, Ann Arbor, MI*

Background: Although trials have shown no survival advantage and only a modest improvement in local control from adjuvant radiotherapy after lumpectomy in older women with stage I, ER+ breast cancer, radiotherapy is commonly administered, raising concerns about overtreatment. Therefore, we sought to evaluate physician attitudes, knowledge, communication, and recommendations in this scenario. **Methods:** We mailed a survey to a national sample of 713 radiation oncologists and 879 surgeons between June to October 2015. Of these, 913 responded (57%). We assessed physicians' attitudes, knowledge of pertinent risk information, and responses to clinical scenarios. **Results:** In patients age > = 70 with stage I, ER+ breast cancer treated with lumpectomy and endocrine therapy, omission of radiotherapy was felt to be unreasonable by 40% of surgeons and 20% of radiation oncologists (p < 0.001). Many surgeons (29%) and radiation oncologists (10%) erroneously associated radiotherapy in older women with improvement in survival. Similarly, 32% of surgeons and 19% of radiation oncologists tended to substantially overestimate the risk of locoregional recurrence in older women with omission of RT. In a scenario with an 81-year-old with multiple comorbidities, 31% of surgeons and 35% of radiation oncologists would still recommend radiotherapy. On multivariable analysis, erroneous attribution of a survival benefit to radiotherapy (OR 6.2; 95% CI 3.9-9.8) and overestimation of remaining life expectancy (OR 6.5; CI 4.2-9.9) were strongly associated with the opinion that radiotherapy omission is unreasonable. **Conclusions:** Many radiation oncologists and surgeons continue to consider omission of radiotherapy as substandard therapy. A sizeable proportion of surgeons overestimate radiotherapy's benefits and consider omission of radiotherapy to be an unreasonable departure from the standard of care, suggesting that surgeon involvement in decisions about radiotherapy omission may be a key factor in reducing overuse of aggressive care in this setting.

563 Poster Session (Board #163), Sun, 8:00 AM-11:30 AM

Evaluation of simplified lymphatic microsurgical preventing healing approach (SLYMPHA) for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection. *First Author: Tolga Ozmen, University of Miami, Department of Surgical Oncology, Miami, FL*

Background: Lymphedema (LE) is a serious complication of axillary lymph node dissection (ALND) with an incidence rate of 16%. Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) has been proposed as an effective adjunct to ALND for the prevention of LE. This procedure however requires microsurgical techniques. The aim of this study was to assess the efficiency of Simplified-LYMPHA (SLYMPHA) in preventing LE in a prospective cohort of patients. **Methods:** All patients, undergoing ALND with or without SLYMPHA between January 2014 and December 2016 were included in the study. SLYMPHA is a slightly modified and simplified version of LYMPHA. It is performed by the operating surgeon performing the ALND. One or more lymphatic channels identified by reverse arm mapping are inserted using a sleeve technique into the cut end of a neighboring vein. During follow-up visits, tape-measuring limb circumference method was used to detect clinical LE. Demographic, clinical, surgical and pathologic factors were recorded. The incidence of clinical LE was compared between ALND with and without SLYMPHA. Univariate and multivariate analysis were used to assess the role of other factors in the appearance of clinical LE. **Results:** 406 patients were included in the study. SLYMPHA procedure was attempted in 81 patients and was completed successfully in 90% of patients. Early complication rates were similar between patients who underwent SLYMPHA and who did not (4% vs. 4.13%; p = 0.948). Median follow-up time was 15±13.73 [1-32] months. Patients, who underwent SLYMPHA, had a significantly lower rate of clinical LE both in univariate and multivariate analysis (3% vs 19%; p = 0.001; OR 0.12 [0.03-0.5]). Excising > 22 lymph nodes and a co-diagnosis of diabetes were also correlated with higher clinical LE rates on univariate analysis, but only excising > 22 lymph nodes remained to be significant on multivariate analysis. **Conclusions:** SLYMPHA is a safe and relatively simple method, which decreases incidence of clinical LE dramatically. It should be considered as an adjunct procedure to ALND for all patients during initial surgery.

565 Poster Session (Board #165), Sun, 8:00 AM-11:30 AM

Prediction of radiation therapy response in breast cancer patients. *First Author: Divya Arora, Baylor Scott and White Hospital, Temple, TX*

Background: While radiation portals are tailored to a patient's unique anatomy and the selection of systemic agents routinely employs biomarker data, the selection of radiotherapy based on a patient's tumor biology is not routinely utilized in breast cancer. The purpose of this study was to identify which genetic markers are possible predictors for local recurrence as a surrogate for radiation response. **Methods:** We identified 200 patients who received radiotherapy for breast cancer. Selected tumor markers included: Androgen receptor (AR), Hypoxia Inducible Factor 1-α (HIF-1), Phosphotidylinosotol-4,5-bisphosphate 3-kinase (PI3K), and Interleukin 13 (IL-13). Biomarkers were analyzed in terms of "extent" and "intensity" on a scale of 0-3 and scored by 2 separate pathologists. The primary endpoint of local recurrence (LR) & secondary endpoint of overall survival were analyzed using Kaplan-Meier survival curves, log-rank test for differences, and Cox regression models. **Results:** Median follow up was 7.98 years. At 5 years, the rate of LR was 92.6% and overall survival was 89.4%. On multivariate Cox regression analysis, a one unit increase in IL-13 extent increased the hazard of LR by 73%. A one unit decrease in AR extent increased the hazard of LR by 134%. The hazard of death increased 3.2 times for each unit increase in HIF1 extent. The hazard of death increased 1.5 times for each unit increase in PI3K extent. PI3K extent and intensity was increased, and AR extent and intensity was decreased in triple negative breast cancer (TNBC) (n = 68) vs non-TNBC ($p < 0.0001$). African Americans had a 4.2 times hazard of LR vs Caucasians. **Conclusions:** Expression of IL-13 was associated with a higher risk of LR; expression of AR was associated with decreased LR. These two markers may be instrumental in predicting radiation response. If this study is validated, cancers that express more IL-13 may require higher doses or targeted therapy. In contrast, those cancers expressing AR may not require as aggressive therapy. Lastly, PI3K and HIF1 α expression were significant predictors of worse overall survival. The clinical implications of these biologic markers are significant as they may help to guide biologically-driven, personalized breast cancer radiotherapy.

566 Poster Session (Board #166), Sun, 8:00 AM-11:30 AM

Locoregional surgery of the primary tumor in stage IV breast cancer patients. *First Author: Ying Wang, Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: Existing guidelines lack clear recommendations for the role of locoregional treatment for the primary tumor in women with stage IV breast cancer. We aimed to compare the effectiveness of locoregional surgery with no surgery of the primary tumour in stage IV breast cancer patients. **Methods:** Eligible studies were randomized clinical trials (RCTs) that investigated the effect of locoregional surgery versus no surgery of the primary tumour in stage IV breast cancer patients. The primary outcome was overall survival (OS), measured as hazard ratios (HRs). Secondly outcomes included 2-year and 3-year OS, expressed as odds ratios (ORs). Meta-analyses and trial sequential analysis (TSA) were conducted. Quality was evaluated using the GRADE. **Results:** Data were included from four RCTs involving 767 participants, including 377 who underwent locoregional surgery and 390 who with no surgery. The median follow-up was 28.6 months (95% confidence interval (CI) 24.1 to 33.9). In a meta-analysis of these trials, the low-quality evidence indicated that locoregional surgery versus no surgery did not significantly affect OS (HR = 0.87, 95% CI 0.59 to 1.29, $P = 0.490$), 2-year OS (OR = 1.23, 0.66 to 2.30, $P = 0.510$), or 3-year OS (OR = 1.08, 0.94 to 1.25, $P = 0.263$). TSA showed that more trials were needed before reliable conclusions could be drawn regarding in both 2-year and 3-year OS. Across the subgroup analysis of OS, we found the moderate-quality evidence that locoregional surgery followed by chemotherapy versus chemotherapy alone resulted into a significantly improved survival (HR = 0.65, 95% CI 0.49–0.87, $P = 0.004$); but no statistically significant difference was identified in term of response to chemotherapy with or without locoregional surgery (HR = 1.06, 95% CI 0.83–1.36, $P = 0.632$). **Conclusions:** The current evidence suggests that locoregional surgery followed by chemotherapy, compared with chemotherapy alone, was beneficial for prolonging OS in patients with stage IV breast cancer, but surgery did not impact OS among patients who have responded to chemotherapy.

567 Poster Session (Board #167), Sun, 8:00 AM-11:30 AM

The combination of preoperative computed tomography lymphography and intraoperative fluorescence imaging navigation for sentinel lymph node biopsy of early breast cancer patients. *First Author: Hajime Abe, Breast Center, Bell Land General Hospital, Sakai, Japan*

Background: This study investigated a usefulness of the combination of fluorescence imaging and computed tomography lymphography (CTLG) for sentinel lymph node biopsy (SLN) biopsy of early breast cancer patients. **Methods:** Between January 2013 and August 2016, 350 breast cancer patients without clinical evidence of lymph node metastasis were treated. Preoperaitve CTLG was performed using 64-row multidetector CT injected contrast agent. The contrasted lymph route and SLN were identified in reconstructed three-dimensional imaging. The SLN spot was indicated by CT laser light navigator system. We established typical pattern of the lymphography: stain defect of SLN, stagnation of lymphatic route for preoperative diagnosis of metastatic SLN. Intraoperative fluorescence images were obtained using the fluorescence imaging system (pde-neo). After dye mixed indocyanine green and indigocarmin was injected, lymphatic route was observed with fluorescence images. SLN biopsy was performed referring to the point by axillary compression technique by plastic device. **Results:** The median age of the 350 patients was 59 (range 28 – 90) years old. CTLG could visualize lymphatic route and accurately identify SLN in 336 (96.0 %) and 343 (98.0 %) cases, respectively, whereas fluorescence imaging identified successfully lymphatic route and SLN in all patients. Lymphatic routes of CTLG were completely consistent with those of fluorescence imaging. The number of SLN identified by CTLG was significantly lower than that by fluorescence imaging (1.1 vs. 1.6, $p<0.01$). Fifty of 350 patients had metastatic SLN pathologically, and 11 of them had micrometastases of SLNs. The accuracy for metastatic diagnosis of SLN using CTLG without micrometastasis was 84.1 %, sensitivity was 82.1 % and specificity was 84.3 %. The positive predictive value was 40.5 % and negative predictive value was 97.3 %. **Conclusions:** This combined navigation method of fluorescence imaging and CTLG revealed more easy and effective to detect SLN than fluorescence imaging alone. In addition, the information from CTLG would be helpful for the preoperative diagnosis of SLN metastasis.

568 Poster Session (Board #168), Sun, 8:00 AM-11:30 AM

Hypofractionated, normofractionated and intraoperative breast irradiation: Long term cosmetic outcome based on photographic evaluation. *First Author: Tarek Ellethy, Department of Radiotherapy and Nuclear Medicine, South Egypt Cancer Institute, Assiut University, Assiut, Egypt*

Background: Photographic documentation of breast changes after breast radiotherapy (RT) is a helpful tool to both subjectively and objectively evaluate cosmesis. The aim of this study was to evaluate cosmesis in breast cancer patients after receiving hypofractionated whole breast RT (HF-WBRT), normofractionated (NF-WBRT), intraoperative RT (IORT) or combined WBRT/IORT. **Methods:** After excluding cases with missing or inadequate photos from three prospective clinical trials, KOSIMA, TARGIT-A & TARGIT-E, 155 and 205 cases were included in a subjective analysis while 132 and 185 cases were included in an objective analysis postoperatively and after 2 years respectively. Subjective evaluation was done by 9 observers using the Harvard scale. Objective evaluation was done by assessing percentage breast retraction (pBRA). Based on the treatment received, patients were divided into 5 groups: 1. HF-WBRT 40/2,67 Gy ± Boost, 2. NF-WBRT 50/2 Gy ± Boost, 3. NF-WBRT 56/2 Gy, 4. IORT 20 Gy, 5. IORT 20 Gy+WBRT 46/2 Gy. **Results:** Subjectively, the rate of excellent-good cosmesis was 92% postoperatively and 84% after 2 years while objectively it was around 56% at both time points. At 2 years, no significant difference was observed between the 5 treatment groups with the subjective excellent-good cosmesis being 82%, 80%, 92%, 83%, 85% ($p = 0.546$) and objective being 56%, 61%, 52%, 53%, 50% ($p = 0.883$) in groups 1-5 respectively. Factors possibly affecting cosmesis at 2 years were examined. No significant difference was observed with age, smoking, BMI, chemotherapy, hormone therapy or type of axillary surgery. Significantly better cosmesis was observed with upper outer tumor location compared to other quadrants ($p < 0.0001$) also with a ratio of excised/total breast volume under 20% ($p < 0.0294$). **Conclusions:** Cosmetic outcome after hypofractionated and IORT was similar to normofractionated breast RT. After 2 years of treatment, cosmetic deterioration remained acceptable, overall < 10%. Tumor location and excised breast volume were the only factors significantly affecting cosmetic outcome.

569 Poster Session (Board #169), Sun, 8:00 AM-11:30 AM

Trends in rates of modified radical mastectomies and bilateral mastectomies in unilateral breast cancer. *First Author: Ajaz Bulbul, Kymera Independent Physicians, Carlsbad, NM*

Background: Women with unilateral breast cancer (BC) without genetic predisposition have a low risk for local and contralateral recurrence with breast conservation surgery (BCS) and adjuvant treatment. We aimed to study the pattern of surgical care across centers in rural New Mexico and its correlation to clinical outcomes. **Methods:** We retrospectively evaluated 533 patients with Stage 1-3 BC diagnosed between January 1989 to October 2015. Clinical Outcomes with BCS, sentinel lymph node dissection (SLND), simple mastectomy (SM), modified radical mastectomy (MRM) and Bilateral Mastectomy (BM) were studied. Descriptive statistics were performed to describe the proportion of surgery types. Predictors of clinical outcomes were evaluated by multivariate logistic regression. **Results:** Out of 533 patients, 510 (82%) had early stage (0-3) resectable BC. Among these, 48% (246/510) had either MRM (209/510) or BM (37/510). MRM was performed in 3% of stage 0 (6/209), 23% (49/209) stage I, 46%(97/209) of stage II and 27% (57/209) of Stage III patients. Overall, the rate of SLND was 42% among Early stage Breast cancer. Of 41 patients treated with bilateral mastectomy, 10 were positive for BRCA mutation, 6 for family history and 3 for contralateral disease. Median age of BM was 53 +12 y. The local recurrence rate was 8.8% (45/510), and metastatic recurrence rate was 15.5% (79/510). Lymphedema rate was 9.2% (47/510). Using MRM as reference, the Odds Ratio (OR) for lymphedema after BM and BCT were 2.15 (95% CI, 0.84-5.50) and 0.58 (0.28-1.22), respectively. With 9.6 years of median follow up, the predictive probabilities of lymphedema after BCT, SM, MRM and BM were 1%, 4%, 9% and 18%. The OR for local recurrence in women with BCT were 1.46 (95^{th} C/I: 0.72-2.95), SM 0.27 (0.03-2.13), BM 2.06 (95^{th} C/I:0.70-6.06). **Conclusions:** Less BCT and more aggressive procedures are being performed, and the latter is associated with more lymphedema. No significant differences were noted in local recurrences. Presence of a genetic mutation was not the sole indicator of BM's in our patient population. There is a need for evidence-based shared decision-making and surgical management of breast cancer, especially in a rural community setting.

570 Poster Session (Board #170), Sun, 8:00 AM-11:30 AM

Effect of neoadjuvant chemotherapy regimen choice in patients with breast cancer with pathologic complete response. *First Author: Anna Weiss, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Breast cancer patients with a pathologic complete response (pCR) to neoadjuvant chemotherapy (NACT) have improved survival. We hypothesize there is no difference in post-surgical recurrence free survival (RFS) between regimens used if pCR has been achieved. **Methods:** Breast cancer patients treated with NACT (using various regimens) between 1996 and 2011 who achieved pCR were examined, using a prospectively maintained electronic database. RFS was estimated by Kaplan-Meier method, differences between groups assessed using log-rank test. Cox proportional hazards regression analysis adjusted for age, menopausal status, stage, grade, tumor subtype, and adjuvant treatments. **Results:** 721 patients were identified: 40.4% Stage IIA, 21.2% IIB, 10.8% IIIA, 9.2% IIIB, 18.3% IIIC. 21.8% were hormone receptor positive (HR), 43.3% HER2 amplified, 32.7% triple negative. 50.9% of patients were treated with adriamycin-based chemotherapy plus taxane (adriamycin+taxane), 7.8% without taxane (adriamycin-taxane), 31.5% HER2 targeted therapy, and 9.8% provider choice. Median follow up was 7.4 years. There was no significant difference in RFS by treatment group (table 1). Adjusted RFS hazard ratios comparing each treatment to adriamycin+taxane were 1.25 (95% confidence interval 0.47-3.35) adriamycin-taxane, 0.90 (CI 0.37-2.20) HER2 targeted, and 1.28 (CI 0.55-2.98) provider choice. **Conclusions:** These data suggest that post-surgical RFS among patients with pCR is not significantly influenced by the type of NACT. Meta-analysis of randomized trial data should be explored to evaluate these findings. If RFS of pCR patients is not affected by regimen, this could allow flexibility in treatment choice and length.

RFS for the total cohort, and by tumor subtype.

	Overall N=721, P=0.45		HR N=143, P=NA		HER2 Amplified N=312, P=0.42		Triple Negative N=216, P=0.59	
Treatment group	N	5yr RFS (%)	N	5yr RFS (%)	N	5yr RFS (%)	N	5yr RFS (%)
Adriamycin+taxane	367	91 (88-94)	124	92 (87-97)	55	89 (80-98)	170	92 (87-96)
Adriamycin-taxane	56	93 (86-100)		*		*	22	86 (73-100)
HER2 targeted	227	93 (89-96)		*	220	93 (90-97)		*
Provider choice	71	85 (78-94)	11	80 (58-100)	33	91 (81-100)	21	85 (72-100)

*missing cells < 10 patient

571 Poster Session (Board #171), Sun, 8:00 AM-11:30 AM

Impact in delay of start of chemotherapy and surgery on pCR and survival in breast cancer: A pooled analysis of individual patient data from six prospectively randomized neoadjuvant trials. *First Author: Sibylle Loibl, German Breast Group, Neu-Isenburg, Germany*

Background: Time interval from diagnostic biopsy to neoadjuvant chemotherapy (NACT) start (TBC) and from last chemotherapy application to surgery (TCS) are influenced by many factors. It is unclear whether a delay of systemic therapy or surgery impacts patients (pts) outcome. **Methods:** 9127 pts with early BC from 6 German neoadjuvant trials receiving an anthracycline-taxane based NACT were included. pCR (ypT0/is ypN0), disease free survival (DFS) and overall survival (OS) were compared according to TBC and TCS length (cut-off of ≤4 vs >4weeks (w)), overall and in subgroups (BC subtypes [luminal, HER2+, triple-negative breast cancer (TNBC)] and pCR [yes vs no] for survival endpoints) adjusted by study. **Results:** Data on TBC were available for 8072 pts, on TCS for 6420, on follow-up (FU) for 7889. Median age was 49 yrs, 25.6% had cT3-4, 48.6% N+, 44.1% G3, 46.0% luminal, 26.4% TNBC, 27.6% HER2+ tumors. Median (m) FU-time was 65 months [0-201]. mTBC was 23 days [0-228] (67.5% ≤4w vs 32.5% >4w), mTCS was 28d [0-204] (53.7% ≤4w vs 46.3% >4w), with inter-study variability for mTBC ranging from 14 to 32d and for mTCS ranging from 24 to 29d from the oldest to the most recently conducted study. TBC did not influence the pCR rate, neither in all patients nor in subgroups. At multivariable logistic regression analysis TBC length did not independently predict pCR. TBC did not influence DFS or OS, neither in all patients nor in subgroups. TCS<4w was associated with a trend towards a better DFS in all patients (HR=1.11 95%CI (0.99-1.24), p=0.08) and in pts not achieving pCR (HR=1.12, 95%CI (0.99-1.26), p=0.08). No difference was observed within BC subtypes. OS was not impacted by TCS length. At multivariable Cox regression analysis TBC or TCS≤4 vs >4w did not independently influence DFS or OS. **Conclusions:** A delay in starting NACT does not impact the pCR rate, DFS or OS and results are independent of the subgroup. However, early surgery after NACT in pts without pCR seems to influence outcome. Our analysis is explorative, but indicates for the first time, that time interval of starting NACT and undergoing surgery might be uncritical. Further research is ongoing.

572 Poster Session (Board #172), Sun, 8:00 AM-11:30 AM

Safety of MEDI4736 (anti-PD-L1 antibody) administered concomitant with weekly nab-paclitaxel and dose dense doxorubicin/cyclophosphamide (ddAC) as neoadjuvant chemotherapy for stage I-III triple negative breast cancer (TNBC): A Phase I/II trial. *First Author: Lajos Pusztai, Yale Cancer Center, New Haven, CT*

Background: Pathologic complete response (pCR) rates to neoadjuvant chemotherapy in TNBC plateaued at 40% with existing regimens, the co-administration of an immune checkpoint inhibitor might increase pCR rate. The objective of the Phase I portion of this trial was to assess the safety of administering MEDI4736 concomitant with sequential taxane and anthracycline chemotherapy. **Methods:** The Phase I part followed the 3+3 design exploring two dose levels of MEDI4736 (3 and 10 mg/kg iv q2wk) in combination with weekly nab-paclitaxel (100 mg/m2) x 12 followed by ddAC x 4. Dose limiting toxicities (DLT) were evaluated during the entire 20 weeks of therapy and were defined as (1) gr 4 immune related adverse event (irAE), (2) gr 3 irAE that did not resolve to gr 2 within 3 days or to $\leq$ gr 1 within 14 days, (3) $>$ gr 3 colitis or pneumonitis, (4) $\geq$ gr 3 non-irAE causally related to MEDI4736. **Results:** 3 patients completed therapy at the 3 mg/kg dose without any DLT, 1 additional patient refused further study medication because of recurrent gr 2 fatigue after 7 weeks of therapy. At the 10 mg/kg dose level, all 3 patients completed the nab-paclitaxel+MEDI4736 treatment without any DLT and 2 patients also completed 3 of the 4 planned treatments with ddAC without DLT. Among all 7 patients who started therapy, 1 at the 3 mg/kg group experienced gr 3 dehydration and dyspnea without chest X ray abnormalities which resolved within 48 hours with hydration. There were no other gr 3 AEs. Among the 3 patients who have completed therapy as per protocol (not including the patient who withdraw consent), 1 achieved pCR, 1 had minimal, and 1 had extensive residual cancer. No surgical AE were seen. All patients at the 10 mg/kg dose level will complete surgery by March 2017 and final Phase I toxicity and efficacy results will be presented. **Conclusions:** Concomitant administration of MEDI4736 10 mg/kg with weekly nab-paclitaxel and subsequently with ddAC neoadjuvant chemotherapy appears safe. The Phase II portion of the trial is open and will accrue a maximum of 50 patients to assess the efficacy of the combination. Clinical trial information: NCT02489448.

573 Poster Session (Board #173), Sun, 8:00 AM-11:30 AM

Association of molecular subtype, proliferation, and immune genes with efficacy of carboplatin versus gemcitabine addition to taxane-based, anthracycline-free neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC): Results of the randomized WSG ADAPT-TN trial. *First Author: Oleg Gluz, West German Study Group, Moenchengladbach, Germany*

Background: In the ADAPT-TN neoadjuvant trial, 12-week nab-paclitaxel (nab- pac)+carboplatin (carbo) was highly effective and superior to nab-pac +gemcitabine (gem). However, within TNBC, reliable predictive markers for carbo use have yet to be identified. **Methods:** Patients with early TNBC (centrally confirmed) were treated by nab-pac 125 mg/m2 with either carbo AUC2 or gem 1000 mg/m2 d 1,8 q21 given for 4 cycles. Genomic data (80 genes) and Prosigna (PAM-50) scores were available in 306 pre-therapeutic samples of 331 treated patients. Fisher's exact test was performed for pCR differences; associations of continuous measurements or scores with pCR were analyzed by the Mann-Whitney statistic. **Results:** pCR was 44.5% to 28.4% (p=.004) in favor of nab-pac - carbo. Specifically within the carbo-containing arm, immunological (CD8, PD1, PFDL1) genes and proliferation markers (proliferation score and ROR scores, MKI67, CDC20, NUF2, KIF2C, CENPF, EMP3, TYMS) were positively associated with pCR ($p<.05$ for all). Specifically within the gem-arm, angiogenesis genes were negatively associated with pCR (ANGPTL4: p=.05; FGFR4: p=.02; VEGFA: p=.03). In the whole collective, basal-like (83.3%) was favorable for pCR (38% vs. 20%, p=.015) compared to other subtypes (HER: 6.4%; luminal-A: 1.7%; normal: 8.7%), as was lower HER-2 score ($p<.001$). Proliferation was positively associated with pCR: i.e., Pam50 proliferation score, ROR scores (all $p<.004$), and higher Ki67 by central IHC ($p<.001$) – though not MKI67 RNA expression, despite their moderate correlation. **Conclusions:** In early TNBC, basal-like subtype, higher Ki67 (by IHC), and lower HER-2 score were associated with chemo-sensitivity for both neoadjuvant arms. Chemo-resistance pathways differed between the two taxane-based combinations (low proliferation and immune marker gene expression for carbo, high angiogenesis for gem). The positive predictive impact of immunological genes in the nab-pac - carbo arm could influence optimal patient selection for immune-modulative therapy. Clinical trial information: NCT01815242.

574 Poster Session (Board #174), Sun, 8:00 AM-11:30 AM

Antitumor activity of trabectedin and lurbinectedin in germline BRCA2 carriers with metastatic breast cancer (MBC) as compared to BRCA1 carriers: Analysis of two phase II trials. *First Author: Judith Balmana Gelpi, Hospital Vall d'Hebron, Barcelona, Spain*

Background: BRCA 1/2-associated breast cancer share homologous recombination deficiency, but also have independent and potentially actionable roles. Novel drugs with innovative mechanism of action, lacking cross-resistance with other used agents are needed for BRCA 1/2 MBC. Trabectedin (TR) and its analog, lurbinectedin (L), have shown to be active in BRCA 1/2 MBC. This study was sought to determine if there was a difference in activity of these agents between BRCA1 and 2 carriers. **Methods:** Safety and efficacy in MBC BRCA 1/2 were analyzed in 2 separate phase II trials of single agent TR and L. **Results:** 88 patients were evaluated: 34 with TR, 54 with L. Median age: 46 and 43, respectively. Median (range) prior chemotherapy lines: TR, 4 (1-10); L, 2 (0-5). Clinical responses were seen in the 2 trials (see table) and were higher in BRCA2 than in BRCA1 (33% vs 9% with TR and 61% vs 26% with L). Main adverse event was myelosuppression (grade 3-4 neutropenia / thrombocytopenia / febrile neutropenia: TR, 62.1%/24.3%/10.8% L, 66.7%/20.4%/20.4%). Non-hematological toxicity was mostly grade 1-2: fatigue, nausea/vomiting and high transaminases (grade 3/4 TR, 40.5%, L 18.5%). **Conclusions:** Remarkable activity of trabectedin and lurbinectedin as single agents was observed in BRCA 2 associated MBC. This finding warrants further investigation. One potential mechanistic rationale is the role of both lurbinectedin and BRCA 2 in transcription. Safety was acceptable and manageable in both studies. Clinical trial information: NCT01525589.

	Trabectedin 1.3 mg/m² D1 q3wks		Lurbinectedin 7 mg FD / 3.5 mg/m² D1 q3wks	
Response	BRCA1 (n=22) n (%)	BRCA2 (n=12) n (%)	BRCA1 (n=31) n (%)	BRCA2 (n=23) n (%)
CR	-	-	2 (6.5)	-
PR	2 (9.1)	4 (33)	6 (19.4)	14 (60.9)
PRnc	2 (9.1)	_	3 (9.7)	1 (4.3)
SD	9 (40.9)	4 (33)	12 (38.7)	7 (30.4)
PD	9 (40.9)	4 (33)	8 (25.8)	1 (4.3)
ORR	9.1	33.3	25.8	60.9
DCR	59.1	66.7	74.2	95.7
DOR (mo)	1.6	2.7	10.2	6.4
PFS (mo)	2.5	4.7	3.0	6.0
OS (mo)	NA	NA	15.0	26.6

CR complete response; DCR disease control rate; DOR duration of response; FD flat dose; mo, months; ORR overall response rate; PD progressive disease; PFS progression-free survival; PR partial response, PRnc non-confirmed PR; SD stable disease; NA not available.

575 Poster Session (Board #175), Sun, 8:00 AM-11:30 AM

A gene signature of chemo-immunization to predict outcome in patients with triple negative breast cancer treated with neoadjuvant chemotherapy. *First Author: Mohamed-Amine Bayar, Service de Biostatistique et d'Epidémiologie, Gustave Roussy, Villejuif, France*

Background: In patients with triple-negative breast cancer (TNBC), the extent of tumor-infiltrating lymphocytes (TILs) in the residual disease after anthracycline-based neo-adjuvant chemotherapy (NACT) is associated with a better prognosis. We aimed to develop a genomic signature from pre-treatment samples to predict the extent of TILs after NACT, and then to test its prognostic value on survival. **Methods:** Using 99 pre-treatment samples (training set), we generated a four-gene signature that predicts post-NACT TILs using the LASSO technique. Prognostic value of the signature on survival was assessed on the training set (n=99) and then evaluated on an independent validation set including 185 patients with TNBC treated with NACT. **Results:** A four-gene signature, assessed on pre-treatment samples and combining the expression levels of HLF, CXCL13, SULT1E1, and GBP1 predicted the extent of lymphocytic infiltration after NACT. In a multivariate analysis performed on the training set, a one-unit increase in the signature value was associated with distant-relapse free survival (DRFS) (HR: 0.28, 95% CI: 0.13-0.63, p=0.002). For the validation set, the four-gene signature was significantly associated with DRFS in the entire set (HR: 0.26, 95%CI: 0.11-0.59, p=0.001) and in the subset of patients with residual disease (HR: 0.23, 95%CI: 0.10-0.55, $p<0{\cdot}001$). **Conclusions:** We developed a four-gene signature of chemotherapy-induced immune-activation, which predicts outcome in patients with TNBC treated with NACT.

Prognostic value of the four-gene signature on distant relapse-free survival.

	Training (n=94)			Validation - Residual disease (n=98)			Validation – Entire set (n=160)		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age	1·01	0·98 – 1·03	0·695	1·00	0·97 – 1·03	0·969	1·00	0·96 – 1·03	0·764
cT			0·310			< 0·001			0·001
T0-1-2	1			1			1		
T3-4	1·39	0·74 – 2·62		4·41	1·92 – 10·13		3·15	1·56 – 6·38	
cN			0·559			0·026			0·010
N0	1			1			1		
N+	1·23	0·61 – 2·47		2·93	1·14 – 7·51		3·31	1·34 – 8·16	
Grade			0·100			0·362			0·414
1-2	1			1			1		
3	1·00	0·48 – 2·10		1·50	0·63 – 3·55		1·42	0·61 – 3·32	
pCR			N.I			N.I			<0·001
Yes							1		
No							8·54	3·30 – 22·05	
1-unit increase in the Four-gene signature	0·28	0·13 – 0·63	0·002	0·23	0·10 – 0·55	< 0·001	0·26	0·11 – 0·59	0·001

N.I, Not included

576 Poster Session (Board #176), Sun, 8:00 AM-11:30 AM

Adjuvant or neoadjuvant chemotherapy in early stage triple negative breast cancer (TNBC) comparison of outcomes in both BRCA positive and BRCA negative patients. *First Author: Katherine Clifton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: NSABP Protocol B-18 was a randomized trial which found no statistically significant difference in overall survival (OS) in patients (pts) receiving neoadjuvant (NAC) or adjuvant chemotherapy (AC), however outcome was not analyzed by breast cancer subtypes. Subsequent retrospective studies in TNBC reported conflicting results with an initial study showing a significant OS benefit with AC and later studies showing a trend toward improved survival with NAC. Furthermore, studies have not included a significant number of pts with BRCA mutations. This study aims to analyze outcomes of AC versus NAC in pts with early stage TNBC with and without BRCA germline mutations. **Methods:** Pts with stage I or II TNBC who had BRCA testing were identified from a prospective cohort study of 4027 pts at MD Anderson Cancer Center. Clinical, demographic, genetic test results, chemotherapy, recurrence, survival data were collected. OS and disease free survival (DFS) were estimated using the Kaplan-Meier method, and log-rank tests were used to compare groups. **Results:** 305 pts with stage I and II TNBC who met eligibility criteria were included in the analysis. Pts who received both NAC and AC or no chemotherapy were excluded. 181 received AC (59.3%) and 124 received NAC (40.7%). The majority of the pts were less than 50 years old (236, 77.4%) and white (194, 63.8%). 134 were BRCA positive (44.1%) and 170 were BRCA negative (55.9%). The majority of the pts received an anthracycline and taxane regimen (223, 73.1%). There was no significant association between OS or DFS and treatment with NAC versus AC in the overall cohort. Furthermore, there were no significant differences between pt subgroups (NAC BRCA positive, NAC BRCA negative, AC BRCA positive, and AC BRCA negative) with respect to either OS or DFS. **Conclusions:** NAC versus AC with standard anthracycline and taxane containing regimens results in similar DFS and OS survival amongst pts with stage I and II TNBC regardless of BRCA status. Further studies are needed to evaluate whether similar results are observed with newer agents, such as platinums, PARP inhibitors and other targeted agents.

577 Poster Session (Board #177), Sun, 8:00 AM-11:30 AM

Pathologic complete response (pCR) rates after neoadjuvant pertuzumab (P) and trastuzumab (H) administered concomitantly with weekly paclitaxel (T) and 5-fluorouracil/epirubicin/cyclophosphamide (FEC) chemotherapy for clinical stage I-III HER2-positive breast cancer. *First Author: Julia Foldi, Yale Cancer Center, New Haven, CT*

Background: Inclusion of H with chemotherapy has increased pathologic complete response (pCR) rates in HER2 positive breast cancer, and dual HER2 blockade involving H + P further increased efficacy. With dual HER2 blockade and taxane-based (+/-carboplatin followed by anthracycline) chemotherapies, pCR rates reach, 75% in estrogen receptor (ER) negative and 45% in ER+ patients. HER2 targeted therapies also increase the efficacy of anthracyclines but are not routinely combined due to potential cardiotoxicity. The goal of this phase II study was to assess pCR rate when H+P is administered during the entire treatment duration, including the anthracycline phase, of weekly T (80 mg/m^2) x 12 followed by FE(75 mg/m^2)C x 4 neoadjuvant chemotherapy. **Methods:** pCR (ypT0/is and ypN0) rate was assessed separately in ER+ and ER- cancers following Simon's two-stage design to detect improvement in pCR rates to 90% and 70% in the ER- and ER+ cohorts, respectively. Eligibility included age <65, stage I-III, HER2+ disease, and normal cardiac function. **Results:** The ER- cohort completed full accrual of 25 patients: 23 completed therapy and surgery, 2 patients are still receiving treatment. The pCR rate is 78% (n=18, 95% CI:58-90%). The ER+ cohort was closed after 23 patients were accrued to the first stage due to lower than expected pCR of 26% (n=6, 95% CI:13-46%) at interim analysis. The incidence of grade 3/4 adverse events was 48% (n=24/50), the most common being neutropenia (n=12) and diarrhea (n=7). No patient experienced symptomatic congestive heart failure, one patient had a drop in LVEF to < 50% following completion of chemotherapy. Thirteen patients (27%) had a >10% asymptomatic drop in their LVEF but remained above 50%, LVEF returned to baseline by the next assessment in half of these cases. **Conclusions:** Neoadjuvant P and H administered concomitantly with weekly T followed by FEC resulted in 78% pCR rate in ER-/HER2+ cancers. This pCR rate is among the highest reported in the literature. The pCR rate was substantially lower in ER+ cancers. Clinical trial information: NCT01855828.

578 Poster Session (Board #178), Sun, 8:00 AM-11:30 AM

Utilization, trend and impact of neoadjuvant endocrine therapy compared to neoadjuvant chemotherapy in postmenopausal breast cancer patients: Analysis of the National Cancer Data Base. *First Author: Alina Basnet, SUNY Upstate Medical University, Syracuse, NY*

Background: Three small prospective trials that compared the efficacy of neoadjuvant endocrine therapy (NET) to neoadjuvant chemotherapy (NCT) showed no statistically significant difference. We report the differences in utilization of NET and NCT using National Cancer Data Base (NCDB) and their trend, response rates (RR) and breast conservation rates (BCR). **Methods:** A retrospective review of hormone receptor positive breast cancer patients ≥ 50 yrs without metastasis using NCDB was performed (2004-2014). Patients underwent NET or NCT prior to definitive surgery. Utilization pattern, practice trend, RR and BCR between NET and NCT was assessed using univariate and multivariate logistic analysis. **Results:** Out of 2,246,279 breast cancer patients reported in NCDB, 38,632 met our inclusion criteria. 9178 received NET and 29,454 received NCT. On multivariate analysis NET use was higher in academic vs community centers [Odds ratio (OR) 1.355, 95% CI 1.270-1.445], age >70 vs < 70 (OR 6.603, 95% CI 6.110-7.137) and high vs low Charlson Deyo comorbidity index (OR 1.817, 95% CI 1.548-2.133). NET use was lower in black vs white (OR 0.790, 95% CI 0.712- 0.875), tumors with higher vs lower grade (OR 0.153, 95% CI 0.138-0.169), higher vs lower T stage (OR 0.372, 95% CI 0.340-0.407), higher vs lower N stage (OR 0.274, 95% CI 0.243-0.310) and private vs no insurance (OR 0.600, 95% CI 0.509- 0.707), (all p<0.0001). A significant upward trend in utilization of NET was observed from year 2011 (25.9%) compared to before (22.2%), p<0.0001. RR was significantly higher for patients receiving NCT (90.5%) compared to NET (77.2%), with an [adjusted OR (aOR) 2.413; 95% CI 2.116-2.752], however the BCR was superior in the NET group (50.0%) compared to NCT group (31.1%) with (aOR 1.676; 95% CI 1.567-1.794). **Conclusions:** Our study is the first to compare NET and NCT utilization and their efficacy using NCDB database. Our results have shown striking differences in outcome among these two strategies as compared to other prospective trials. Despite high RR, more patients underwent mastectomy in the NCT group. We also see a steady upward trend in usage of NET from year 2011.

579 Poster Session (Board #179), Sun, 8:00 AM-11:30 AM

EarlyR genomic signature to predict pathological complete response following neoadjuvant anthracycline-taxane chemotherapy in estrogen-receptor positive (ER+) breast cancer. *First Author: Steven Allen Buechler, University of Notre Dame, Notre Dame, IN*

Background: EarlyR is a prognostic signature computed from expression values of *ESPL1, SPAG5, MKI67, PLK1* and *PGR* that stratifies ER+ breast cancer (BC) into EarlyR^{Low}, EarlyR^{Int}, and EarlyR^{High} risk strata. Here, we show that EarlyR is also predictive of pathological complete response (pCR) following neoadjuvant anthracycline-taxane (AT) based chemotherapy. **Methods:** The ability of EarlyR gene signature to predict pCR was assessed in Affymetrix microarrays datasets (GSE25065, GSE25066, GSE20194, GSE20271; n = 541, pCR = 42 (7.8%) collectively labeled as Cohort A) derived from patients with ER+ breast cancer treated with neoadjuvant TFAC or FEC. For 2 of these datasets (GSE25065, GSE25066 (n = 291)) distant metastasis-free survival (DMFS) results were also available. The DMFS data in cohort A were compared to that of BC patients not treated with chemotherapy (denoted Cohort B, n = 1269) derived from ER+ samples from 7 GEO datasets (GSE3494, GSE7390, GSE12093, GSE6532, GSE2034, GSE11121, GSE17705). **Results:** In cohort A, EarlyR is a significant predictor of pCR ($p = 1.0 \times 10^{-6}$) (EarlyR^{Low}, n = 273, pCR = 5, 1.8%; EarlyR^{Int}, n = 11, pCR = 1, 9.1% and EarlyR^{High}, n = 256, pCR = 36, 14.1%). Notably, 86% of the 42 cases with pCR have EarlyR^{High}. Of the 291 patients with 8-year DMFS data from Cohort A, who had received chemotherapy, the survival of EarlyR^{High} [0.79 (95%CI 0.70-0.89)] was nearly the same as that of EarlyR^{Low} [0.82 (95%CI 0.74-0.90)]. In contrast, in cohort B, who were not treated with chemotherapy, 8-year DMFS is significantly ($p = 5 \times 10^{-15}$) lower in EarlyR^{High} [0.57 (95%CI 0.51-0.64)] than in EarlyR^{Low}[0.81 (95%CI 0.78-0.84)]. **Conclusions:** EarlyR is a strong predictor of pathological complete response in patients treated with TFAC or FEC. In addition, EarlyR also predicts poor DMFS outcomes for patients in EarlyR^{High} not receiving chemotherapy. More importantly, neoadjuvant chemotherapy dramatically improved survival of patients in EarlyR^{High}. These results document that EarlyR identifies a set of patients, EarlyR^{High}, with a high risk of distant metastasis, who are also likely to respond favorably to chemotherapy.

580 Poster Session (Board #180), Sun, 8:00 AM-11:30 AM

Effect of neoadjuvant pertuzumab-containing regimens on pathologic complete response rates in stage II-III HER2-neu positive breast cancer: A retrospective, single institutional experience. *First Author: Rashmi Krishna Murthy, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pertuzumab (P) in combination with trastuzumab (H) based chemotherapy is currently FDA- approved as a standard neoadjuvant treatment for patients with clinical stage II-III HER2-positive (HER2+) breast cancer (BC). The chemotherapy backbone of HER2-targeted therapy varies and may include taxane (T) and/or anthracycline (A), or carboplatin (C). The goal of this study was to retrospectively evaluate the pathologic complete response (pCR) rate for HP-containing regimens compared to H containing regimens for stage II-III HER2+ BC. **Methods:** We identified all patients (n = 1150) with stage II-III HER2+ BC who received neoadjuvant HER2-targeted therapy from 2005 to 2016 through an institutional database. All patients underwent primary breast and lymph node surgery. pCR was defined as ypT0/is, ypN0. Univariate/multivariate logistic regression and chi-squared test for comparing proportions was used for the statistical analysis. **Results:** pCR was significantly higher for the HP group (n = 200) compared to the H group (n = 950): 44% vs. 41%, odds ratio = 1.8 (95% CI = 1.3, 2.5; P = 0.0002). Even with adjustment for all clinically significant factors (age, stage, tumor grade, hormone receptor (HR) status, A or C exposure), the improvement was statistically significant (adjusted OR = 2.1 (95% CI = 1.5, 2.9; P < 0.0001). The pCR rate by stage and HR status for the HP group is 62% vs. 55% (stage II vs. III) and 71% vs. 51% (HR- vs. HR+). The effect of P was not modified by HR status (HR-, OR = 2.3; HR+, OR = 1.7, P = 0.39) or by A (A-yes, OR = 1.8; A-no, OR = 2.6) (P = 0.28 for interaction) or C (C-yes, OR 2.6; C-no, OR = 1.8) (P = 0.30 for interaction). P was significantly more likely to be given to patients without A (36% vs. 10%, P < 0.0001) and more likely to be given to patients with C (30% vs. 14%, P < 0.001). In both groups, significant predictors of pCR were found to be stage, HR status, and C exposure. **Conclusions:** Pertuzumab containing regimens yield higher pCR rates compared to non-Pertuzumab containing regimens in stage II- III HER-2 positive breast cancer. The effect of Pertuzumab is not modified by anthracycline or carboplatin use.

581 Poster Session (Board #181), Sun, 8:00 AM-11:30 AM

Comparing outcomes of neoadjuvant endocrine therapy versus chemotherapy in ER-positive breast cancer: Results from a prospective institutional database. *First Author: Nathalie LeVasseur, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: While neoadjuvant chemotherapy (NACT) has been established as the standard of care for medically fit patients, there has been renewed interest in utilizing neoadjuvant endocrine therapy (NET) for the treatment of women with estrogen-receptor (ER) positive, HER-2 negative breast cancer. Rates of pCR are known to be low in this population, but there is inconsistent data regarding downstaging and long-term outcomes in a non-trial setting with NET vs NACT. **Methods:** A prospective institutional databaseof breast cancer patients treated with neoadjuvant therapy at the British Columbia Cancer Agency from 2012-2016 was analyzed to identify all medically fit patients with ER positive, HER2 negative breast cancer. Patients were then divided into two groups: those who received NET or NACT. Baseline characteristics were compared between groups. A matched analysis (age, stage and grade) was then performed to compare rates of downstaging, pCR and scores from a validated neoadjuvant therapy outcomes calculator (CPS+EG). **Results:** A total of 154 patients met eligibility criteria for this study. One hundred and six patients (69%) received NACT and 48 (31%) received NET. Women offered NACT were significantly younger (51 vs 64y, p < 0.001) than those offered endocrine therapy and presented with a higher clinical stage (LR 27.93, p = 0.002). According to multiple linear regression for downstaging, clinical stage followed by NACT were the most important predictors of downstaging. When matched for age, stage and grade, downstaging was significantly higher with NACT (31/48, 65%) as compared to NET (12/48, 25%), p < 0.001. Of these, 12.5% achieved pCR with NACT as compared to 2.1% with NET, LR 4.243, p = 0.039. No significant differences in CPS+EG scores were identified when comparing NACT to NET. **Conclusions:** Significantly higher rates of downstaging were achieved with NACT as compared to NET when patients were matched for age, stage and grade. Rates of pCR remain low for ER-positive breast cancer patients. Although not validated with the use of NET, CPS+EG scores predicting long-term outcomes were not significantly different with NET compared to NACT.

582 Poster Session (Board #182), Sun, 8:00 AM-11:30 AM

Results of multicenter phase II WSG Neo-Predict trial: Predictive markers for evaluation of response to neoadjuvant paclitaxel+trastuzumab+lapatinib in HER2-positive early breast cancer. *First Author: Christian Eichler, Krankenhaus Köln-Holweide, Cologne, Germany*

Background: Trastuzumab (T) and Lapatinib (L) containing neoadjuvant chemotherapy (NACT) increases pathological complete response (pCR) (vs. T or nihil) in HER2+ early breast cancer (EBC). Early clinical response markers (e.g. Ki67) in a 3-week biopsy or in residual tumor correlate with therapy efficacy and risk of relapse. This WSG Neo-Predict trial aimed to define early predictive markers for therapy response in a dual blockade (T+L) NACT setting. **Methods:** Patients with cT1c-cT4c HER2+ EBC were treated by paclitaxel (P) (80 mg/m^{2}weekly) with L (750 mg p.o. daily) + T (2 mg/kg) weekly for 12 weeks. Adjuvant treatment with 4 cycles of Epirubicin/Cyclophosphamide (omission allowed in patients with pCR) and T for an additional 40 weeks was recommended. Primary objectives were pCR (ypT0/is/ypN0) and identification of a dynamic predictive test for pCR using a re-biopsy after three weeks of NACT (early response defined as central Ki67 decrease >30% (vs. baseline) and/or low cellularity (<500 invasive tumor cells)). **Results:** From 2013-2015, 64 patients (n=80 planned) were recruited. Overall pCR was 41% (41% for HER2+/HR+ (n=34) and 45.5% for HER2+//HR- (n=22)). A 0% pCR in the "non-responder" (n=7) group (vs. 50% in the "responder" (n=34) and 42% in the "missing response" (n=20) groups) is intriguing despite methodological limitations. Missing data for early response assessment in a substantial number of patients and negative DFS data from the ALTTO trial did not justify trial continuation. 27% of patients experienced severe adverse events (AE). 11.5% had > grade 3 AEs (including diarrhea, septic shock, leukopenia, and pneumonia). **Conclusions:** We observed a clinically meaningful pCR with moderate toxicity with only 12 weeks of paclitaxel weekly with dual HER2 blockade (T+L). Effect of additional chemotherapy in patients with pCR after 12 weeks of monochemotherapy remains questionable due to a strong prognostic effect of pCR in HER2+ EBC. In view of 0% pCR (by hypothesis-generating explorative analysis), a different treatment approach should be investigated in patients without "early response" by further prospective trials. Clinical trial information: 2012-003679-21.

583 Poster Session (Board #183), Sun, 8:00 AM-11:30 AM

Effect of TCHL-based therapy on immune cell content in on-treatment, neoadjuvant-treated HER2-positive breast cancer patients. *First Author: Niamh M. Keegan, St. James's Hospital, Dublin, Ireland*

Background: In the TCHL trial (NCT01485926) 78 women with HER2-positive breast cancer (BC) underwent neo-adjuvant treatment with either TCH (Docetaxel, Carboplatin, Trastuzumab) or TCHL (TCH + Lapatinib) therapy. Of the 78 patients, 24 consented to an optional on-treatment biopsy 20 days after 1 cycle of therapy. We analysed the impact of tumour infiltrating lymphocytes (TILs) on pathological complete response (pCR) and also determined the impact of TCH/TCHL therapy on immune cell modulation after 20 days of treatment. **Methods:** We assessed TIL and stromal lymphocytes (SL) counts using immunohistochemical staining with Haemotoxalyin+Eosin, AE1/AE3 and CD45 in formalin fixed paraffin embedded (FFPE) baseline biopsy samples and in fresh frozen (FF) biopsies taken 20-days post cycle 1 (Day-20) of TCH/TCHL. RNA libraries were generated, using the Truseq mRNA library prep kit on the Neoprep platform and sequenced on the NextSeq 500. We measured the transcriptomic profile of 8 pre and on-treatment sample pairs and then used the Microenvironment Cell Populations (MCP)-counter method to measure the abundance of 10 immune cell populations (T cells, CD8 T cells, cytotoxic lymphocytes, NK cells, B lineage, myeloid dendritic cells, neutrophils, endothelial cells and fibroblasts). **Results:** We found that higher baseline levels of TILs (p = 0.045) but not SL were associated with an increased likelihood of a patient achieving a pCR to TCH/L based therapy. We found in day 20 on-treatment biopsies of women that subsequently went onto have a pCR that levels of SLs but not TILs were significantly higher (p = 0.049) than in those women who did not have a pCR. Finally we found significant increases in the level of monocytes (p = 0.05) and fibroblasts (p = 0.01), but not other immune cell populations, in the day 20 on-treatment biopsies in comparison with the mutated pre-treatment biopsies. **Conclusions:** In our study baseline TILs but not SLs have a predictive role in the likelihood of a patient achieving a pCR. We also found that TCHL based therapy significantly altered both monocytes and fibroblasts, indicating a possible role for these immune subtypes in response to TCHL therapy.

584 Poster Session (Board #184), Sun, 8:00 AM-11:30 AM

The impact of quality and quantity of visceral fat on survival outcome of early-stage breast cancer patients with prior chemotherapy. *First Author: Toshiaki Iwase, Breast Medical Oncology, MD Anderson Cancer Center, Houston, TX*

Background: Obesity not only increases morbidity, but also chemo-resistance of breast cancer (BC). Several studies focusing on body mass index (BMI) of BC patients have been performed; however, a recent report suggested that the quality of visceral adipose tissue (VAT) plays a crucial role in fat cell function. We set out to clarify the effect of quality and quantity of VAT on survival outcome of BC patients who underwent chemotherapy. **Methods:** From 2,230 patients who underwent treatment for BC at our institution from January 2004 to December 2015, we included 271 patients who received chemotherapy in neo-adjuvant (NAC) or adjuvant setting. Quantification was performed using computed tomography (CT) 3-dimensional volumetric software and quality of VAT was assessed based on the CT Hounsfield Unit of VAT (VAT-HU) using electrically stocked CT images. The correlation between BMI, amount of VAT (aVAT), and VAT-HU were analyzed using Pearson's correlation test. The effect of these factors on pathologic complete response (pCR) was evaluated using Logistic regression model with the following covariates: menopausal status, size, nodal status, and subtype. Furthermore, survival analysis for distant disease-free survival (DDFS) was performed using Kaplan Meier method and Cox proportional hazard model. **Results:** aVAT and VAT-HU were significantly correlated with patient BMI ($p<0.05$). Forty-six patients achieved pCR (24%). Logistic regression model for pCR showed that aVAT and VAT-HU did not affect pCR (p=0.60 and 0.36). After a median follow-up of 112 months, tertile stratification revealed that the third tertile of aVAT had significantly shorter DDFS in the NAC setting ($p<0.05$). When adjusted by covariates in the Cox proportional regression model, aVAT and VAT-HU demonstrated significant contribution to worse DDFS ([$p<0.05$, hazard ratio {HR} 1.39; 95% confidence interval {CI} 1.11 to 1.75] and [$p<0.05$, HR 1.20, 95% CI 1.01 to 1.43], respectively). **Conclusions:** The quantity and quality of VAT was significantly related to the survival outcome especially in the NAC setting. This new insight would enable prediction of recurrence risk in obese BC patients with prior chemotherapy.

585 Poster Session (Board #185), Sun, 8:00 AM-11:30 AM

Improving pathological response in locally advanced triple negative breast cancer: Comparison between CbD and AC-T regimens. *First Author: Daniel Enriquez, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru*

Background: Pathological complete response (pCR) is a well-known surrogate for DFS and OS in triple negative breast cancer (TNBC). New approaches are being tested to increase pCR rate. We compared the standard of care (AC-T) vs Carboplatin/Docetaxel (CbD) for locally-advanced TNBC. Our objective is to determine whether CbD will increase the pCR rate, with PFS and OS as secondary objectives. **Methods:** A single arm phase II prospective trial with historical controls. 61 stage II-III TNBC patients were included between 2013-2014 at Instituto Nacional de Enfermedades Neoplasicas (Peru). 27 patients received Carboplatin 6AUC + Docetaxel 75mg/m^2 q21d for 6cy, and 34pts, Adriamycin 60mg/m^2 + Cyclophosphamide 600mg/m^2 q21d for 4cy followed by weekly paclitaxel 80mg/m^2 for 12 weeks. The Miller and Payne method was used to evaluate pathological response after definitive surgery. **Results:** Median age was 47 years, most patients were premenopausal (55.7%), median tumor size was 61 mm (T3=32.8%, T4=50.8%) and most patients had LN+ve (77%). There was a significantly greater tumor size in the CbD arm (mean 72.8 vs 52.2mm, p=0.007), no toxicity differences were noted. Only pCR was independently associated with OS/PFS on multivariate analysis. pCR was achieved in 37% (n=10) and 23.5% (n=8) in the CbD and AC-T groups, respectively (p=0.44). Partial pathological response was achieved in 37% (n=10) and 38.2% (n=13) patients in AC-T and CbD respectively. No characteristics were associated to pCR on logistic regression. At 2-year follow-up, all patients with pCR were alive and without recurrence, while patients with partial response achieved a 2-year PFS of 75% and, 2-year OS of 83.5%. The non-respondent group had the worse outcomes (2-year PFS: 32.7%, 2-year OS: 58.7%). The CbD group had a better 2-year PFS and OS (73.1% and 84%, respectively) than the AC-T group (59.3% and 71%, respectively), however no-statistical difference was found. **Conclusions:** CbD is an effective and promising neoadjuvant chemotherapy regimen for TNBC. Despite a larger mean tumor size in the CbD group, a non-significant trend towards higher pCR rate and longer PFS and OS was observed and warrants further exploration.

TPS586 Poster Session (Board #186a), Sun, 8:00 AM-11:30 AM

ABC trial (A011502): A randomized phase III double blinded placebo controlled trial of aspirin as adjuvant therapy for node positive breast cancer. *First Author: Wendy Y. Chen, Dana-Farber Cancer Institute, Boston, MA*

Background: In-vitro and in-vivo evidence suggest that aspirin, an inexpensive and widely available drug may have anti-tumor activity via effects on multiple pathways. Multiple epidemiologic studies have reported improved breast cancer survival among regular aspirin users compared to non-users. Furthermore, pooled data from randomized trials of aspirin for cardiovascular disease have also reported a decreased risk of metastatic cancer among aspirin users, especially metastatic adenocarcinoma (RR 0.52 (95% CI 0.35-0.75). In order for aspirin to be considered standard of care, the exact benefits and risks for breast cancer survivors need to be confirmed in a randomized trial. **Methods:** The primary objective is to compare the effect of aspirin versus placebo upon invasive disease-free survival (iDFS) in stage II-III node-positive HER2 negative breast cancer patients. Secondary objectives include effects on overall survival and cardiovascular disease and to collect toxicity and adherence. A biospecimen repository will be created for future correlative analyses including tumor collection at baseline and blood and urine samples at baseline and 2 years. Questionnaires assessing lifestyle factors associated with inflammation (pain, sleep, stress, and depression) will also be collected at baseline and 2 years. Study design: Subjects will be randomized (1:1) to aspirin 300 mg vs placebo daily for 5 years in a double-blinded fashion. Stratification factors include hormone receptor status (positive vs negative), body mass index ($<$ or $\geq$ 30 kg/m2), and stage (II vs III).Subjects will be followed every 6 six months while on study drug and then annually until 10 years from registration. 2936 patients will be enrolled with 80% power to detect HR 0.75. Eligibility: Eligible subjects include patients aged 18-70 diagnosed with a primary invasive stage II or III node positive HER2 negative breast cancer in the past year. Patients who currently use any oral or injectable anticoagulant or those with a prior history of GI bleeding, atrial fibrillation, myocardial infarction, or grade IV hypertension will be excluded. Patients who regular used aspirin over the past year will be excluded. Clinical trial information: NCT02927249.

TPS587 Poster Session (Board #186b), Sun, 8:00 AM-11:30 AM

PEARLY: A randomized, multicenter, open-label, phase III trial comparing anthracyclines followed by taxane versus anthracyclines followed by taxane plus carboplatin as (neo)adjuvant therapy in patients with early triple-negative breast cancer. *First Author: Gun Min Kim, Yonsei University College of Medicine, Seoul, Republic of Korea*

Background: Triple-negative breast cancer (TNBC) is an aggressive tumor with poor prognosis. There are no molecular targets for TNBC, and there is an unmet need to provide new drugs to patients with TNBC. Platinum agents are known to have an anti-tumor activity in TNBC, especially in BRCA-mutated tumor. Addition of carboplatin significantly increased pathologic complete response rates with neoadjuvant chemotherapy in recent randomized studies. There are no data about adjuvant role of carboplatin for TNBC in a randomized trial. **Methods:** PEARLY is a randomized, multicenter, open-label, phase III trial comparing anthracyclines followed by taxane versus anthracyclines followed by taxane plus carboplatin as (neo)adjuvant therapy in patients with triple-negative breast cancer (TNBC). Patients with stage II or III TNBC who need adjuvant or neoadjuvant chemotherapy were included. Any prior systemic therapy for breast cancer was not allowed. Bilateral, metastatic, and inflammatory breast cancer are excluded. A total of 840 patients will be enrolled for 3 years. Patients were randomized 1:1, stratified based on the node positivity (N0 vs N+), institution, treatment setting (neoadjuvant vs. adjuvant), and BRCA mutation status (positive vs. negative). Standard arm treatment consists of doxorubicin 60 mg/m2 IV + cyclophosphamide 600 mg/m2 IV every 3 weeks for 4 cycles followed by taxane treatment (paclitaxel 80 mg/m2 IV weekly for 12 doses or docetaxel 75mg/m2 IV every 3 weeks for 4 cycles). Experimental arm added carboplatin AUC5 IV every 3 weeks for 4 cycles during taxane treatment. The primary objective was to evaluate 5-year event free survival (EFS) rate. Secondary objectives included overall survival, distant recurrence free survival, pathologic complete response, and tolerability. The analysis is planned at 248 EFS events, which provides approximately 80% power to detect superiority of standard treatment plus carboplatin versus standard treatment using a log-rank test, assuming a hazard ratio of 0.7 at a two sided alpha of 0.05. Data is expected in 2023. Clinical trial information: NCT02441933.

TPS588 Poster Session (Board #187a), Sun, 8:00 AM-11:30 AM

A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (JCOG1017 PRIM-BC). *First Author: Tadahiko Shien, Okayama University Hospital, Okayama, Japan*

Background: The possibility of improving the survival of stage IV breast cancer patients by primary tumor resection (PTR) has been reported by several retrospective studies; however, these studies essentially suffer from biases such as arbitrary patient selection, diverse timing of surgery or various regimens of systemic therapy. Five prospective randomized trials including our trial have evaluated the efficacy of PTR for them. Two have reported final results, but those results were inconsistent. Therefore, this subject still remains a hotly debated topic at major breast conferences. **Methods:** Our trial is being conducted to confirm the superiority of PTR plus systemic therapy over systemic therapy alone in stage IV pts who are sensitive to primary systemic therapy (PST) in this study. The inclusion criteria are untreated pts with histologically confirmed invasive breast cancer with one or more measurable distant metastatic lesions diagnosed by radiological examination.All pts receive PST according to the ER and HER2 status of the primary breast cancer after the first registration. After three months, the pts who are sensitive to PST are randomized to the PTR plus systemic therapy arm or the systemic therapy alone arm. After randomization and surgery in the former arm, or after randomization in the latter arm, the same systemic therapies are continued until progression of diseases and next appropriate regimens are started after that. The primary endpoint is the overall survival, and the secondary endpoints are proportion of pts without tumor progression at the metastatic sites, yearly local recurrence-free survival, proportion of local ulcer/local bleeding, yearly primary tumor resection-free survival, adverse events (AEs) of chemotherapy, operative morbidity, and serious AEs. Sample size for randomized pts was determined to attain at least 80% of power to detect a 6 months difference with one-sided alpha of 0.05.The pts accrual was started in May 2011. Enrollment of 410 pts for randomization is planned over a 7-year accrual period. 307 pts have been randomized until Jan 2017. This trial was registered at UMIN-CTR[umin.ac.jp/ctr/] as UMIN000005586. Clinical trial information: UMIN000005586.

TPS589 Poster Session (Board #187b), Sun, 8:00 AM-11:30 AM

NRG Oncology/NSABP B-51/RTOG 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) reduces invasive breast cancer recurrence free interval (IBCRFI) in patients (pts) with positive axillary (PAx) nodes who are ypN0 after neoadjuvant chemotherapy (NC). *First Author: Eleftherios P. Mamounas, NSABP/NRG Oncology, and UF Cancer Center at Orlando Health, Orlando, FL*

Background: This phase III post-NC trial evaluates if CWRNRT post-Mx or whole breast irradiation (WBI) with RNRT after BCS significantly reduces the IBCR-FI rate in pts with PAx nodes that are negative after NC. Secondary aims are OS, LRR-FI, DR-FI, DFS-DCIS, second primary cancer, and comparison of RT effect on cosmesis in reconstructed Mx pts. Correlative science examines RT effect by tumor subtype, molecular outcome predictors for residual disease pts, and predictors for the degree of reduction in locoregional recurrence. **Methods:** Clinical T1-3, N1 IBC PAx nodes (FNA or core needle biopsy) pts complete ≥12 weeks of NC (anthracycline and/or taxane). HER2+ pts receive anti-HER2 therapy. Following NC BCS or Mx, sentinel node biopsy (≥3 nodes) and/or Ax dissection with histologically negative nodes is performed. ER/PR and HER-2neu status before NC is required. Pts receive required systemic therapy. Radiation credentialing with a facility questionnaire/case benchmark is required. Random assignment for Mx pts is to no CWRNRT or CWRNRT and for BCS pts to WBI or WBI RNRT. Statistics: 1636 pts to be enrolled over 5 yrs (definitive analysis at 7.5 yrs). Study is powered at 80% to test that RT reduces the annual hazard rate of events for IBCR-FI by 35% for an absolute risk reduction of 4.6% (5-yr cumulative rate). Intent-to-treat analysis with 3 interim analyses (43, 86, and 129 events) and a 4th/final analysis at 172 events. Pt-reported outcomes focusing on RT effect will be provided by 736 pts before random assignment and at 3, 6, 12, and 24 mos. Accrual as of 2-2-17 is 534 (32.64%). Contacts: Questions: NRG Oncology Pgh Clin Coord Dpt: 1-800-477-7227 or ccd@nsabp.org. Support: U10 CA-2166; -180868, -180822; 189867; Elekta Clinical trial information: NCT01872975.

TPS590 Poster Session (Board #188a), Sun, 8:00 AM-11:30 AM

A randomized, triple negative breast cancer enrolling trial to confirm molecular profiling improves survival (ARTEMIS). *First Author: Clinton Yam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Following neoadjuvant chemotherapy (NACT), patients (pts) with triple negative breast cancer (TNBC) achieving pathologic complete response/residual cancer burden-0 (pCR/RCB-0) or minimal residual disease (RCB-I) have an improved relapse free survival when compared to pts with more extensive residual disease (RCB-II/III) (Symmans et al, JCO 2017). Pts with chemo-resistant TNBC have a poor prognosis as there are currently no FDA-approved targeted agents available for TNBC. We previously reported the ability of a novel gene expression signature (GES) to predict sensitivity to NACT (Hatzis et al, JAMA 2011). Here we seek to prospectively validate the use of this GES in combination with imaging to predict response to NACT and establish the clinical impact of selecting pts predicted to have non-responsive disease (NRD) for enrollment in clinical trials of targeted therapy. **Methods:** All pts will undergo a biopsy of the primary tumor for molecular characterization (MC) and will be randomized 2:1 to know their MC results (intervention arm) or not (control arm). A maximum of 360 pts will be enrolled and randomized using a group sequential design with one-sided O'Brien-Fleming boundaries, with two equally spaced binding interim tests for futility and superiority and one final test, having an overall Type I error of 0.05 and power of 0.80 to detect an improvement in pCR/RCB-I from 50% to 64%. Secondary endpoints include rates of clinical trial enrollment, disease free survival and integrated biomarker analyses. All pts will receive 4 cycles of anthracycline-based NACT with imaging done every 2 cycles to assess response. After completion or progression on anthracycline-based NACT, pts predicted to have NRD based on MC/imaging (intervention arm) or imaging alone (control arm) will be offered enrollment on a clinical trial. Pts are eligible if they have stage I-III TNBC with a primary tumor that is ≥1.5cm. Pts with contraindications to anthracyclines and/or taxanes are excluded. Enrollment began in November 2015. 105 pts have been enrolled to date with 71 and 34 pts randomized to the intervention and control arms, respectively. Clinical trial information: NCT02276443.

TPS591 Poster Session (Board #188b), Sun, 8:00 AM-11:30 AM

PARTNER: Randomised, phase II/III trial to evaluate the safety and efficacy of the addition of olaparib to platinum-based neoadjuvant chemotherapy in triple negative and/or germline BRCA mutated breast cancer patients. *First Author: Helena Margaret Earl, Cambridge University Hospitals, Cambridge, United Kingdom*

Background: No specific targeted therapies are available for Triple Negative Breast Cancers (TNBC), an aggressive and diverse subgroup. The basal TNBC sub-group show some phenotypic and molecular similarities with germline BRCA (gBRCA). In gBRCA patients, and potentially other homologous recombination deficiencies, these already compromised pathways may allow drugs called PARP inhibitors (olaparib) to work more effectively. Aims: To establish if the addition of olaparib to neoadjuvant platinum based chemotherapy for basal TNBC and/or gBRCA breast cancer is safe and improves efficacy (pathological complete response (pCR)). Trial design: 3-stage open label randomised phase II/III trial of neoadjuvant paclitaxel and carboplatin +/- olaparib, followed by clinicians' choice of anthracycline regimen. Stage 1 and 2: Patients are randomised (1:1:1) to either control (3 weekly carboplatin AUC5/weekly paclitaxel 80mg/m2 for 4 cycles) or one of two research arms with the same chemotherapy regimen but with two different schedules of olaparib 150mg BD for 12 days. Stage 3: Patients are randomised (1:1) to either control arm or to the research arm selected in stage 2. **Methods:** Stage 1 - Safety: both research arms combined. Stage 2 - Schedule selection criteria: pCR rate and completion rate of olaparib protocol treatment. It is a "pick-the-winner" design with 53 patients in each research arm. This allows a 90% power, 5% one-sided significance level to test null hypothesis of pCR ≤35% versus an alternative hypothesis of pCR ≥55% in each of the research arms. Stage 3 - Efficacy: anticipated pCR ~55-60% for all trial patients and ~60-65% for gBRCA patients. The trial is powered to detect an absolute improvement of 15% (all patients) and 20% (gBRCA patients) by adding olaparib to chemotherapy (enriched design). TNBC patient recruitment will be capped, to ensure required gBRCA patients are enrolled. Enrichment design is applied with overall significance level 0.05(α) = 0.025(αall)+ 0.025(αgBRCA) and 80% power. Target accrual: 527 [gBRCA 220] Current accrual: 17 Sites activated: 12 [expected number of sites 30-50].

TPS592 Poster Session (Board #189a), Sun, 8:00 AM-11:30 AM

Phase II trial of neoadjuvant (neo) palbociclib (Palbo) plus anastrozole (ana) in endocrine resistant clinical stage 2/3 estrogen receptor positive and HER2 negative (ER+ HER2-) breast cancer (BC). *First Author: Nusayba Ali Bagegni, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Persistent cell proliferation (Ki67 > 10%) on tumor biopsies as early as 2-4 weeks (wks) on neo endocrine therapy (ET) identifies resistant tumors in ~20% patients (pts) with early stage ER+ HER2- BC who are at high risk of relapse. Palbo plus ET significantly improves progression free survival in pts with ET naïve or resistant advanced ER+ HER2- BC, and is being evaluated in the adjuvant setting. However, biomarkers predictive of palbo sensitivity are unknown. Ki67 analysis of serial tumor biopsies in the neo palbo and ana (NeoPalAna) trial demonstrated that 2 wks of palbo plus ana potently inhibited Ki67 and induced complete cell cycle arrest (CCCA, Ki67≤2.7%) in tumors with high Ki67 post 4 wks ana run-in. This study is therefore aimed to prospectively investigate the biological activity of palbo plus ana in ET resistant ER+ HER2- BC. **Methods:** The primary objective is to assess the rate of CCCA (central Ki67 ≤2.7%) after 2 wks of neo palbo and ana. Secondary objectives include analysis of tumor biopsies to explore response biomarkers. Key inclusions include women with clinical stage 2/3 ER+ HER2- BC, central Ki67 > 10% after ≥2 wks of any neo ET, adequate organ function. Key exclusions include prior CDK 4/6 inhibitor, treatment of BC except ET, concomitant use of strong CYP3A4 inhibitor. Pts receive palbo (125mg PO daily, days 1-21, 28-day cycle), ana (1 mg PO daily) and goserelin (if premenopausal). Pts with C1D15 Ki67 > 10% will discontinue study. If C1D15 Ki67 ≤10%, pt will receive 4 cycles of treatment, and additional 10-12 days of palbo if counts normalized within 3 wks post C4D28. Following surgery, pts are eligible for 2 years of adjuvant palbo. A sample size of 37 (stage 1, n = 12, stage 2 n = 25) by simon optimal two stage phase II design will be employed to assess whether the rate of CCCA is ≤5% vs ≥20% (90% power, alpha 0.1). Stage 2 will proceed if ≥1 had CCCA in stage 1. If ≤3 of 37 had CCCA, this regimen will be considered ineffective. The study is active and has enrolled 4 pts. Clinical trial information: NCT01723774.

TPS593 Poster Session (Board #189b), Sun, 8:00 AM-11:30 AM

Towards omitting breast cancer surgery in select patient groups: Assessment of pathologic complete response after neoadjuvant systemic therapy using biopsies—The MICRA trial. *First Author: Marieke Van Der Noordaa, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Background: Improvements in systemic treatments for breast cancer patients has led to increasing rates of pathologic complete response (pCR). In addition, the identification of a pCR has been greatly improved with magnetic resonance imaging (MRI). In patients with a pCR, surgical resection of (part of) the original tumor area is performed to confirm the absence or presence of pCR and is not likely to contribute to locoregional control. With the MICRA trial (Minimally Invasive Complete Response Assessment) we aim to omit breast surgery in breast cancer patients achieving pathologic complete response (pCR) after neoadjuvant systemic therapy (NST) using biopsies, thus preventing overtreatment and improving quality of life. **Methods:** The MICRA trial is a multi-center observational prospective cohort study. In all breast cancer patients receiving NST, a marker is placed in the center of the tumor area before NST. 440 patients with radiologic complete response or partial response (0.1-2.0 cm residual contrast enhancement, ≥30% decrease in tumor size according to RECIST criteria) on contrast enhanced MRI will be included in the MICRA trial. Patients with hormone receptor positive, triple negative and Human Epidermal growth factor Receptor 2 tumors are eligible. After NST, 8 ultrasound-guided biopsies are obtained in the region surrounding the marker, while the patient is under general anesthesia. Immediately hereafter, breast surgery is performed and pathology results of the biopsies and resected specimens are compared. The primary endpoint is specificity of post-NST biopsies. In addition, sensitivity and positive and negative predictive value will be calculated. We will perform a multivariable analysis using data on MRI and ultrasound findings, pre-NST pathology parameters and post-NST biopsy results to determine what the most reliable method is to assess pCR and how many biopsies are needed for this purpose. Conclusion: With the MICRA-trial we aim to select a group of breast cancer patients in whom surgery of the breast after NST can be omitted, by predicting the presence of a pCR on biopsies. Clinical trial information: NTR6120.

TPS594 Poster Session (Board #190a), Sun, 8:00 AM-11:30 AM

CORALLEEN: A phase 2 clinical trial of chemotherapy or letrozole plus ribociclib as neoadjuvant treatment for postmenopausal patients with luminal B/HER2-negative breast cancer. *First Author: Joaquín Gavilá, Fundación Instituto Valenciano de Oncología, Valencia, Spain*

Background: Dysregulation of cyclin D-CDK4/6-Rb pathway is associated with endocrine resistance in hormone receptor–positive (HR+) breast cancer. Recently, a CDK4/6 inhibitor has shown unprecedented efficacy in metastatic disease, leading to its regulatory approval. Several others are currently in clinical development for the management of HR+ breast cancer in the early and advanced settings. However, it is vital to gain insights into the molecular and biological effects of this class of agents and could identify patients who can benefit the most, delaying or avoiding the use of chemotherapy.The neoadjuvant setting provides an ideal scenario to carry out these investigations. Hence, we propose to conduct an exploratory study to evaluate the biological effects and the efficacy of ribociclib in patients with primary luminal B tumors.We hypothesize that the combination of ribociclib plus letrozole may offer clinical benefit in the preoperative setting. **Methods:** This is a parallel, multicenter, two-arm, randomized exploratory study in postmenopausal women with primary operable HR+/HER2-negative Luminal B breast cancer designed to evaluate the clinical benefit of ribociclib plus letrozole. Eligibility includes stage I-III operable breast cancer, Luminal B by PAM50, ECOG 0-1. They will be randomized 1:1 to receive either six 28-days cycles of ribociclib (600mg; 3-weeks-on/1-week-off) plus daily letrozole (2.5mg) or chemotherapy: four cycles of AC (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 every 21 days) followed by weekly paclitaxel during 12 weeks. Baseline, Day 15 on-treatment, and surgical specimens will be collected for molecular characterization and evaluation of response (decrease in Ki67, change to ROR low disease) The primary endpoint is the rate of Residual Cancer Burden (RCB) per MD Anderson Cancer Center procedures. A rate of RCB 0 and 1 score at surgery, with a rank between 20% to 25% with 47 evaluable patients by group of treatment will offer a precision between 11.5% and 12.4%, respectively (95%CI). Ninety-four patients will be enrolled in 20 sites across Spain.

TPS595 Poster Session (Board #190b), Sun, 8:00 AM-11:30 AM

A feasibility study of neoadjuvant talazoparib for early-stage breast cancer patients with a germline *BRCA* pathogenic variant: NCT02282345. *First Author: Jennifer Keating Litton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Poly-(adenosine diphosphate [ADP]-ribose) polymerase (PARP) is a family of enzymes responsible for DNA repair via base excision repair as well as maintenance of genetic stability. BRCA mutation carriers appear to have significant sensitivity to PARP inhibitors, not only from synthetic lethality but also potentially PARP trapping in the metastatic setting. A 2-month window study of talazoparib was reported at ESMO in 2016. In 13 patients treated, the median % tumor shrinkage by ultrasound was 88% (range 30-98%) and the study was halted early to allow for this expansion of neoadjuvant talzoparib as the only treatment prior to surgery to evaluate pathologic response. Primary Objective: Evaluate the rate of pathologic complete response (pCR)/RCB-0 + residual cancer burden (RCB)-I responses in patients with early stage breast cancer and a known BRCA pathogenic variant. **Methods:** 20 patients with stage I-III breast cancer and a known BRCA mutation will be accrued on this IRB-approved study. Patients will receive 4-6 months of neoadjuvant talazoparib and then proceed to surgery. Radiation, chemotherapy and endocrine therapy will be given when appropriate in teh adjuvant setting. Brief Eligibility Criteria: Patients with an identified BRCA pathogenic variant and diagnosed with a stage I-III breast cancer at least 1 cm in size are eligible. Tumors can have any ER or PR status but HER2 over-expressed cancers were excluded. Prior systemic or radiation therapy for previous breast cancer is excluded, but prior surgical treatment for contralateral DCIS is allowed. Correlative Science: Blood and biopsies prior to initiation of therapy will be collected to evaluate biomarkers of therapy efficacy as well as to initiate patient derived xenograft (PDX) models. Other studies will include: immunohistochemistry, targeted or whole exome sequencing for BRCA pathway mutations and other somatic and germline alterations; RNA sequencing; immune response; transcriptional profiles to assess TNBC subtype, reverse phase protein array (RPPA); generation of PDX models and mammosphere cultures. Clinical trial information: NCT02282345.

1000 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

MONARCH 2: Abemaciclib in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer who progressed on endocrine therapy *First Author: George W. Sledge, Stanford University School of Medicine, Stanford, CA*

Background: Abemaciclib, an oral, selective inhibitor of CDK4 & 6, dosed on a continuous schedule, demonstrated clinical activity as monotherapy in patients (pts) with treatment refractory hormone receptor positive (HR+) metastatic breast cancer (MBC). The tolerability and activity of abemaciclib + fulvestrant (F) supported Phase 3 evaluation. **Methods:** MONARCH 2 is a double-blind Phase 3 trial of abemaciclib + F vs placebo (P) + F in women with HR+/HER2- advanced breast cancer. Women who progressed on (neo) adjuvant endocrine therapy (ET), ≤12 months from end of adjuvant ET, or on first line ET for MBC and who had not received chemotherapy for metastatic disease were eligible. Pts were randomized 2:1 to receive abemaciclib at 150 mg Q12H (or 200 mg prior to amendment) or P plus F (500 mg, per label) and stratified by metastatic site (visceral, bone only, or other) and resistance to prior ET (primary vs secondary). Pre/perimenopausal pts received a gonadotropin-releasing hormone agonist. The primary objective was investigator-assessed progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) and other efficacy and safety endpoints. Assuming a hazard ratio (HR) of 0.703 in favor of abemaciclib + F, 378 events were needed for 90% power at one sided α=.025. **Results:** 669 pts were randomized to abemaciclib + F (N=446) and to P + F (N=223). 56% of pts had visceral disease, 72% had measurable disease, 25% had primary ET resistance, and 82% were postmenopausal. In the ITT population 379 PFS events were observed with a median PFS of 16.4 m for abemaciclib + F and 9.3 m for P + F (HR: 0.553; 95% CI: 0.449, 0.681, P<.0000001 by log-rank test). In pts with measurable disease, the ORR was 48.1% (3.5% complete response [CR]) for abemaciclib + F and 21.3% (0% CR) for P + F. The most frequent treatment emergent adverse events for abemaciclib + F vs P + F were diarrhea (86.4% vs 24.7%), neutropenia (46.0% vs 4.0%), nausea (45.1% vs 22.9%), and fatigue (39.9% vs 26.9%). **Conclusions:** Abemaciclib + fulvestrant was an effective treatment in patients with HR+/HER2- advanced breast cancer who progressed on endocrine therapy with significantly improved PFS and ORR. Clinical trial information: NCT02107703.

1001 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Overall survival results from the randomized phase II study of palbociclib (P) in combination with letrozole (L) vs letrozole alone for frontline treatment of ER+/HER2– advanced breast cancer (PALOMA-1; TRIO-18). *First Author: Richard S. Finn, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: Preclinical data identified a synergistic role for P and hormone blockade in blocking growth of ER+ breast cancer (BC) cell lines. PALOMA-1 was an open-label phase II trial comparing progression-free survival (PFS) in patients (pts) with advanced ER+/HER2– BC treated with P+L or L alone. Median PFS increased with addition of P to L to 20.2 mos (vs 10.2 mos with L alone; HR = 0.488), with an acceptable safety profile, leading to accelerated approval by the US FDA. These results were confirmed in the phase 3 PALOMA-2 trial. At the time of the final PFS analysis, overall survival (OS) data were immature with only 61 events in both arms and a median follow-up of < 30 mos with a trend in favor of P+L vs L (37.5 vs 33.3 mos; HR = 0.813; *P*= 0.211). Here we present final OS results. **Methods:** PALOMA-1 was a 2-part study evaluating P+L in ER+/HER2– advanced BC. Part 1 enrolled postmenopausal pts with this subtype using only ER+/HER2– while Part 2 enrolled pts of this subtype additionally screened for CCND1 amplification and/or loss of p16. The primary endpoint was investigator-assessed PFS. Secondary endpoints included objective response rate, OS, safety, and correlative biomarker studies. A total of 165 pts were randomized; 66 in Part 1 and 99 in Part 2. Baseline characteristics were balanced between treatment arms. In both parts, pts were randomized 1:1 to receive P+L or L alone. OS data were collected as well as post-study therapy. **Results:** As of Dec 2016, there were 116 OS events. Median OS was 37.5 mos (95% CI: 31.4, 47.8) with P+L vs 34.5 mos (95% CI: 27.4, 42.6) for L (HR = 0.897 [95% CI: 0.623, 1.294]; *P*= 0.281). Median OS was 37.5 vs 33.3 mos (HR = 0.837; *P*= 0.280) for Part 1 and 35.1 vs 35.7 mos (HR = 0.935; *P*= 0.388) for Part 2. 78.6% of pts in the P+L arm received post-study systemic therapy vs 86.4% in the L arm. More pts in the L arm received ≥3 lines of therapy (37% vs 18%). Further subgroup analyses and details on post-study therapies will be presented. **Conclusions:** In PALOMA-1, P+L provided a statistically non-significant trend towards an improvement in OS. Survival data from the phase III, PALOMA-2 study is awaited. Sponsor: Pfizer; Clinical trial information: NCT00721409.

1002 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

A phase II trial of the CDK4/6 inhibitor palbociclib (P) as single agent or in combination with the same endocrine therapy (ET) received prior to disease progression, in patients (pts) with hormone receptor positive (HR+) HER2 negative (HER2−) metastatic breast cancer (mBC) (TREnd trial). *First Author: Luca Malorni, Sandro Pitigliani Medical Oncology Department, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy*

Background: P is approved for treatment of HR+/HER2− mBC combined with ET. There is paucity of clinical data of single-agent P in ET resistant pts. Pre-clinical data suggest P may partially reverse endocrine resistance, though this is yet to be tested in pts. **Methods:** This Phase II, open-label, multicenter study enrolled post-menopausal pts with HR+ HER2− mBC who progressed on 1 or 2 prior ETs. Pts were randomized to P (125 mg/d 3 w on/1 w off) alone or to continue their current ET (aromatase inhibitor or fulvestrant) in combination with P (same schedule as P arm). The primary endpoint was clinical benefit rate (CBR) [complete response (CR), partial response (PR) and stable disease (SD) for > 6 months (mo)]. Secondary endpoints were adverse events (AE) and additional measures of efficacy. A two-stage optimal design assessed treatment activity in each arm assuming activity as CB≥40% (α and β = 10%). Exploratory comparisons were planned for safety and efficacy endpoints. **Results:** 115 pts were enrolled (ITT population) 58 in the P arm and 57 in the P+ET arm. In both arms, 67% of pts had the study treatment as second line ET, 33% as third line, and about 1/3 of pts also received 1 prior chemotherapy for mBC. CBR was similar in both arms: 54% (95% CI 42 - 67%) with P+ET, and 60% (95% CI 48 -73%) with P alone. Median duration of CB was longer with P+ET (11.5 mo; 95% CI 8.6 – 17.8) than with P (6 mo; 95% CI 3.9 - 9.9) (HR 0.31, 95% CI 0.1 - 0.7, p-value 0.001, exploratory). Objective response rate (ORR; CR, PR) was 11% (95% CI 3 - 19%) and 7% (95% CI 0.4 -13%) with P+ET and P, respectively. PFS was 10.8 mo (95% CI 5.6 - 12.7) with P+ET and 6.5 mo (95% CI 5.4 - 8.5) with P alone (HR 0.69, 95% CI 0.4 - 1.1, p-value 0.13, exploratory). AEs were in line with previous data. **Conclusions:** Single agent P has clinical activity in ET pre-treated HR+/HER2− mBC pts. The observed increase in PFS and duration of CB with P+ET may suggest that P could reverse resistance to the prior line of ET. Translational studies are ongoing to explore potential biomarkers in this setting. Clinical trial information: NCT02549430.

1003 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Phase III, randomized study of first-line trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs. trastuzumab + taxane (HT) treatment of HER2-positive MBC: Final overall survival (OS) and safety from MARIANNE. *First Author: Edith A. Perez, Genentech, Inc., San Francisco, CA*

Background: In MARIANNE (NCT01120184), patients with HER2-positive advanced breast cancer were randomized to trastuzumab + docetaxel or paclitaxel (HT; n=365), T-DM1 + placebo (T-DM1; n=367), or T-DM1 + P (T-DM1 + P; n=363) as first-line therapy. In the primary analysis, T-DM1–based treatment exhibited noninferior, but not superior, progression-free survival relative to HT (Perez EA, et al. J Clin Oncol 2016). OS was similar between treatments in the first interim analysis. Here we report OS from the final descriptive analysis. **Methods:** Enrolled patients had centrally assessed HER2-positive (IHC3+ or ISH+) progressive/recurrent locally advanced breast cancer or previously untreated MBC with a ≥6-month interval since (neo)adjuvant treatment with taxanes or vinca alkaloids. **Results:** At the clinical cutoff date of May 15, 2016, median follow-up was 54 months and 512 patients had died. Median OS was 50.9, 53.7, and 51.8 months with HT, T-DM1, and T-DM1 + P, respectively (Table). A sensitivity analysis in which HT-treated patients who received T-DM1 and/or P after disease progression (n=85) were censored prior to treatment switch found similar results. There were numerically fewer grade ≥3 adverse events (AEs) with T-DM1. **Conclusions:** With this longer follow-up, the T-DM1 safety profile was consistent with the primary analysis and prior experience. While OS was similar across treatment arms, a median OS of 53.7 months and fewer grade ≥3 AEs (vs other arms) supports T-DM1 as an effective and tolerable alternative first-line treatment for HER2-positive MBC patients. Clinical trial information: NCT01120184.

	HT (n=365)	T-DM1 (n=367)	T-DM1 + P (n=363)
Median follow-up, months	54.1	54.4	54.4
OS	169	175	168
N	50.9	53.7	51.8
Median, months	-	0.93 [0.73–1.20] vs HT	0.86 [0.67–1.11] vs HT 1.00 [0.78–1.28] vs T-DM1
Stratified HR [97.5% CI]			
OS sensitivity analysis	141	175	168
N	49.8	53.7	51.8
Median, months	-	0.92 [0.70–1.19] vs HT	0.87 [0.66–1.13] vs HT
Stratified HR [97.5% CI]			
Grade 3−5 AEs, %	55.8	47.1	48.6
Most common grade 3–5 AEs, %			
Neutropenia	19.3	4.4	3.8
Thrombocytopenia	0	6.6	9.0
Anemia	2.8	5.0	7.1
Hypertension	3.1	4.7	5.5
ALT increased	0.8	4.4	6.0

1004 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Phase III study of lapatinib (L) plus trastuzumab (T) and aromatase inhibitor (AI) vs T+AI vs L+AI in postmenopausal women (PMW) with HER2+, HR+ metastatic breast cancer (MBC): ALTERNATIVE. *First Author: William John Gradishar, Robert H. Lurie Cancer Center of Northwestern University, Chicago, IL*

Background: Combination ofHER2-targeted therapy+AI improved clinical benefit in patients (pts) with HER2+, HR+ MBC vs AI alone in two previous trials, median progression free survival (mPFS) 4.8 vs 2.4 mo (TAnDEM), and 8.2 vs 3.0 mo (EGF30008). Dual HER2 blockade enhances clinical benefit vs single HER2 blockade. This study evaluated the safety and efficacy of dual vs single HER2 blockade (L+T vs T/L)+AI in HER2+, HR+ MBC progressing on (neo)adjuvant/first-line T+chemotherapy (CT). HER2 and HR status were assessed for eligibility at local lab. **Methods:** PMW were randomized 1:1:1 to receive T (8mg/kg followed by 6mg/kg IV Q3W)+L (1000mg/d)+AI or T+AI or L (1500mg/d)+AI. AI was per investigator's choice. Pts were excluded if they were intended for CT. The primary endpoint was to assess superiority of PFS with L+T vs T. Secondary endpoints included PFS (L vs T), overall survival (OS), overall response rate (ORR), and safety. **Results:** 369 pts were enrolled; current analysis included 355 pts (data cutoff, March 11, 2016); L+T (n = 120), T (n = 117) or L (n = 118). Final PFS data were analyzed after 137 events. Baseline characteristics were balanced across all treatment (tx) arms. The primary endpoint was met; superior PFS was observed with L+T vs T (mPFS, 11 vs 5.7 mo; HR = 0.62, 95% CI [0.45, 0.88], *P*= 0.0064). This benefit of L+T was consistent in key subgroups. mPFS with L vs T was 8.3 vs 5.7 mo (HR = 0.71, 95% CI [0.51, 0.98], *P*= 0.0361). ORR with L+T, T, and L was 32%, 14%, and 19% respectively. OS data are immature. Most common adverse events (AEs) with L+T, T and L (≥15%, any arm) were diarrhea (69%, 9%, 51%), rash (36%, 2%, 28%), nausea (22%, 9%, 22%), and paronychia (30%, 0, 15%). Hepatic abnormalities of > 3 ULN ALT/AST levels were noted in 4%, 6%, and 16% respectively. Incidence of tx-related SAEs was 5%, 2%, and 4% and on-tx deaths was 3%, 4%, and 5%, respectively. **Conclusions:** Dual HER2 blockade with L+T+AI showed superior PFS benefit vs T+AI, in pts with HER2+, HR+ MBC. Incidence of AEs was increased with L+T. This combination can potentially offer an effective CT-sparing tx option in subgroup of HER2+, HR+ pts without aggressive disease and who are not candidates for CT. Clinical trial information: 2010-019577-16.

1005 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

TBCRC 022: Phase II trial of neratinib + capecitabine for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM). *First Author: Rachel A. Freedman, Dana-Farber Cancer Institute, Boston, MA*

Background: Evidence-based treatments (tx) for metastatic, HER2+ BCBM are limited. We previously found a central nervous system (CNS) objective response rate (ORR) of 8% (95% CI 2-22%) for the irreversible, EGFR/HER2-targeted kinase inhibitor, neratinib. To enhance CNS activity, we evaluated the combination of neratinib + capecitabine in a subsequent cohort, and report results here. **Methods:** Pts with measurable BCBM (≥ 1 cm in longest dimension) and no prior lapatinib or capecitabine were eligible. All but 3 had CNS progression after local CNS tx. During 21 day cycles, pts received capecitabine 750 mg/m2 twice daily x 14 days followed by 7 days off + neratinib 240 mg orally once daily. Loperamide prophylaxis (16 mg total daily) was recommended during cycle 1. Brain MRI and non-CNS imaging were repeated every 2 cycles until 18 wks, then every 3 cycles. The primary endpoint was composite CNS ORR, requiring all of the following: ≥50% reduction in volumetric sum of target CNS lesions (central review, VORR), no progression of non-target or non-CNS lesions, no new lesions, no escalating steroids, and no progressive neurologic signs/symptoms. We used a two-stage design with hypotheses ORR 15% and 35% (error rates 5% and 20%), responses in ≥5/19 pts to enter 2ndstage; responses in ≥9/35 [26%] pts to be promising. **Results:** 39 pts enrolled between 4/2014-11/2016 (2 withdrew before tx, 37 analyzed); median age 51, median prior metastatic lines 2 (range 0-6), 65% had prior WBRT. As of 11/15/16, 23 (62%) patients are alive and 7 remain on protocol tx; median number of cycles initiated = 5 (range 1-26). 18 women (49%) had a VORR (95% CI 32-66%, neurologic exams not yet available on all pts). Overall 12-month survival is 63% (95% CI 43%-77%); 4/7 pts still on protocol therapy have not yet reached 6 cycles. No pts had grade 4 toxicity; 18 (49%) had grade 3 toxicity, with diarrhea most common (32%), and 6 pts discontinued tx for toxicity. **Conclusions:** The combination of neratinib and capecitabine is active for BCBM with VORR in nearly half of pts, supporting further development of the regimen for BCBM. Updated results will be presented at the meeting. Clinical trial information: NCT01494662.

1006 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Association of a four-gene decision tree signature with response to platinum-based chemotherapy in patients with triple negative breast cancer. *First Author: Jelmar Quist, King's College London, London, United Kingdom*

Background: Approaches to capture the molecular complexity of triple negative breast cancers (TNBCs) are lacking. We sought to classify TNBCs into subgroups with common biological features based on transcriptomic and genomic data using a Bayesian algorithm. **Methods:** Matched gene expression and copy number microarray data was available for the Guy's (n = 88) and METABRIC (n = 112) TNBC cohorts. CONEXIC was used to derive a decision tree signature for classification. Performance of the signature was tested in 7 TNBC cohorts (total n: 1,368), including 2 clinical trials assessing the efficacy of gemcitabine and carboplatin with and without iniparib. In the early-stage PrECOG 0105 Phase II neoadjuvant trial (n = 43), subtypes were evaluated in relation to response by residual cancer burden (RCB). In the metastatic Sanofi Phase III trial (n = 224), subtypes were assessed by RECIST. Results were compared to the BL1 TNBCtype-4 subtype and assessed using a multivariate analysis. **Results:** The integrative analysis using CONEXIC identified a four-gene signature. Across 7 TNBC cohorts this classification identified 6 entities, including 5 smaller groups and 1 major. Characterisation of the latter subgroup, referred to as MC6, revealed enrichment of CD4+ and CD8+ immune signatures, increased genomic instability and reduction in negative regulation of the MAPK signalling pathway. In PrECOG, 25 out of 41 MC6-TNBCs (61%, OR = 1.19, 95% CI = 0.37 to 3.81, P = 0.79) had RCB 0/I. Similarly, 65% of the BL1-TNBCs had an RCB 0/I, however in a smaller population (11 out of 17, OR = 1.30, 95% CI = 0.35 to 5.31), P = 0.77). In Sanofi Phase III, the objective response rate (ORR) in MC6-TNBCs was 46% versus 30% in non-MC6-TNBCs (OR = 1.97, 95% CI = 1.03 to 3.77, P = 0.04), in comparison to BL1-TNBCs with an ORR of 41% versus 32% in non-BL1-TNBCs (OR = 1.47, 95% CI = 0.75 to 2.86), P = 0.26). **Conclusions:** These results demonstrate that a four-gene signature can identify a subgroup of TNBCs responsive to platinum-based chemotherapy in the metastatic setting. The distinct features of these TNBCs suggest investigation of alternative actionable interventions with immunotherapy or MEK inhibitors in relation to this signature.

1007 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Final results of a phase 2 study of talazoparib (TALA) following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline *BRCA1/2* mutations (ABRAZO). *First Author: Nicholas C. Turner, Royal Marsden Hospital, The Institute of Cancer Research, London, United Kingdom*

Background: TALA is a dual-mechanism PARP inhibitor that traps PARP on DNA. This study was designed to assess the activity of TALA in pts with g*BRCA1/2*mutation previously exposed to platinum or multiple prior cytotoxic regimens. **Methods:** ABRAZO (NCT02034916) is a 2-cohort, 2-stage phase 2 study of TALA (1 mg/d) following platinum-based therapy (Cohort 1 [C1]) or ≥ 3 platinum-free cytotoxic-based regimens (Cohort 2 [C2]) in pts with locally advanced or metastatic breast cancer (MBC) and g*BRCA1/2*mutation. Pts had ECOG PS ≤ 1 and measurable disease by RECIST v1.1. Five responses per cohort were required in ≤ 35 pts to progress to stage 2. The primary endpoint was confirmed ORR by independent radiology facility (IRF). Secondary endpoints: clinical benefit rate ≥ 24 weeks (CBR24), DOR, PFS, and OS. **Results:** From May 2014 to Feb 2016, 84 pts were enrolled (C1, n = 49; C2, n = 35). At data cutoff (1 Sep 2016), 9 pts continued on treatment. Both cohorts proceeded to stage 2 before enrollment closed. Median age was 50 (range, 31–75) years; 58% of pts had an ECOG PS of 0. TNBC/HR+ incidence in C1 and C2 was 59%/41% and 17%/83%, respectively. Median number of prior cytotoxic regimens administered for advanced disease was 2 in C1 and 4 in C2. ORR by IRF for *BRCA1/BRCA2* was 24%/34%, and ORR by IRF for TNBC/HR+ was 26%/29%. Common all grade AEs: anemia (52%), fatigue (45%), nausea (42%), diarrhea (33%), thrombocytopenia (33%), and neutropenia (27%). Grade ≥ 3 AEs: anemia (35%), thrombocytopenia (19%), and neutropenia (15%). Nonhematological AEs grade ≥ 3 did not occur. AEs related to TALA led to drug discontinuation in 3 pts (4%); 4 AEs resulted in death, none related to TALA. **Conclusions:** TALA was well tolerated in MBC pts with a g*BRCA1/2* mutation, exhibiting promising antitumor activity in C1 and C2. TALA vs physician's choice of treatment in g*BRCA1/2*-mutated MBC is being evaluated in the phase 3 EMBRACA trial (NCT01945775). Clinical trial information: NCT02034916.

	C1 (n = 48)	C2 (n = 35)
ORR by IRF, n (% [95% CI])	10 (21% [10, 35])	13 (37% [21, 55])
DOR by IRF, mo (95% CI)	5.8 (2.8, not reached)	3.8 (2.8, 10.1)
CBR24 by INV, n (% [95% CI])	18 (38% [24, 53])	23 (66% [48, 81])
PFS by INV, mo (95% CI)	4.0 (2.8, 5.4)	5.6 (5.5, 7.8)

1008 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A. *First Author: Sylvia Adams, Perlmutter Cancer Center, New York University School of Medicine, New York, NY*

Background: In KEYNOTE-012, pembro showed durable activity and manageable safety in patients (pts) with PD-L1+ mTNBC. Cohort A of KEYNOTE-086 (NCT02447003) examined the efficacy/safety of pembro in previously treated mTNBC, regardless of PD-L1 expression. **Methods:** Pts with centrally confirmed mTNBC, ≥1 prior chemotherapy for metastatic disease, and ECOG PS 0-1 had pembro 200 mg Q3W for up to 24 mo; imaging q 9 wk for the first 12 mo, then q 12 wk. Clinically stable pts with PD could remain on pembro until PD confirmed on next assessment. Primary endpoints: ORR (RECIST v1.1, central review) in all pts and pts with PD-L1+ tumors, and safety. Secondary endpoints: DOR, disease control rate (DCR; CR + PR + SD ≥24 wk), PFS, and OS. Planned enrollment was 160 pts; analysis based on data as of Nov 10, 2016. **Results:** 60% of screened PD-L1-evaluable pts had PD-L1+ tumors (combined positive score ≥1%). Of 170 pts enrolled (100% women; median age 54 y), 44% had ≥3 prior lines of therapy, 51% had elevated LDH, 74% had visceral mets and 62% had PD-L1+ tumors. After a median follow-up of 10.9 mo, 9 (5%) pts remained on pembro. Treatment-related AEs (TRAEs) of any grade and grade 3-4 occurred in 60% and 12% of pts, respectively; 4% discontinued due to TRAEs. There were no deaths due to AE. Overall ORR was 5% regardless of PD-L1 expression (Table). Best overall response was 0.6% CR, 4% PR, 21% SD; not evaluable (3%). DCR was 8% (95% CI 4-13). Median DOR was 6.3 mo (range 1.2+ to 10.3+); 5 (63%) responders w/o PD at data cutoff. Median PFS and OS were 2.0 mo (95% CI 1.9-2.0) and 8.9 mo (95% CI 7.2-11.2), with 6-mo rates of 12% and 69%, respectively. ORR was numerically lower in pts with poor prognostic factors (e.g., high LDH, liver/visceral mets; Table). **Conclusions:** In KEYNOTE-086 Cohort A, pembro monotherapy showed manageable safety and durable responses in a subset of pts with heavily pretreated mTNBC. Randomized studies of monotherapy and combination therapy are ongoing. Clinical trial information: NCT02447003.

	ORR, % (95% CI)
Overall	5 (2-9)
PD-L1, + / –	5 (2-11) / 5 (1-13)
ECOG PS, 0 / 1	4 (1-11) / 5 (2-13)
Prior therapy, 2&3L / 4L+	5 (2-12) / 4 (1-12)
LDH, ≤ULN / >ULN	7 (3-15) / 2 (0.1-9)
Liver mets, no / yes	7 (3-12) / 0 (0-NR)
Visceral mets, no / yes	11 (5-24) / 2 (0.5-7)

1009 Poster Discussion Session; Displayed in Poster Session (Board #1), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

LOTUS (NCT02162719): A double-blind placebo (PBO)-controlled randomized phase II trial of first-line ipatasertib (IPAT) + paclitaxel (P) for metastatic triple-negative breast cancer (TNBC). *First Author: Rebecca Alexandra Dent, Division of Medical Oncology, National Cancer Centre, Singapore, Singapore*

Background: The oral Akt inhibitor IPAT is being evaluated in cancers with a high prevalence of PI3K/Akt pathway activation, including TNBC. **Methods:** Eligible patients (pts) had measurable inoperable locally advanced/metastatic TNBC previously untreated with systemic therapy. Pts were stratified by prior (neo)adjuvant therapy, chemotherapy-free interval and tumor PTEN status, and randomized 1:1 to P 80 mg/m^2 (d1, 8 & 15) with either IPAT 400 mg or PBO (d1–21) q28d until progression or unacceptable toxicity. Co-primary endpoints were progression-free survival (PFS) in the ITT population and pts with PTEN-low tumors by IHC. Secondary endpoints included objective response rate (ORR), duration of response (DoR) and overall survival in the ITT and IHC PTEN-low populations, efficacy in pts with *PIK3CA/AKT1/PTEN*-altered tumors by next-generation sequencing (NGS), and safety. **Results:** Baseline characteristics were generally balanced between arms. Efficacy is shown below. The most common grade ≥3 AEs (grouped terms) were diarrhea (23% IPAT+P vs 0% PBO+P; no grade 4 or colitis in either arm), neutropenia (18% vs 8%), asthenia (5% vs 6%), peripheral neuropathy (5% vs 5%) and pneumonia (5% vs 0%). More pts receiving IPAT+P than PBO+P had an AE leading to dose reduction of IPAT/PBO (21% vs 6%) or P (38% vs 11%) but median cumulative dose intensity was similar (IPAT/PBO: 99% vs 100%; P: 100% vs 100%). AEs led to IPAT/PBO discontinuation in 13% vs 11% of pts, respectively; 2 pts (3%) discontinued IPAT for grade 3 diarrhea. **Conclusions:** Adding IPAT to P for TNBC modestly improved PFS in the ITT pts. The effect was more pronounced in the prespecified subgroup with *PIK3CA/AKT1/PTEN* alterations, warranting further evaluation of IPAT in these pts. AEs were manageable. Clinical trial information: NCT02162719.

	ITT		PTEN low by IHC		*PIK3CA/AKT1/PTEN*-altered by NGS	
Endpoint	**IPAT+P**	**PBO+P**	**IPAT+P**	**PBO+P**	**IPAT+P**	**PBO+P**
PFS						
Events/pts (%)	39/62 (63)	45/62 (73)	16/25 (64)	18/23 (78)	12/26 (46)	13/16 (81)
Median, mo	6.2	4.9	6.2	3.7	9.0	4.9
HR (90% CI)	0.60 (0.40–0.91)[a]		0.68 (0.39–1.21)[b]		0.44 (0.22–0.87)[b]	
ORR, %	40	32	48	26	50	44
Median DoR, mo	7.9	7.4	6.5	7.5	11.2	6.1

[a]Stratified, [b]Unstratified.

1010 Poster Discussion Session; Displayed in Poster Session (Board #2), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Everolimus (EVE) plus endocrine therapy in patients with estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (BC): First- and second-line data from the BOLERO-4 study. *First Author: Fatima Cardoso, Breast Unit, Champalimaud Clinical Centre, Champalimaud Foundation, Lisbon, Portugal*

Background: Initial first-line (1L) data from the phase 2 BOLERO-4 (NCT01698918) study of EVE + letrozole (LET) in postmenopausal patients (pts) with ER+, HER2− metastatic BC (MBC) or locally advanced BC (LABC) have been previously reported. Here, we present updated 1L progression-free survival (PFS) data, plus new data describing second-line (2L) EVE + exemestane (EXE) in pts with disease progression after EVE + LET. **Methods:** Postmenopausal pts with ER+, HER2− MBC or LABC with no prior therapy for advanced disease received EVE 10 mg/day + LET 2.5 mg/day. After disease progression, pts could receive EVE + EXE 25 mg/day until further disease progression, unacceptable toxicity, or withdrawal of consent. Primary endpoint: 1L PFS. Secondary endpoints: overall response rate (ORR), clinical benefit rate (CBR), 2L PFS, overall survival (OS), and safety (1L and 2L). **Results:** Among 202 pts (median age, 64 years) with 1L MBC (96%) or LABC (4%), median PFS (95% CI) was 21.7 (18.123.9) months, ORR was 43.6%, and CBR was 74.3%. 42 pts (median age, 62 years) with MBC (88%) or LABC (12%) who progressed on 1L EVE + LET received optional 2L EVE + EXE. 2L median PFS (95% CI) was 3.7 (1.89.1) months, ORR was 4.8%, and CBR was 21.4%. Common 1L adverse events (all grades, regardless of drug relationship) were stomatitis (69%), weight loss (44%), diarrhea (40%), nausea (37%), and anemia (35%); 2L adverse events included stomatitis (19%) and weight loss (19%). Median duration of follow-up from start of 1L to the data cutoff for these new analyses (17 June 2016) was 23.5 months. OS will be analyzed at a later data cut. **Conclusions:** EVE + LET is an effective regimen in 1L ER+, HER2− advanced BC. Thesedata support previously reported BOLERO-2 data demonstrating a PFS improvement from addition of EVE to an aromatase inhibitor. 2L data, although limited by the small number of pts, show preliminary evidence of EVE activity when continued beyond disease progression. No new safety signals were seen. Lower rates of stomatitis in 2L were noted. Clinical trial information: NCT01698918.

1011 Poster Discussion Session; Displayed in Poster Session (Board #3), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

LCCC 1025: Phase II study of everolimus, trastuzumab, and vinorelbine for HER2+ breast cancer brain metastases (BCBM). *First Author: Carey K. Anders, University of North Carolina, Chapel Hill, NC*

Background: HER2+ BC is an aggressive subset of BC with high rates of BM and poor survival. Two-thirds of BCBM demonstrate activation of the PI3K/mTOR pathway driving resistance to anti-HER2 therapy (Rx). This phase II study evaluated everolimus (E), a brain permeable mTOR inhibitor, added to trastuzumab (T) and vinorelbine (V) in patients (pts) with HER2+ BCBM. **Methods:** Eligible pts had progressing HER2+ BCBM. Pts received E (5mg PO QD), T (2mg/kg IV weekly) and V (25mg/m^2 IV d1, 8 of 21d cycle). The primary endpoint was intracranial response rate (RR [CR+PR], modified RECIST); secondary objectives (CNS clinical benefit rate [CBR, CR+PR+SD], extracranial RR, time to progression (TTP), overall survival (OS), and correlative studies). Targeted DNA sequencing of 20 tissues from 18 pts was performed. We used a two-stage design to distinguish ORR of 5% vs 20%. **Results:** 32 pts were evaluable for toxicity; 26 for efficacy. Median age was 53 (28–70 yrs). 31/32 pts had prior radiation: 13 (42%) WBRT, 8 (26%) radiosurgery, 9 (29%) both. Median prior lines of metastatic Rx was 2 (0–7). 30 (94%) received anti-HER2 Rx: 91% T, 69% lapatinib, 38% pertuzumab, 25% TDM1. Intracranial RR was 4% (1 PR, 6 SD > 6 mos, 10 SD > 3 mos, 9 PD). CNS CBR (6 mos) was 27%; CNS CBR (3 mos) was 65%. Extracranial RR was 46%. Median TTP was 4 mos (95% CI, 2.2 –5). OS was 12.2 mos (95% CI, 0.6 – 20.2). Grade 3-4 toxicities included neutropenia (41%), anemia (16%), and stomatitis (16%). DNA sequencing showed heterogeneous HER2 copy number amplification (CN amp): only 11/20 show HER2 CN amp (median 40X v 0.7X; 5/11 BC, 4/4 BCBM, 1/2 liver mets, 1/3 LN). BCBM exhibited high-level HER2 CN amp (median 49X) vs other sites (16X). While 11/20 show both HER2 CN amp and PI3K pathway mutation, this was not associated TTP; RAD21 CN amp was associated with TTP < 3 mos. Lack of HER2 CN amp plus a HER2 Tyr-kinase domain mutation was seen in a pt with nonresponse and short OS. **Conclusions:** While intracranial RR to ETV was low in pts with HER2+ BCBM, a substantial proportion had CNS CBR; OS was 1 year for this pt population. No new toxicity signals were observed. Further evaluation of DNA heterogeneity, including degree of HER2 CN amp in HER2+ BCBM, and association with outcome is warranted. Clinical trial information: NCT01305941.

1012 Poster Discussion Session; Displayed in Poster Session (Board #4), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Evaluating the addition of bevacizumab (Bev) to endocrine therapy as first-line treatment for hormone-receptor positive (HR+)/HER2-negative advanced breast cancer (ABC): Pooled-analysis from the LEA (GEICAM/2006-11_GBG51) and CALGB 40503 (Alliance) trials. *First Author: Miguel Martin, Hospital Gregorio Maranon, Universidad Complutense., Madrid, Spain*

Background: Data from randomized trials comparing ET v ET-Bev in 1st line HR+/HER2- ABC pts showed controversial results. We performed a pooled-analysis of two randomized trials (LEA and CALGB 40503) to refine the Bev value in this patient population. **Methods:** We analysed 749 ABC pts with ET (letrozole-673, tamoxifen-39, fulvestrant 250mg-37) +/- Bev. Primary objective was to compare progression-free survival (PFS). Secondary endpoints were: safety; other efficacy (overall response rate [ORR], clinical benefit rate [CBR] and overall survival [OS]) in all pts; and efficacy in de novo pts and by previous endocrine-sensitivity (-/+ 24 months [mo] without recurrence under ET in adjuvant setting). Multivariable Cox models were fitted for PFS adjusted by study co-variables and controlled for study level differences. **Results:** Median age was 61 years (yr) (range: 25-87); 40% had de novo ABC and 60% recurrent disease (with disease free interval of $\leq$ 1 yr in 5%, 1-2 yr in 7% and $>$ 2 yr in 88%); 82% of recurrent pts had previous ET sensitivity. Median PFS was 14.3 mo in the ET arm v 19 mo in the ET+Bev arm (HR 0.77; 95% CI 0.66-0.91; $p<0.01$). ORR and CBR with ET v ET+Bev were 40 v 61% ($p<0.01$) and 64 v 77% ($p<0.01$). OS did not differ between arms (HR 0.96; 95% CI 0.77-1.18; p=0.68). PFS for de novo ABC pts was 14.6 and 19.3 mo in the ET and ET+Bev arms (HR 0.82; 95% CI 0.63-1.06; p=0.13). PFS differed between arms for previous sensitive pts (HR 0.68; 95% CI 0.53-0.89; p=0.004) but not for ET-resistant pts (HR 0.73; 95% CI 0.4-1.3; p=0.29). Grade 3-5 hypertension (2.2 v 20.1%), proteinuria (0 v 9.3%), cardiovascular events (0.5 v 4.2%) and liver events (0 v 2.9%) were significantly higher in the ET+Bev arm (all $p<0.01$). Multivariable analyses showed age ($p<0.01$), PgR status ($p<0.01$), type of prior ET ($p<0.01$) and treatment arm ($p<0.01$) to be associated with PFS. **Conclusions:** The addition of Bev to ET increased PFS but not OS. Analyses to define subgroups with prolonged benefit from ET alone or ET-Bev are ongoing. Support: U10CA180821, U10CA180882, Breast Cancer Research Foundation, Genentech, Roche. Clinical trial information: NCT00545077 / NCT00601900.

1013 Poster Discussion Session; Displayed in Poster Session (Board #5), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

FGFR gene amplification and response to endocrine therapy in metastatic hormone receptor positive (HR+) breast cancer. *First Author: Joshua Z. Drago, Massachusetts General Hospital, Boston, MA*

Background: Amplification in Fibroblast Growth Factor Receptor (FGFR) genes occurs in 10% of breast cancers, is associated with poor prognosis, and appears to drive resistance to endocrine therapies in vitro. However, the role of FGFR in modulating the clinical response to endocrine therapies is unclear, and could have important implications given that FGFR is a potential therapeutic target. This study aims to evaluate the association between FGFR amplification and clinical response to endocrine therapy in HR+ metastatic breast cancer (MBC). **Methods:** Primary or metastatic tumor specimens from patients with HR+/HER2 negative MBC underwent dual-color fluorescence in situ hybridization (FISH) of the FGFR1 locus on chromosome 8p. FISH ratios of $\geq$2 were considered positive for gene amplification (FGFR+). Time to progression (TTP) on first line endocrine therapy was evaluated in FGFR+ versus wild type (WT) patients using actuarial analysis. **Results:** Between 2012 and 2016, we identified 95 patients with HR+ MBC who underwent FGFR FISH testing. Of these, 24 (25.3%) were FGFR+. FGFR+ and WT patients did not differ in being postmenopausal at initial breast cancer diagnosis (28.6% vs. 31.7%; p = 1.0), having de-novo MBC (16.7% vs. 21.1%; p = 0.773), having received adjuvant chemotherapy (75% vs. 76.8%; p = 1.0) or having received adjuvant endocrine therapy (90% vs. 91.1%; p = 1.0). However, FGFR+ patients tended to be younger than WT patients (54.3 vs. 59.3 years; p = 0.045), and more likely to have PR-negative MBC (50.0% vs. 19.1%; p = 0.011). While there was no difference in TTP on first-line chemotherapy in FGFR+ vs. WT patients (5.0 vs. 6.2 months; p = 0.8), FGFR+ patients had a shorter median TTP on first-line endocrine therapy than WT (8.5 vs. 10.8 months; p = 0.047). These results were similar when stratified by presence of de-novo metastatic disease. **Conclusions:** In patients with HR+ MBC, FGFR gene amplification is associated with shorter time to progression on first line endocrine therapy. Further studies are needed to confirm these findings, and to investigate potential strategies for endocrine therapy and FGFR-directed combinatorial therapy in FGFR+ breast cancer.

1014 Poster Discussion Session; Displayed in Poster Session (Board #6), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Evaluation of RAD1901, a novel investigational, selective estrogen receptor degrader (SERD), for the treatment of ER-positive (ER+) advanced breast cancer. *First Author: Aditya Bardia, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: The treatment of advanced ER+ breast cancer remains a clinical challenge with the majority of patients eventually progressing due to resistance to endocrine therapy. RAD1901 is a novel, nonsteroidal, oral SERD that has demonstrated dose dependent degradation of ER, and ER regulated genes in preclinical studies. In multiple in vivo patient derived xenograft models of breast cancer, including those harboring ESR1 mutations, RAD1901 demonstrated significant antitumor activity. **Methods:** In a phase-1 Study RAD1901-005 (ClinicalTrials.gov ID: NCT02338349), patients with advanced ER+ breast cancer were enrolled in dose escalation cohorts, followed by a safety expansion cohort. Key inclusion criteria include postmenopausal women aged 18 years or older, with advanced ER+, HER2- breast cancer, who have received $\leq$ 2 prior chemotherapy regimens in the metastatic setting and $>$ 6 months of prior endocrine therapy. ESR1 mutation status was determined from circulating tumor DNA (ctDNA) samples. Clinical outcomes were evaluated based on RECIST v1.1 criteria. **Results:** As of January 25, 2017, total of 39 patients were enrolled at the 400 mg qd dose. Patients were heavily pre-treated (median lines of prior therapy = 3), with 38% and 41% having previously received fulvestrant and palbociclib/CDK4/6 inhibitor, respectively. RAD1901 was generally well-tolerated, with the most common adverse events being low grade nausea (Grade 3/4 = 0%) and dyspepsia (Grade 3/4 = 0%). ESR1 mutations, including D538G, Y537S/N/C, L536H/P/R, S436P and E380Q, were detected at baseline in 44% of patients and dynamic changes in the allele frequency of ESR1 mutations were observed in response to treatment. Confirmed partial responses were observed in patients with ESR1 mutations, and those who had previously received fulvestrant and palbociclib. **Conclusions:** RAD1901 has demonstrated evidence of single agent activity, with confirmed partial responses in heavily pre-treated patients with advanced ER+ breast cancer, including those with ESR1 mutations, warranting additional clinical development. Clinical trial information: NCT02338349.

1015 Poster Discussion Session; Displayed in Poster Session (Board #7), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA (ctDNA) in metastatic breast cancer. *First Author: Charlotte Victoria Fribbens, Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: Selection of resistance mutations may play a major role in the development of endocrine resistance. *ESR1* mutations are rare in primary breast cancer but have a high prevalence in patients treated with aromatase inhibitors (AI) for advanced breast cancer. We investigated the evolution of genetic resistance to first line AI therapy using sequential ctDNA sampling in patients with advanced breast cancer. **Methods:** Seventy-one patients on first line AI therapy for metastatic breast cancer were enrolled in a prospective study to collect plasma samples for ctDNA analysis every three months on therapy, and at disease progression. All plasma samples were analysed with *ESR1* multiplex digital PCR assays, and samples at disease progression were analysed by InVision (enhanced tagged-amplicon sequencing). Mutations were tracked back through samples prior to disease progression to study the evolution of mutations on therapy. **Results:** Of the 34 patients who progressed on first line AI, 53% (18/34) had *ESR1* mutations detectable at progression. Sequencing of progression plasma ctDNA identified polyclonal *RAS* mutations in 10.7% (3/28) progressing patients (2 polyclonal *KRAS*, 1 monoclonal *HRAS*), all of whom also had *ESR1* mutations, and a patient with an activating p.R248C *FGFR3* mutation. *ESR1* mutations were subclonal in 78.6% (11/14) patients, with all *RAS* mutations being rare subclones. In serial tracking prior to progression, *ESR1* mutations were detectable in plasma with a median of 5.3 months (95% CI 2.9-NA) prior to clinical progression. **Conclusions:** *ESR1* mutations are found at high frequency in patients progressing on AI, but are frequently subclonal and may not be the sole driver of AI resistance in these patients. Polyclonal *KRAS* mutations are identified as a novel mechanism of resistance to AI, associated with detection of *ESR1* mutations.

1016 Poster Discussion Session; Displayed in Poster Session (Board #8), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Genomic profiling of circulating tumor DNA (ctDNA) from patients (pts) with metastatic breast cancer (mBC). *First Author: Lajos Pusztai, Yale Cancer Center, New Haven, CT*

Background: Clonal evolution during progression to and treatment of mBC highlights the importance of genomic profiling of recent samples to guide clinical decision making. We undertook this study to characterize genomic alterations (GA) in ctDNA from pts with mBC during the course of clinical care. **Methods:** Hybrid-capture based genomic profiling of 62 genes (FoundationACT) was performed on ctDNA from 255 BC pts. The fraction of ctDNA in the blood was estimated using the maximum somatic allele frequency (MSAF) for each sample. **Results:** 168 pts were ER+ [16 HER2+, 134 HER2(-), 18 HER2 unknown (unk)]; 51 were ER(-) [7 HER2+, 38 triple negative (TNBC), 6 HER2 unk]; 36 were ER unk; 95% were stage 4. For pts with treatment information, 90% had prior chemotherapy and 90% ER+ pts had prior aromatase inhibitor therapy (AI). ≥1 GA was reported in 78% of all cases and in 88% of cases with evidence of ctDNA in the blood (MSAF >0). For 226 cases with MSAF >0, an average of 2.7 GA/case were reported. The most common GA for ER+ pts were in *TP53* (44%), *PIK3CA* (39%), *ESR1* (36%), *CDH1* (11%), *KRAS* (10%) and *ERBB2* (*HER2,* 9%). 101 *ESR1* GA were identified in 61 pts [54 ER+, 7 ER unk], including 4 HER2+ pts. For ER+ pts with treatment information: 37% (22/60) with prior AI had *ESR1* GA; all pts with *ESR1* GA had prior AI. 24 pts had >1 *ESR1* GA, with instances of GA in *cis*. Frequent *ESR1* GA were Y537S/N (n=47), D538G (n=29) and E380Q (n=7); rearrangement (n=3) and amplification (n=1) were also detected. Concurrent GA with *ESR1* were found in *PIK3CA* (41%), *FGFR1* (13%), *BRCA1/2* (5%), *HER2* (5%) and *AKT1* (3%). In ER(-) pts, the most common GA were in *TP53* (74%), *PIK3CA* (17%), *NF1* (11%), *BRCA1* (9%) and *EGFR* (9%). *HER2* activating mutation occurred in 3% of cases that were HER2(-) by prior testing. Kinase fusions in *FGFR2/3* (3 ER+) and *EGFR* (1 TNBC) were observed. **Conclusions:** In this study, evidence of ctDNA in the blood was observed in 89% of cases. *PIK3CA* and *ESR1* GA frequencies were similar to those reported in previous studies of ctDNA from ER+ pts after AI. Diverse *ESR1* GA and co-occurring GA suggest therapeutic approaches for AI refractory ER+ mBC. Our results demonstrate that genomic profiling of ctDNA may be a complementary approach to tissue-based genomic testing for pts with mBC.

1017 Poster Discussion Session; Displayed in Poster Session (Board #9), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Genomic alterations driving breast cancer (BC) metastases and their relationship with the subtype switch in the GEICAM ConvertHER study. *First Author: Joan Albanell, Medical Oncology, Hospital del Mar, Barcelona, Spain*

Background: To understand the mechanisms underlying the evolution of tumors in the process of metastasis, we studied 61 paired primary-relapse BC from the GEICAM ConvertHER study. While some of the metastases maintained the clinical (ER/PR and HER2 status) and/or intrinsic subtype (defined by expression arrays) of the original tumor (concordant), others exhibited a subtype shift (discordant). We aimed to identify the genomic alterations driving the metastases and, particularly, their relationship with the subtype switch. **Methods:** We detected the somatic variants (mutations and copy number alterations (CNAs)) affecting 202 genes across the 61 sample pairs via targeted sequencing. We employed the Cancer Genome Interpreter (cancergenomeinterpreter.org), a bioinformatics approach to identify the alterations most likely driving tumorigenesis, and subsequently identified those whose cancer cell fraction markedly changed in the metastases. We explored the clonal remodeling in metastasis comparing the cell fractions of driver mutations in both concordant and discordant tumors. **Results:** We found that 156 genes had 747 somatic mutations and 171 genes suffered 1042 somatic CNAs in the 61 studied tumor pairs. We identified a median of 11 and 9 mutations in primaries and metastases, respectively. Several frequent BC mutational drivers, such as *TP53*, *PIK3CA*, *MLL3*, *MAP3K1*, and *NOTCH2* were amongst the more frequently changed their cancer cell fraction in metastases with respect to primaries. We found that driver mutations of discordant tumors exhibited a significantly higher increase of clonal cell fraction. Moreover, whether the clonal status of a driver mutation was conserved in the metastasis was significantly associated to whether the tumor maintains its clinical subtype but not its intrinsic subtype. **Conclusions:** Our results suggest that a shift in the clinical subtype of BC undergoing metastasis is accompanied by more significant changes at the genomic level than those suffered by tumors that maintain their clinical subtype. This remodeling of the landscape of drivers could open new therapeutic opportunities to specifically target discordant BC.

1018 Poster Discussion Session; Displayed in Poster Session (Board #10), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Predicting sensitivity to palbociclib with early circulating tumor DNA dynamics in the PALOMA-3 trial. *First Author: Ben O'Leary, Royal Marsden Hospital, The Institute of Cancer Research, London, United Kingdom*

Background: Palbociclib improves progression free survival (PFS) in patients with advanced, hormone receptor positive, HER2-negative breast cancer. There are currently no biomarkers to predict sensitivity to palbociclib. We investigated if early circulating tumour DNA (ctDNA) dynamics could predict clinical outcome on palbociclib (Palbo) and fulvestrant (F) in the PALOMA-3 trial. **Methods:** Plasma samples were prospectively collected in PALOMA-3 for ctDNA analysis at baseline, cycle 1 day 15 (D15) and end of treatment (EOT), and were screened for *PIK3CA* and *ESR1* mutations using digital PCR. The primary objective was to assess whether early dynamic changes in *PIK3CA* mutations would predict PFS in patients treated with Palbo + F. Suppression of *PIK3CA* ctDNA levels below an optimised cut-off at cycle 1 D15, relative to baseline levels, was termed a 'circulating DNA ratio (CDR) response. **Results:** *PIK3CA* mutations were identified in 22.0% (100/455) of screened baseline samples with 52 of these randomised to Palbo + F and having matched D15 samples. Patients on Palbo + F with a CDR response had a median PFS of 11.2 months (95%CI 11.1 – undefined) whereas patients on Palbo + F without a CDR response had a median PFS of 4.1 months (95%CI 3.6 – 5.5) (HR for no CDR response 4.92, 95% CI 1.98 – 12.26, p = 0.0002). Overall, Palbo + F suppressed D15 *PIK3CA* ctDNA levels to a greater extent than placebo + F (p<0.0001). *ESR1* mutations were identified in 25.6% (114/445) of screened baseline samples, 65 having matched D15 samples. *ESR1* mutations showed greater ctDNA suppression than *PIK3CA* mutations, and were more frequently undetectable at EOT (25.8% *ESR1* undetectable 8/31, v 2.6% for *PIK3CA*, 1/38, p=0.004). Clearance of *ESR1* mutation at EOT was associated with early loss of *ESR1*at D15 (p = 0.027). **Conclusions:** Early circulating tumor DNA assessment may predict sensitivity to palbociclib and fulvestrant, and if validated by further analysis may allow treatment to be adapted prior to progression. *ESR1* mutations are frequently lost after treatment with palbociclib and fulvestrant.

1019 Poster Discussion Session; Displayed in Poster Session (Board #11), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Abemaciclib for the treatment of brain metastases (BM) secondary to hormone receptor positive (HR+), HER2 negative breast cancer. *First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Boston, MA*

Background: Abemaciclib is an oral selective CDK4 and CDK6 inhibitor administered on a continuous dosing schedule, which has demonstrated clinical activity and an acceptable safety profile in patients (pts) with heavily pre-treated HR+ metastatic breast cancer (MBC). Abemaciclib has been shown preclinically to cross the blood-brain barrier, providing rationale for testing this agent in pts with BM. Furthermore, as previously presented, levels of abemaciclib similar to plasma were detected in resected BM in a subset of pts with HR+, HER2- MBC in this study. **Methods:** Study I3Y-MC-JPBO is an open-label, Phase 2, Simon 2-Stage trial evaluating the safety and efficacy of abemaciclib 200 mg BID in pts with new or progressive BM secondary to HR+ MBC, NSCLC, or melanoma. Eligible pts in Part B (the focus of this presentation) include pts with HR+, HER2- MBC who have ≥1 measurable brain lesion. The primary objective was objective intracranial (IC) response rate as defined by Response Assessment in Neuro-Oncology BM response criteria. Secondary objectives (IC related) include best overall response, duration of response, disease control rate, and clinical benefit rate. Exploratory objectives include assessment of drug concentrations in resected tumors. Safety, tolerability, and PK of abemaciclib were also assessed. Stage 1 includes 23 pts; if < 2 of the 23 pts respond to abemaciclib, futility is met. However, if ≥2 respond, 33 additional pts are to be enrolled to Stage 2. **Results:** This Stage 1 efficacy analysis included 23 pts; 32 pts were included in the safety analysis. Although 5 pts were considered nonevaluable, 2 pts (8.7%) had confirmed partial response (PR) (meeting the predefined threshold for advancement to Stage 2); enrollment is ongoing. At the time of the analysis, the 2 pts with PR had completed 14 and 15 cycles each (21d cycles) of therapy. The majority of adverse events were gastrointestinal in nature, consistent with previous studies of abemaciclib. **Conclusions:** This study has provided preliminary evidence that abemaciclib penetrated BM in pts with HR+, HER2- MBC and had antitumor activity in this population. Final results will be presented following Stage 2 analyses. Clinical trial information: NCT02308020.

1020 Poster Discussion Session; Displayed in Poster Session (Board #12), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Health-related quality of life (HRQoL) of postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) treated with ribociclib + letrozole: Results from MONALEESA-2. *First Author: Sunil Verma, Tom Baker Cancer Centre, Calgary, AB, Canada*

Background: In the MONALEESA-2 trial, ribociclib + letrozole significantly improved progression-free survival (PFS) and showed higher overall response rates vs letrozole alone in HR+, HER2− ABC. To place these clinical results in the context of patient experience, here we present key patient-reported outcomes (PROs) including HRQoL. **Methods:** 668 patients were randomized (1:1); 334 each to the ribociclib + letrozole and placebo + letrozole arms. PROs were evaluated during treatment and at progression using the EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L questionnaires. Changes from baseline in all subscales were analyzed using a linear mixed-effect model and time to 10% deterioration was compared between treatment arms using the stratified log-rank test. **Results:** Questionnaire compliance rates were high (≥90%). During treatment, HRQoL (global health status/QoL score) was maintained and similar in both treatment arms. At progression/end of treatment, HRQoL worsened numerically in both arms. Time to definitive 10% deterioration of HRQoL was similar between treatment groups, slightly favoring the ribociclib + letrozole arm (hazard ratio: 0.89; 95% confidence interval: 0.67–1.18). No statistically or clinically relevant differences were observed for key symptoms using EORTC QLQ-C30 including fatigue, nausea, and vomiting. There was a clinically relevant ($>$ 5 points) improvement in pain from baseline to post-baseline (up to Cycle 15) in the ribociclib + letrozole arm while there was only mild improvement ($<$ 5 points) observed in the placebo + letrozole arm. **Conclusions:** In addition to significantly improving PFS, ribociclib + letrozole maintains HRQoL when compared with letrozole + placebo. A numerical trend was observed favoring ribociclib + letrozole for pain reduction. Clinical trial information: NCT01958021.

1021 Poster Session (Board #13), Sun, 8:00 AM-11:30 AM

Long-term survival of de novo stage IV human epidermal growth factor receptor 2 (HER2)-positive breast cancers treated with HER2 targeted therapy. *First Author: Yao Wong, Yale School of Medicine, New Haven, CT*

Background: An increasing number of metastatic HER2 positive cancers represent *de novo* stage IV disease as fewer early stage patients relapse. We hypothesize that a subset of these has long progression free survival (PFS) after initial combined modality HER2-targeted therapies. **Methods:** 483 patients with *de novo* stage IV HER2 positive breast cancer diagnosed between 1998-2015 were identified through the medical records at Yale and MD Anderson Cancer Centers, respectively. Treatment, clinical variables and survival were extracted and compared between those who achieved "no evidence of disease" (NED) status with initial therapy and those who did not. **Results:** All patients received trastuzumab and 94 (20%) also received pertuzumab as first line therapy.The median OS was 5.5 years (95% CI: 4.8-6.2); OS rates at 5 and 10 years were 54% (95% CI: 48%-60.4%) and 18% (95% CI: 11.4%-28.3%), respectively and PFS were 41% (95% CI: 35%-48%) and 41% (95% CI: 35%-48%). Sixty-three patients (13.0%; 95% CI: 10.2% -16.4%) achieved NED. The PFS and OS at 5 and 10 years were the same 100% and 98% (95% CI: 94.6%-100%), respectively. For patients with no-NED (n = 420), the median OS was 4.7 years (95% CI: 4.2-5.3), the PFS and OS rates at 5 and 10 years were 12% (95% CI: 4.5%-30.4%) and 0% and 45% (95% CI: 38.4%-52.0%) and 4% (95% CI: 1.3%-13.2%), respectively. NED patients had significantly longer progression free survival (log-rank test p≤0.001) and overall survival (log-rank test p≤0.001), more frequently had single organ site metastasis (76% vs 57%, p = 0.005), and more frequently had surgery for primary tumor (59% vs. 25%, p ≤0.001) than no-NED patients, but there was no significant difference in age, grade, race, year of diagnosis, ER status, treatment distribution, or radiation between the groups. **Conclusions:** About 13% of *de novo*, stage IV, HER-2 positive MBC patients achieved NED with HER-2 targeted therapies, all of these patients were progression free at 5 years and overall survival at 10-years was 98% compared to 4% among those with no-NED in our data sets. These results suggest that aggressive multimodality therapy of newly diagnosed stage IV HER2 positive cancers to render them NED may be warranted.

1023 Poster Session (Board #15), Sun, 8:00 AM-11:30 AM

Efficacy of trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (MBC) previously treated with pertuzumab (P). *First Author: Ander Urruticoechea, Onkologikoa Foundation, San Sebastian, Spain*

Background: T-DM1 was approved for pts with HER2+ MBC previously treated with trastuzumab (H) and a taxane based on the phase III EMILIA study. P in combination with H + docetaxel (T) later became the first-line standard of care for HER2+ MBC, but there are limited data on T-DM1 efficacy in pts who previously received P. We present exploratory efficacy results from pts treated with T-DM1 any time after P from 2 phase III studies: CLEOPATRA and PHEREXA. **Methods:** CLEOPATRA (NCT00567190) and PHEREXA (NCT01026142) are randomized, 2-arm trials evaluating P-based regimens for HER2+ MBC. CLEOPATRA studies H + T + P vs HT + placebo in pts with no prior anti-HER2 treatment (tx) or chemotherapy for MBC, while PHEREXA studies H + capecitabine (C) +/− P in pts who progressed during/after previous H tx for MBC. We assessed overall survival (OS) in an exploratory analysis of pts who either received or did not receive T-DM1 at any time after discontinuing study-assigned tx in CLEOPATRA or PHEREXA. **Results:** Of 408 pts who received HTP in CLEOPATRA and 228 pts who received HCP in PHEREXA, 32 and 43 pts received subsequent T-DM1, respectively (Table). Median duration of T-DM1 tx was 7.1 mo (range 0−44) and 4.2 mo (range 0−22), respectively, and median time from discontinuation of P to start of T-DM1 was 3.5 mo (range 1−47) and 10.6 mo (range 1−28). **Conclusions:** Although data are limited in these exploratory analyses, our results provide additional evidence of T-DM1 clinical activity in pts with HER2+ MBC who progressed on prior P + H, a finding with real-world implications. Clinical trial information: NCT00567190, NCT01026142.

	No T-DM1	T-DM1
CLEOPATRA		
HT + placebo, n	362	34
Pts with event, n (%)	198 (54.7)	20 (58.8)
Median OS, mo (95% CI)	39.6 (35–47)	46.2 (34–57)
HR[a](95% CI)		0.93 (0.58–1.49)
		P=0.7538[b]
HTP, n	376	32
Pts with event, n (%)	158 (42.0)	11 (34.4)
Median OS, mo (95% CI)	61.4 (49–NR)	NR (49–NR)
HR[a](95% CI)		0.62 (0.33–1.14)
		P=0.1196[b]
PHEREXA		
HC, n	179	39
Pts with event, n (%)	98 (54.7)	16 (41.0)
Median OS, mo (95% CI)	23.7 (20–29)	40.1 (31–57)
HR[a](95% CI)		0.45 (0.26–0.81)
		P=0.0061[b]
HCP, n	185	43
Pts with event, n (%)	82 (44.3)	16 (37.2)
Median OS, mo (95% CI)	32.8 (28–39)	38.3 (34–NR)
HR[a](95% CI)		0.53 (0.30–0.94)
		P=0.0283[b]

[a]vs no T-DM1. [b]Log-rank P-value. HR, hazard ratio; NR, not reached.

1024 Poster Session (Board #16), Sun, 8:00 AM-11:30 AM

Circulating PD-L1 (programmed death-ligand 1) and outcomes in a HER2-positive metastatic breast cancer cohort treated with first-line trastuzumab. *First Author: Ayesha Ali, Penn State Milton S. Hershey Medical Center, Hershey, PA*

Background: Recently the immune checkpoint inhibitors (ICIs) have demonstrated efficacy across a wide variety of cancers, but have been less effective in breast cancer. PD-L1 (B7-H1, CD274) is a ligand produced by many tumor cells and some immune cells, and suppresses the T cell immune response. This allows tumor cells to escape immune detection. PD-L1 is used as a companion tumor tissue IHC biomarker for patient selection for some of the FDA-approved ICIs (pembrolizumab), but not for others (nivolumab, atezolizumab). Circulating PD-L1 has been detected in multiple myeloma, renal, lung, and gastric cancer, but not in breast cancer. Here we correlated serum PD-L1 levels with outcome in a HER2-positive metastatic breast cancer cohort treated with trastuzumab. **Methods:** Pretreatment serum was obtained from 63 metastatic breast cancer patients before starting first-line trastuzumab-containing therapy. A novel ELLA microfluidic channel immunoassay platform (ProteinSimple, San Jose, CA) was employed to quantitate serum PD-L1. Serum PD-L1 levels were analyzed using continuous, quartile, and dichotomous (25%, median, and 75%) cutpoints. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. **Results:** On a continuous basis, patients with higher serum PD-L1 had a significantly reduced PFS (p = 0.045) and overall survival OS (p = 0.004) compared to patients with lower serum PD-L1 levels. Patients with the higher quartiles of serum PD-L1 also trended to have reduced PFS (0.11) and significantly reduced OS (p = 0.015) compared to the lower quartiles of serum PD-L1. Finally, using either the 25th or 75th percentile of serum PD-L1 as dichotomous cutpoint, patients with higher serum PD-L1 had significantly reduced OS (p = 0.04). **Conclusions:** Higher circulating PD-L1 levels were prognostic for reduced PFS and OS in HER2-positive metastatic breast cancer patients treated with first-line trastuzumab. Circulating PD-L1 deserves further study for prognostic and predictive biomarker utility in larger trials of immune checkpoint inhibitors and other immunotherapies in breast and other cancers. AA, LK contributed equally.

1025 Poster Session (Board #17), Sun, 8:00 AM-11:30 AM

Eribulin in combination with pertuzumab plus trastuzumab for HER2-positive advanced or recurrent breast cancer (JBCRG-M03). *First Author: Kazutaka Narui, Breast and Thyroid Surgery, Yokohama City University Medical Center, Yokohama, Japan*

Background: Pertuzumab (P) provided overall and progression-free survival (PFS) benefits in HER2-positive metastatic breast cancer (MBC) in the CLEOPATRA study as a first-line therapy. However, long-term administration of intravenous docetaxel at a dose of 75 mg/m^2 every 3 weeks in MBC patients is difficult. Eribulin (E) is a well-tolerated cytotoxic agent. We report the efficacy and safety of E in combination with trastuzumab (T) plus P as first- and second-line therapy for metastatic or advanced BC in a multicenter, open-label phase II study (UMIN000012232). **Methods:** HER2-positive advanced or recurrent BC patients with no or a single prior therapy as advanced or recurrent chemotherapy were enrolled. All patients were administered T and taxane as adjuvant or first-line chemotherapy. Treatment consisted of E 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle and T (8 mg/kg loading dose $>$ 6 mg/kg) plus P (840 mg loading dose $>$ 420 mg) once every 3 weeks, all given intravenously. The primary end point was PFS. **Results:** From November 2013 to April 2016, 50 patients were enrolled. Forty-nine patients were eligible for safety analysis; full analysis set (FAS) includes 46 patients. The median patient age was 56 years (range 23–70), and 8 (16%) and 41 (84%) patients were treated in first- and second-line settings, respectively. Twenty-eight patients out of 49 patients (57%) continued the protocol therapy at the end of 8 cycles and median PFS was not yet reached. The response rate by RECIST ver.1.1 was 56.5% in FAS. The relative dose intensity of E, T, and P were 93.3% (range 77.0%–100%), 100% (range 96.0%–100%) and 100% (range 89.7%–100%), respectively in FAS. The grade 3/4 adverse effects (AE) were neutropenia in 5 patients (10.2%) including 2 patients (4.1%) with febrile neutropenia, hypertension in 3 patients (6.1%), and other AEs in only one patient. Average of the ejection fraction did not decrease significantly. Symptomatic left ventricular systolic dysfunction was not observed. **Conclusions:** E in combination with T plus P was well-tolerated and could be an alternative to docetaxel-based combination therapy for HER2-positive MBC. Clinical trial information: 000012232.

1026 Poster Session (Board #18), Sun, 8:00 AM-11:30 AM

Phase I study of alpelisib (BYL-719) and T-DM1 in HER2-positive metastatic breast cancer after trastuzumab and taxane therapy. *First Author: Sarika Jain, Northwestern University Division of Hematology/Oncology, Chicago, IL*

Background: Constitutive activation of the phosphatidylinositol-3-kinase (PI3K) signaling pathway is a mechanism of trastuzumab resistance in HER2-positive metastatic breast cancer (MBC). Alpelisib (BYL-719) is the first oral PI3K inhibitor that selectively inhibits the *PI3K*α isoform. We aimed to determine the maximum tolerated dose (MTD), safety, and activity of alpelisib with ado-trastuzumab emtansine (T-DM1) in HER2-positive MBC that failed standard therapy. **Methods:** In this phase I study, pts received alpelisib daily (cohort 1: 300 mg, (-1): 250 mg) and T-DM1 3.6 mg/m^2 on Day 1 every 21 days using a 3+3 design with dose expansion at MTD. Dose-limiting toxicity (DLT) was defined as CTCAE Grade 3/4 adverse events (AE) during cycle 1. Data cut-off is Jan. 1, 2017. **Results:** 17 pts were enrolled. Median age was 53 (40-66). Median prior lines of therapy in metastatic setting was 4.5 (0-13) including 9 pts who progressed on prior T-DM1 (after median 8 cycles). Median number of metastatic sites was 2 (1-5). Median number of cycles per pt who completed at least 1 cycle was 8 (1-19). Five pts were enrolled in cohort 1 with 2 DLTs (grade 3 rash), leading to cohort (-)1, in which there were no DLTs. The most common alpelisib-related AEs were hyperglycemia (n = 9, 53%), fatigue (n = 9, 53%), nausea (n = 7, 35%), and rash (n = 8, 47%). Grade 3 alpelisib-related AEs included rash (n = 7), hyperglycemia (n = 3), weight loss (n = 1), hypertension (n = 2), and pancreatitis (n = 1). Grade 3 rash occurred during cycle 1, which resolved with interruption and subsequent dose reduction of alpelisib and use of steroids. Grade 3 hyperglycemia was reversible with oral anti-diabetic treatment. One Grade 4 AE occurred (thrombocytopenia) likely due to T-DM1. MTD for alpelisib was established as 250 mg daily. Median follow-up was 11.6 months (0.3-19.5). Median PFS was 6 months (95% CI 2.9-10.6). In 11 pts without prior T-DM1 mPFS was 4.3 months (95% CI 2.0-8.8) and in 6 pts with prior T-DM1 it was 10.6 months (95% CI 1.6-12.6), p = 0.18. **Conclusions:** The combination of alpelisib 250 mg daily and T-DM1 appears to be safe in HER2-positive MBC pts with significant anti-tumor activity, even in pts previously treated with T-DM1. A phase II study is planned. Clinical trial information: NCT02038010.

1027 Poster Session (Board #19), Sun, 8:00 AM-11:30 AM

TBCRC 036: Window of opportunity clinical trial reveals adaptive kinome reprogramming in single and combination HER2-targeting in breast cancer (BrCa). *First Author: Steven P Angus, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: HER2 targeting is challenging due to heterogeneity in response and resistance. Adaptive kinome reprogramming (AKRP) is a resistance mechanism to kinase-targeted therapy (Rx) in TNBC (*Cancer Discovery*2017). We studied AKRP in HER2+ BrCa by comparing transcriptome and kinome profiles before and after Rx with FDA-approved anti-HER2 drugs and combinations: trastuzumab (T), pertuzumab (P), T+P, or T+ lapatinib (T+L). Profiling was by RNA sequencing (RNAseq) and multiplexed inhibitor beads coupled with mass spectrometry (MIB/MS). MIB affinity-purification selectively enriches the functional kinome ($>$ 250 kinases per sample) for identification/quantification by MS. **Methods:** Eligible patients (pts) had biopsy then randomization to: T (8 mg/kg iv), P (840 mg iv), T+P (same doses), or T+L (8mg/kg iv x1, 1000 mg po/d) 7 days before breast surgery. RNAseq and MIB/MS on paired pre- and post-Rx samples were analyzed using DESeq2 (comparison of mean difference in $\log_2$fold change (post/pre)) and MaxQuant (kinome response profiling) software. **Results:** Of 23 evaluable pts, we obtained informative paired RNAseq data in 13 (5 T, 3 P, 3 T+P, 2 T+L), and identified distinct expression responses ($p_{adj} \leq 0.05$) between Rx arms, such as FGFR4 increase in P vs T or T+P. All samples had HER2 enrichment by RNAseq. Kinome response profiling from 11 pts (3 T, 3 P, 4 T+P, 2 T+L) revealed consistent increases in MIB binding (abundance a/o activity) of several tyrosine kinases regardless of Rx, including immune-related kinases SYK, IRAK4, FGR, and FES. Other kinases, such as p90Rsk and GSK3B, exhibited increased binding in response to T and T+P, but not P alone. While not quantifiable in every sample due to detection limits, HER2 inhibition was observed by loss of MIB binding in select post-Rx versus pre-Rx comparisons. **Conclusions:** HER2 inhibition upregulates and activates specific receptor tyrosine kinases in tumor cells as well as alterations that may reflect changes in the immune compartment. HER2+ BrCa exhibit plasticity, characterized by distinct expression and kinome profile changes within 1 week of initiating Rx, and reprogramming in both immune responses and BrCa cells. Clinical trial information: NCT01875666.

1028 Poster Session (Board #20), Sun, 8:00 AM-11:30 AM

Impact of 2013 ASCO/CAP guidelines on HER2 determination of invasive breast cancer: A single institution experience using frontline dual-color FISH. *First Author: Elisa Gasparini, Breast Unit Arcispedale S. Maria Nuova-Irccs, Reggio Emilia, Italy*

Background: ASCO/CAP new guidelines published in 2013 (AC2013) significantly modified the scoring criteria for HER2-FISH. We retrospectively evaluated the impact of AC2013 in a five-year cohort of consecutive invasive breast cancers (IBCs) underwent frontline dual-color FISH. Furthermore, we applied three different reflex tests and investigated clinical outcomes of patients with HER2-equivocal IBC. **Methods:** 2788 consecutive IBCs that underwent frontline HER2/CEP17 determination in our institution from January 2009 to December 2013 were reclassified based on the AC2013 guidelines. FISH HER2-equivocal cases underwent reflex tests: HER2-IHC, *RARA*-FISH, and *SMS*-FISH. Clinico-pathological correlation was performed. **Results:** Two hundred HER2-negative cases (7.2%) were classified differently based on the AC2013: 0.3% (8/2788) became HER2-positive and 6.9% (192/2788) HER2-equivocal. AC2013 equivocal-IBCs represented a subgroup of grade 3, luminal-like subtype IBCs, in patients with a higher age. After reflex tests, among 190 equivocal cases 102 (53.7%) were reclassified as HER2-positive, 51 (26.8%) negative and 37 (19.5%) equivocal. IHC resulted negative in 44.7% (85), whereas *SMS*-FISH showed the highest percentage of positive results (45.8%). No statistically significant differences were identified in the disease-free and overall survival. **Conclusions:** AC2013 compared with AC2007 significantly increased initial HER2-equivocal cases (6.9%vs1.6%, $p < 0.001$). After reflex testing, 4.5% of patients not treated with anti-HER2 therapy (either HER2-positive or "ultimate equivocal") resulted eligible to trastuzumab, but showed clinical outcome comparable with AC2007 HER2-positive patients, treated with trastuzumab. Our findings belittle the clinical impact of AC2013 HER2-equivocal reclassification; accordingly further studies are necessary to justify this category and the reclassification efforts by additional reflex tests.

1029 Poster Session (Board #21), Sun, 8:00 AM-11:30 AM

Burden of out-of-pocket spending among high-deductible health plan members with metastatic breast cancer. *First Author: Christine Leopold, Harvard Medical School and Harvard Pilgrim Heatlh Care Institute, Department of Population Medicine, Boston, MA*

Background: 50% of workers have high-deductible health plans (HDHP) that require major outofpocket (OOP) spending for cancerrelated care. The OOP burden among patients with advanced cancer in HDHPs is unknown. Our objective was to estimate OOP spending for women with metastatic breast cancer (mbc) stratified by health plan type. **Methods:** Our data source was administrative health insurance claims and enrollment data of members insured though a large national health plan. We included 7142 women age 25-64 with mbc who had at least 6 months enrollment before the diagnosis and at least 12 months followup. We used a time series design and plotted OOP spending stratified by HDHP vs low-deductible plan. Primary outcome measures included: (1) 20042012 calendar trends in total annual OOP spending, (2) monthly total OOP spending in the 6 months before and 24 months after women were diagnosed with mbc, and (3) monthly total OOP spending in the last 6 months of life. Plots were adjusted for age, socioeconomic status, race/ethnicity, and US region of residence, and we then conducted linear regression to assess for statistical significance of trends. **Results:** In 2004, average annual OOP spending for women with mbc cancer in low-deductible health plans was $1196.2 and increased to $2570 in 2012, a yearly increase of $159.2 (113.2205.2). For women in HDHP average OOP spending in 2004 amounted to $2648 and increased to $3736.4 in 2012, representing an annual increase of $160.4 per year (105.4215.4) Average OOP spending per person month peaked in the month of diagnosis to $1633.8 for women in HDHPs and to $643 among low-deductible plan members. Average OOP spending in the last 6 months of life were $285.7 per person month among low-plan ($1714.2 per 6 months) and $607.3 among HDHP ($3644 per 6 months). **Conclusions:** To our knowledge, this is the first analysis to estimate OOP spending for women with mbc accounting for enrollment in HDHPs versus low-deductible plans. We found that OOP spending is increasing over time and is high in the last 6 months of life. HDHP members with mbc faced much higher OOP spending than women in traditional plans across all analyses. Findings raise concerns that HDHPs could worsen access to mbc treatments.

1030 Poster Session (Board #22), Sun, 8:00 AM-11:30 AM

A mouse-human phase I co-clinical trial of taselisib in combination with TDM1 in advanced HER2-positive breast cancer (MBC). *First Author: Otto Metzger Filho, Dana-Farber Cancer Institute, Boston, MA*

Background: PI3K blockade has the potential to revert resistance to anti-HER2 therapies. **Methods:** Pre-clinical experiments were conducted in parallel to a phase Ib study with the PI3-kinase inhibitor Taselisib + T-DM1 in HER2+ MBC. **Results:** Pre-clinically, HER2+ cell lines (HCC1954, MDA-MB-361, MDA-MB453) treated with T-DM1 until resistance had decreased HER2 expression. Tx with Taselisib restored HER2 levels in T-DM1 resistant cells. In vivo, the combination of T-DM1 + Taselisib was superior to either agent alone in transgenic mammary carcinomas driven by *HER2* with or without a *PIK3CA* H1047R transgene. The phase Ib study enrolled 26 pts with HER2+ MBC. Median age was 57 (38-95), ER+ (58%), ER- (42%). *PIK3CA* wild type (35%) mutant (23%) pending results (42%). Pts had a median of 2 lines of prior tx for MBC. Prior T-DM1 was given to 38.5% of pts. Median duration of tx among 18 pts was 4 cycles (2-19). 8 pts remain on tx. No DLTs were observed in the 2 dose levels explored: T-DM1 (3.6mg/Kg) q3 wk with either Taselisib 2mg QD or Taselisib 4mg QD. 20 patients were included in the expansion phase. Most common G3 G4 AEs were thrombocytopenia (19.2%), diarrhea (15.4%), vomiting (7.7%), lipase increase (7.7%) and hyperglycemia (7.7%). Pneumonitis was reported in 4 cases (3 G1, 1 G2); further evaluation revealed elevated beta-glucan in 3 of the 4 cases raising suspicion for pneumocystis pneumonia (PJP). 24/26 pts were evaluable for confirmed response: (4% CR, 29% PR, 50% SD). Confirmed PR/CR according to prior TMD1 (yes 30% no 36%) and PIK3CA mut status (40% mut, 22% wild type; 9/23 PIK3CA results pending). Median PFS was 7.6 mos (95% CI 2.9 to NR). **Conclusions:** The combination of Taselisib + T-DM1 is superior to either agent alone in mouse models of HER2+ BC. In the phase Ib study, T-DM1 + Taselisib had an acceptable safety profile although PJP prophylaxis should be considered for this regimen. Thrombocytopenia was reversible with no bleeding events. Preliminary evidence of efficacy was observed regardless of *PIK3CA* status or prior tx with T-DM1. This co-clinical trial allowed for the rapid translation of lab observations to the clinical setting and provided data to facilitate interpretation of the clinical results. Clinical trial information: NCT02390427.

1031 Poster Session (Board #23), Sun, 8:00 AM-11:30 AM

DS-8201a, a HER2-targeting antibody-drug conjugate, to elicit immune responses and benefits in combination with an anti-PD-1 antibody. *First Author: Tomomi Nakayama Iwata, Daiichi Sankyo Co., Ltd., Tokyo, Japan*

Background: DS-8201a, a HER2-targeting antibody–drug conjugate (ADC), with a topoisomerase I inhibitor, exatecan drivative (DX-8951 derivative, DXd) has been shown to have antitumor effects in preclinical xenograft models and clinical trials, but the involvement of the immune system in the antitumor efficacy of DS-8201a has not been elucidated yet. **Methods:** The antitumor efficacy of DS-8201a individually and in combination with an anti-PD-1 antibody was determined in a syngeneic mouse model with human HER2-expressing CT26.WT (CT26.WT-hHER2) cells. Mice whose tumors had been cured by DS-8201a treatment were rechallenged with CT26. WT-hHER2 cells; their splenocytes were co-cultured with CT26.WT-hHER2 or CT26.WT-mock cells, and IFN-g secretion by these cells was determined. To investigate effects of DXd and DS-8201a on dendritic cells (DCs), the expression of DC markers on bone marrow derived DCs (BMDCs) and intratumoral DCs was analyzed by flow cytometry. Furthermore, MHC class I and PD-L1 expression on tumor cells was analyzed. **Results:** At a weekly dosage of 10 mg/kg, DS-8201a showed significant antitumor effects in the mouse model. Mice whose tumors had been cured by DS-8201a treatment rejected the rechallenge with CT26.WT-hHER2 cells, and splenocytes from these mice were activated by both CT26.WT-hHER2 and CT26. WT-mock cells. In the mouse model, DS-8201a treatment raised a population of intratumoral DCs ($CD45^+CD11c^+$MHC class II^+) and increased DC expression of CD86, a DC activation marker; DXd also up-regulated CD86 expression on BMDCs in vitro. Furthermore, DS-8201a up-regulated PD-L1 and MHC class I expression on tumor cells. Notably, antitumor effects of the combination of DS-8201a with an anti-PD-1 antibody were better than those of monotherapy. **Conclusions:** DS-8201a elicits immune responses via mechanisms other than cytotoxic effects on tumor cells. This finding suggests additional benefits of combining DS-8201a with an immune checkpoint inhibitor (ICI). The combination of DS-8201a and an anti-PD-1 antibody was effective in tumor suppression, indicating that DS-8201a may be successfully combined with an ICI in human clinical applications.

1032 Poster Session (Board #24), Sun, 8:00 AM-11:30 AM

Survival by HER2 receptor status in stage IV breast cancer: SEER 2010-2012. *First Author: Alexandra Thomas, Wake Forest Baptist School of Medicine, Winston-Salem, NC*

Background: Therapeutic advances have altered the course of once highly lethal HER2+ breast cancer (BC). We report survival in a recent population-based cohort by HER2 status, overall, and within hormone receptor(HR)+ BC. **Methods:** Surveillance, Epidemiology, and End Results Program data were queried to identify women diagnosed 2010-2012 with Stage IV BC as first cancer. Patients were grouped by HER2 and HR status. Kaplan Meier estimates of 3-yr observed survival (OS) were compared with log-rank tests. A multivariate cox model was fitted for the HER2+ cohort. **Results:** 3-yr OS for HER2+(any HR), HR+/HER- and triple-negative (TN) BC was 52.3%, 48.4% and 16.0% respectively ($p<0.01$ HER2+(any HR) vs TNBC; p=0.20 HER2+(any HR) vs HR+/HER2-). Across registries, OS for HER2+(any HR) BC ranged from 29.2% to 61.7% (p=0.05). On Cox model, survival in HER2+(any HR) BC was associated with age 50+ (Hazard ratio (HR) 1.84, 95% CI 1.45-2.34), HR+ status (HR 0.70, 0.58-0.84), high histologic grade (HR 1.30, 0.58-0.84), surgery (HR 0.40, 0.33-0.49), separated marital status (HR 1.72, 1.4-2.13), year 2012 (HR 0.81, 0.64-1.04), and registry (varies by reference group). For HR+ BC, OS also differed by HER2 status: 55.3% for HR+/HER+ and 48.4% for HR+/HER2- ($p<0.01$). 3-yr OS by HER2 status for women presenting with HR+ BC is shown (Table). **Conclusions:** Survival in de novo Stage IV HER2+ BC in the United States exceeds that in HER2- BC, with median survival >3 yrs. Survival was significantly better for HR+/HER+ BC than HR+/HER- BC. Disparate OS in HER2+ BC suggest opportunities may remain to fully realize advances in HER2-directed therapy. Given recent therapeutic advances, the trend of HER2+ survival gains from 2010 to 2012 will likely continue.

		HR+/HER2-		HR+/HER2+			
		N	%	N	%	p*	p**
Full Sample		4073	48.4	1136	55.3	<0.01	
Age	<50	824	56.1	310	70.5	<0.01	<0.01
	50+	3249	46.4	826	49.4	0.15	
Surgery	No	2725	40.3	713	45.7	0.06	<0.01
	Any	1319	63.3	412	70.7	0.02	
Marital Status	Married	1743	54.7	508	59.1	0.08	<0.01
	Separated	1219	40.4	287	42.8	0.70	
	Never	883	47.3	271	58.4	0.01	
Year* **	2010	1285	78.8	345	78.6	0.83	0.26
	2011	1427	79.2	369	82.2	0.21	
	2012	1361	79.5	422	83.0	0.15	

* comparing HR+/HER2- vs HR+/HER2+; ** comparing OS within characteristic for HR+/HER2+ BC; *** 1-year OS, for consistent follow-up.

1033 Poster Session (Board #25), Sun, 8:00 AM-11:30 AM

Safety of trastuzumab emtansine (T-DM1) in HER2-positive advanced breast cancer (BC) patients (pts): Primary results from KAMILLA study cohort 1. *First Author: Carlos H. Barrios, PUCRS School of Medicine, Porto Alegre, Brazil*

Background: KAMILLA is a single-arm, open-label, phase 3b safety study of T-DM1 in pts with HER2-positive advanced BC from 278 sites in 40 countries. We report the primary analysis of the first study cohort (N = 2003). **Methods:** Pts with HER2-positive, locally advanced or metastatic BC (locally confirmed) with progression after prior treatment with chemotherapy and a HER2-directed agent for metastatic BC or within 6 mo of completing adjuvant therapy were enrolled. Pts received T-DM1 3.6 mg/kg every 3 wks until unacceptable toxicity, withdrawal, or disease progression. The primary outcome was safety. **Results:** A total of 2002 pts were treated (median age 55 yrs, range, 26–88). Most pts had a baseline ECOG score of 0 (n = 1110, 55.4%) or 1 (n = 775, 38.7%), and 1232 (61.5%) had ER and/or PR positive tumors. Median time since initial BC diagnosis was 5 yrs (range, 0–53). Most pts had received ≥2 prior lines of therapy (0–1 prior lines: 29.7%; ≥2: 66.0%); 1855 (92.8%) received prior targeted therapy in the locally advanced/metastatic setting. Median T-DM1 exposure was 5.6 mo (range, 0–46). Adverse events (AEs) were reported in 93.0% (n = 1862). Serious AEs occurred in 21.3% (n = 427), most commonly vomiting (17, 0.8%), pneumonia (16, 0.8%), anemia (13, 0.6%), and pyrexia (13, 0.6%). Grade ≥3 AEs occurred in 40.8% (n = 816), most commonly anemia (60, 3.0%), thrombocytopenia (55, 2.7%), and fatigue (50, 2.5%). Additional AEs of grade ≥3 (multiple individual items grouped) were thrombocytopenia/platelet count decrease (74, 3.7%), hepatic disorders (139, 6.9%), and hemorrhage (46, 2.3%). Grade 5 AEs occurred in 2.2% (n = 45). Treatment discontinuation was most often due to disease progression (1495, 78.1%). Median progression-free survival was 8.3 (95% CI: 8.0–9.7), 6.5 (5.6–8.0), 5.9 (5.6–8.1), 5.6 (5.0–5.9), and 5.6 (5.4–6.6) mo in pts with 0–1, 2, 3, 4, and 5+ prior lines of therapy. Median overall survival was 27.2 mo (95% CI: 25.5–28.7). **Conclusions:** KAMILLA isthe largest (to date) cohort of T-DM1 treated pts and these data are consistent with safety and efficacy seen in prior randomized studies, thereby supporting T-DM1 as therapy for previously treated HER2-positive advanced BC pts. Clinical trial information: NCT01702571.

1034 Poster Session (Board #26), Sun, 8:00 AM-11:30 AM

A phase II study of eribulin mesylate in combination with trastuzumab and pertuzumab in patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC). *First Author: Ines Maria Vaz Duarte Luis, Dana-Farber Cancer Institute, Boston, MA*

Background: As a single agent, eribulin is an active agent among MBC pts. In the first-line setting, pertuzumab improves progression free and overall survival when added to trastuzumab and chemotherapy (CT); however there are limited data in the second line or beyond. The primary aim of this study was to evaluate the activity of eribulin in combination with trastuzumab and pertuzumab in pts with HER2+ MBC whose cancers are refractory to trastuzumab containing regimens. Safety and toxicity were examined and correlative studies are also planned. **Methods:** Single center, single-arm, phase II, 2 cohorts study planned to enroll up to 81 pts. The studied combination would be of clinical interest if the true overall response rate (ORR) was 40% among those without prior pertuzumab exposure (Cohort A) and 30% among those with prior pertuzumab exposure (Cohort B). The trial was stopped prematurely due to low accrual. Prior to the start of the phase II study, a run-in established dose of eribulin with standard dose of trastuzumab and pertuzumab (1.4mg/m2 days 1, 8 /21 days). **Results:** Of 32 pts enrolled, 6 were in the run-in, 19 in Cohort A and 7 in Cohort B. Most pts were heavily pre-treated (median [range] lines of CT for metastatic disease, run-in: 4[2-11], cohort A: 2.5 [0-7], cohort B: 3[1-8]). In cohort A, 5 pts had partial responses (ORR = 26% [95% CI 9-51%]), 1 (5%) experienced stable disease (SD) lasting ≥ 6 months and 11 (58%) had a SD lasting < 6 months. In cohort B, the ORR was 0% [95% CI 0-41%]), 1(14%) experienced SD lasting ≥ 6 months and 5 (75%) had a SD lasting < 6 months. The combination was well tolerated, most adverse events (AE) were mild to moderate. Hematologic toxicity was the most frequent grade 3-4 AE. Analyses looking at tissue genomic markers and cell free DNA will be presented. **Conclusions:** We observed modest activity of the treatment combination in those without prior pertuzumab exposure but limited activity in unselected pts with HER2+ MBC. The study was limited by small sample size. Correlative studies may help us to understand resistance and response to eribulin with anti-HER2 therapy and the interplay between CT and targeted therapy. Clinical trial information: NCT01912963.

1035 Poster Session (Board #27), Sun, 8:00 AM-11:30 AM

Phase 1 dose escalation of ZW25, a HER2-targeted bispecific antibody, in patients (pts) with HER2-expressing cancers. *First Author: Funda Meric-Bernstam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The HER2 receptor is expressed across a range of cancers (ca) although expression and heterogeneity vary greatly within and between tumors. FDA approved HER2-targeted therapies (tx) have shown clinical benefit only in HER2 high (IHC3+ or IHC2+/FISH+) breast and gastric ca. ZW25, built on the Azymetric™ platform which utilizes unique Fc mutations to create IgG1-like bispecific antibodies, binds to the same extracellular domains of HER2 as trastuzumab (T) and pertuzumab (P) with increased binding and internalization compared to T alone. In preclinical studies ZW25 was well tolerated and active in models of HER2 low to high ca. **Methods:** Eligible pts (HER2 IHC 1-3+, progression after standard of care (SOC) tx, normal LVEF) were enrolled in a 3+3 dose escalation study of ZW25 (5, 10 or 15 mg/kg) IV weekly in 4 week cycles. Assessments included adverse events (AEs), LVEF, tumor response and PK. **Results:** 9 pts have received ZW25 at 5 (n = 3) or 10 mg/kg (n = 6); 15 mg/kg is ongoing. All pts were HER2 high (breast = 4; gastric/GEJ = 4; adnexal = 1). Prior tx included T in all pts; P and T-DM1 in 4 and lapatinib (L) in 3 of 4 breast pts. The most common AEs (all Gr 1/2) were infusion reaction (IR) (5/9), diarrhea (4/9), and fatigue (3/9), with no DLTs and one related Gr 3 AE of hypophosphatemia. The IRs occurred only with 1st dose and did not recur with prophylactic tx (primarily acetaminophen and diphenhydramine; steroids included for 2 pts). At 5 mg/kg, peak drug levels after C1D1 = ~100 ug/ml, accumulating ~50% higher by dose 4. Best response in 8 pts (1 too early): 2 PR (both breast ca with prior T, P, T-DM1, and L; 10 mg/kg, 55% and 33% target lesion decrease, respectively, after 2 cycles), 1 SD (breast ca, 5 mg/kg, ongoing after 4 cycles), and 5 PD. 5 pts currently active; includes 1 gastric pt (10 mg/kg) with PD (new nodal lesions) and clinical benefit with decrease in target lesions and CEA (33 to 1.5 ng/ml). **Conclusions:** ZW25 has been well tolerated with promising anti-tumor activity in pts with HER2-expressing ca progressing after SOC therapy. These early signs of activity support the therapeutic potential for bispecific antibodies using the Azymetric platform. Development of ZW25 is ongoing, including in lower HER2-expressing ca. Clinical trial information: NCT02892123.

1036 Poster Session (Board #28), Sun, 8:00 AM-11:30 AM

Quantification of intratumoral heterogeneity of HER2 status in breast cancer. *First Author: Rie Horii, Department of Pathology, Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: Intratumoral heterogeneity (ITH) occurs as a consequence of epigenetic aberrations in tumor cells with genetic diversity. HER2 ITH can be classified into genetic (a mixture of tumor cells with and without HER2 gene amplification) and epigenetic ITH (a mixture of HER2 gene-amplified tumor cells with and without HER2 protein overexpression). However, the both effects of genetic and epigenetic ITH on HER2-targeted therapy have not been clearly demonstrated. In order to implement ITH as a referenced factor for treatment selection, the ITH quantification is necessary. Gene-protein assay (GPA), in which immunohistochemistry and dual in situ hybridization are simultaneously performed on a single slide, allows bright-field analyses of both gene and protein status. We aimed to quantify HER2 ITH by the combination of gene and protein status and clarify its clinical significance. **Methods:** Fifty three patients with HER2-positive breast cancer, who underwent neoadjuvant trastuzumab with chemotherapy, were examined. Five representative microscopic images were captured from a GPA slide of a pretherapeutic biopsy material. All evaluable tumor cells in the images were scored according to the HER2 status determined by the combination of gene copy number and protein expression (Table). We investigated the relationship between the HER2 scores and pathological complete response (pCR) to the neoadjuvant treatment by the logistic analysis. **Results:** The average of HER2 scores, indicating the degree of the HER2 status, varied from 2.21 to 5.98. It was significantly related to pCR (Estimate: 1.21, Std. error: 0.46, RR: 3.34, P=0.009, 95%CI: 1.35-8.25). The standard deviation of HER2 scores, indicating the degree of the HER2 ITH, varied from 0.13 to 1.37. It was significantly related to pCR (Estimate: -2.09, Std. error: 0.83, RR: 0.12, P=0.012, 95%CI: 0.02-0.63). **Conclusions:** HER2 ITH, quantified by GPA, is a predictive factor for the therapeutic effect to trastuzumab-based treatment in HER2-positive breast cancer.

HER2 score by GPA.

		HER2 protein		
		0, 1+ (negative)	2+ (equivocal)	3+ (positive)
HER2 gene copy number	<4 (negative)	Score 1	Score 2	Score 4
	4,5 (equivocal)	Score 2	Score 3	Score 5
	≥6 (positive)	Score 4	Score 5	Score 6

1037 Poster Session (Board #29), Sun, 8:00 AM-11:30 AM

Phase II study of gemcitabine (G), trastuzumab (H), and pertuzumab (P) for HER2-positive metastatic breast cancer (MBC) after prior pertuzumab-based therapy. *First Author: Neil M. Iyengar, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The combination of taxanes with HP for first line treatment of HER2-positive MBC is associated with improved progression-free (PFS) and overall survival (OS). Treatment per physician's choice with anti-HER2 therapy after second line therapy is associated with a median PFS of 3 months. While continued use of H in therapeutic combinations after progression on H-based therapy is standard, the efficacy of continuing HP-based treatment after progression on P-based therapy is unknown. **Methods:** This is a single arm phase II trial of G with HP. Eligible patients (pts) had HER2-positive (IHC 3+ or FISH $>$ 2.0) MBC with prior HP-based treatment and $\leq$ 3 prior chemotherapies. Pts received G (1200 mg/m^2) on days 1 and 8 of a q 3 week (w) cycle, and H (8 mg/kg load $\rightarrow$ 6 mg/kg) and P (840 mg load $\rightarrow$ 420 mg) q3w. The primary endpoint is PFS at 3 months. Secondary endpoints include OS, safety and tolerability. An exploratory endpoint is to compare PFS by RECIST criteria versus 18-F FDG-PET response criteria. The study therapy will be considered successful if at least 27/45 (60%) patients are progression free at 3 months. **Results:** As of 1-27-17, 41 of 45 pts are enrolled; 34 are evaluable at 3 months and 7 have not had 3-month evaluation. At 3 months, 26/34 (76%) are progression free (1 CR, 8 PR, 17 SD); 8 pts progressed. There are no cardiac or febrile neutropenic events to date. 4 pts required G dose reduction (3 grade 3 neutropenia and 1 grade 3 vomiting) and the study was amended to lower initial G dose to 1000 mg/m^2. **Conclusions:** The preliminary 3 month-PFS is 76% in evaluable pts (95% CI 60% to 88%). The updated 3 month-PFS results will be presented. Continuation of P beyond progression is associated with apparent clinical benefit. A randomized trial is justified to confirm this clinically important observation. Clinical trial information: NCT02252887.

1038 Poster Session (Board #30), Sun, 8:00 AM-11:30 AM

Updated results from MONALEESA-2, a phase 3 trial of first-line ribociclib + letrozole in hormone receptor-positive (HR+), HER2-negative (HER2–), advanced breast cancer (ABC). *First Author: Gabriel N. Hortobagyi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Endocrine therapy (ET) is the basis of first-line (1L) treatment for HR+ ABC. However, ET resistance are almost universal. At the first interim analysis (IA) of MONALEESA-2 (NCT01958021), ribociclib (RIB; cyclin-dependent kinase 4/6 inhibitor) + letrozole (LET) significantly prolonged progression-free survival (PFS) vs placebo (PBO) + LET in patients (pts) with HR+, HER2– ABC.[1] Here we report updated efficacy and safety data from MONALEESA-2 with a further ~11 months of follow-up. **Methods:** Postmenopausal women with no prior therapy for ABC were randomized 1:1 toRIB (600 mg/day, 3-weeks-on/1-week-off) + LET(2.5 mg/day, continuous) vs PBO + LET. The primary endpoint was locally assessed PFS. Secondary endpoints include overall survival (OS; key) and safety. OS significance was defined by a p-value threshold of 3.15 x 10^{-5}. Tumor assessments were performed every 8 weeks for the first 18 months, and every 12 weeks, thereafter. **Results:** 668 pts were enrolled (334 in each arm). At the second IA for OS (data cut-off Jan 2, 2017), the median duration of follow-up was 26.4 months; 116 deaths and 345 PFS events had occurred. OS data remain immature, with 15.0% vs 19.8% of pt deaths in the RIB + LET vs PBO + LET arm (HR = 0.746; 95% CI: 0.517–1.078; p= 0.059). Updated PFS analyses confirmed continued treatment benefit in the RIB + LET vs PBO + LET arm. The 24-month PFS rates (RIB + LET vs PBO + LET) were 54.7% vs 35.9%. Treatment benefit was consistent across pt subgroups. The most common Grade 3/4 laboratory abnormalities ($\geq$10% of pts; RIB + LET vs PBO + LET) were decreased neutrophils (62.6% vs 1.5%), decreased leukocytes (36.8% vs 1.5%), decreased lymphocytes (16.2% vs 3.9%), and elevated alanine aminotransferase (11.4% vs 1.2%). **Conclusion:** After 26+ months of follow-up, treatment benefit with 1LRIB + LET persists in postmenopausal women with HR+, HER2– ABC. The study remains immature for OS analysis. The safety profile of RIB + LET remains manageable. 1. Hortobagyi G, *et al. N Engl J Med* 2016;375:1738–48. Clinical trial information: NCT01958021.

1039 Poster Session (Board #31), Sun, 8:00 AM-11:30 AM

Palbociclib (PAL) + letrozole (L) as first-line (1L) therapy (tx) in estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC): Efficacy and safety across patient (pt) subgroups. *First Author: Richard S. Finn, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: Hormone tx (HT) is the primary 1L tx for ER+ ABC. In the PALOMA-2 study (NCT01740427), PAL+L as 1L ABC tx prolonged progression-free survival (PFS; hazard ratio [HR] 0.58; $P<.001$) (Finn et al, *NEJM*. 2016). **Methods:** Postmenopausal pts with ER+/HER2– ABC and no prior systemic treatment in the advanced setting were randomized 2:1 to PAL (125 mg/d oral [3 wk on, 1 wk off]) + L (2.5 mg QD) or placebo (P) + L. Key endpoints were investigator-assessed PFS and safety. **Results:** 666pts (444, PAL+L; 222, P+L) were enrolled. Pts were similarly distributed between arms for visceral (48%) and nonvisceral (52%) disease and prior HT (56%) and no prior HT (44%); more pts had disease-free interval (DFI) $>$12 mo (40%) than $\leq$12 mo (22%). Median PFS (mPFS) was improved in all subgroups by adding PAL to L (Table). Adverse events were consistent across subgroups, as described for the full study population. **Conclusions:** PAL+L improved mPFS vs P+L with manageable toxicity across all subgroups including those with visceral disease. PAL+L provides a 1L option that should be considered for all pts with ER+/HER2- ABC. Sponsor: Pfizer Clinical trial information: NCT01740427.

PFS for ER+/HER2–ABC pt subgroups.

	PAL+L mPFS (95% CI)	P+L mPFS (95% CI)	PAL+L vs P+L HR (95% CI)	*P* Value
Visceral	19.3 (16.4-22.2)	12.9 (8.4-16.6)	0.63 (0.47-0.85)	.0011
Liver	13.7 (10.9-16.6)	8.4 (5.5-12.9)	0.62 (0.41-0.95)	.0255
Lung	22.2 (16.8-25.4)	13.6 (8.4-18.5)	0.59 (0.41-0.83)	.0025
Visceral and ECOG PS 0/1 or 2	16.8 (13.9-25.4)	11.0 (5.5-13.6)	0.48 (0.32-0.71)	.0002
Nonvisceral	NE (25.1-NE)	16.8 (13.7-22.2)	0.50 (0.36-0.70)	<.0001
Bone only (per tumor site)	NE (24.8-NE)	11.2 (8.2-22.0)	0.36 (0.22-0.59)	<.0001
DFI >12 mo	25.4 (22.2-NE)	13.8 (9.6-18.2)	0.52 (0.37-0.73)	<.0001
DFI ≤12 mo	16.5 (13.9-22.0)	11.0 (5.6-12.9)	0.50 (0.33-0.76)	.0005
No prior HT	25.7 (22.4-NE)	19.6 (13.9-23.5)	0.63 (0.44-0.90)	.0050
Prior HT	22.2 (17.0-25.4)	11.3 (9.6-16.3)	0.53 (0.40-0.70)	<.0001
Prior CT	22.4 (18.8-27.6)	13.7 (10.3-16.6)	0.53 (0.40-0.72)	<.0001
No prior CT	25.7 (22.2-NE)	17.0 (13.6-22.2)	0.61 (0.44-0.84)	.0012

CT=chemotherapy; NE=not estimable.

1040 Poster Session (Board #32), Sun, 8:00 AM-11:30 AM

Assessment of ESR1 and ERBB2 mutations in estrogen receptor positive (ER+) metastatic breast cancers (MBC). *First Author: Gargi D. Basu, Ashion Analytics, Phoenix, AZ*

Background: Mutations (mut) in ESR1 have been reported in ER+ breast cancers (BC) as an acquired resistance mut to aromatase inhibitor (AI) therapy. Acquired ERBB2 mut have also been reported in MBC patients (pts) that cause activated ERBB2 signaling. The emergence of acquired secondary mut presents challenges in effective treatment approaches. **Methods:** Comprehensive genomic profiling was performed on 83 BC samples with 48 metastatic; 34 primary samples. Targeted next-generation sequencing was performed on 562 cancer associated genes in paired tumor and blood DNA (germline) samples. **Results:** ESR1-mut were found in 23%(11/48) of ER+ MBC tissues with no mut detected in primary ER+ BCs. Mutations-D538G, Y537S and E380Q in the ligand binding domain of ER were the most common alterations, found in 54.5%, 18% and 18% of ESR1 mut samples, respectively. An ER+ HER2- liver biopsy obtained after 20 mos on AI + everolimus had ESR1-D538G and TSC2 structural event. Protein array showed high expression of androgen receptor (AR) and p-AR and activation of ERBB1/2/3, p-SRC and p-4EBP1 in this sample. Further, a functionally uncharacterized ESR1 mut was found in ER+, HER2+ and a triple negative MBC tissue (the primary BC had been ER+). Mut in PI3K pathway (PIK3CA, ARID1A, TSC1/2, PTEN) were present in 8/11 samples with ESR1 mut. Activating mut in ERBB2 were found in 3/83 samples; all 3 were in ER+ MBC samples with one case harboring mut in both ERBB2 and ESR1 (E380Q – uncertain degree of constitutive activity). Interestingly, a BC sample with ER+ HER2- liver met harbored both ERBB2 (V777L) and ERBB3 (E928G) mut; this pt responded well to trastuzumab/pertuzumab (HP) therapy. A pt with ER+ HER2-ERBB2-L755S mut met to gallbladder found after 7 mos on letrozole/palbociclib therapy responded well to HP and T-DM1 therapy. All 3 ERBB2-mut cancers had a CDH1 frameshift mut suggesting enrichment in pretreated lobular MBCs (Ross J. CCR, 2013). **Conclusions:** This study shows a 23% and 6% ESR1 and ERBB2 mut rate in MBC samples. No ESR1 and ERBB2 mut were present in primary BC samples. Our findings suggest that pts with lobular MBC should be monitored for acquired ERBB2 mut, and that ERBB2 mut may not arise in BCs which harbor known constitutively active ESR1 mut.

1041 Poster Session (Board #33), Sun, 8:00 AM-11:30 AM

A phase II, randomized, open-label 3-arm clinical trial of fulvestrant (F) plus goserelin (G) versus anastrozole (A) plus goserelin (G) versus goserelin (G) alone for hormone receptor (HR) positive, tamoxifen (T) pretreated premenopausal women with recurrent or metastatic breast cance r(MBC) (KCSG BR10-04). *First Author: Ji-Yeon Kim, Samsung Medical Center, Seoul, Republic of Korea*

Background: Endocrine therapy(ET) is the preferred treatment for HR(+) MBC. For premenopausal patients who were pretreated with T, ovarian function suppression with G ± aromatase inhibitor(A.I.) is a reasonable option. Fulvestrant yields favorable outcomes in postmenopausal women with MBC. We investigated the efficacy and safety of F+G and A+G in comparison with G alone in premenopausal women with HR(+), T-pretreated MBC. **Methods:** In this multicenter, open-label, randomized phase 2 study, women > 18 years with HR(+), T-pretreated MBC were stratified by presence of visceral metastasis and recurrence within or after 1 year of completion of adjuvant T. Premenopausal women with T-pretreated MBC eligible for ET were randomly assigned (1:1:1) to F+G (F 500 mg IM + G 3.6 mg SC Q 4 wks), or A +G (A 1 mg P.O. qd + G 3.6 mg SC Q 4 wks) or G (G 3.6 mg SC Q 4 wks). The primary endpoint was time to progression(TTP), analyzed by intention to treat with log-rank test. Secondary endpoints included overall survival, overall response rate, clinical benefit rate and toxicities according to NCI CTCAE v3.0 (ClinicalTrials.gov, No. NCT01266213). **Results:** Of 138 eligible pts, 44 were randomly assigned to F+G, 47 to A+G, 47 to G. The median duration of follow-up was 28.8 months(mo) and median age was 43 (range; 23.0-55.0). The median TTP was 16.3 mo(95% C.I. 7.5-25.1) for F+G, 14.5 mo(95% C.I. 11.0-18.0) for A+G, and 13.5 mo(95% C.I. 10.3-16.8) for G alone, respectively. For the comparison of each experimental arm to control arm, 24-mo TTP were analyzed: F+G vs G(%±SE): 40.5±7.5 vs. 25.3±7.0, one-sided P = 0.048, A+G vs G(%±SE): 23.9± 7.2 vs. 25.3±7.0, one-sided P = 0.304. Grade 3/4 toxicities were rarely observed. Most common adverse events were grade 1 joint stiffness and arthralgia which were more frequently observed in F+G compared to A+G and G (P = 0.018 and 0.015, respectively). **Conclusions:** The combination of F+G as well as G ±A.I. might be a valid option for HR(+) premenopausal women with T-pretreated MBC and further investigation is warranted. Clinical trial information: NCT01266213.

1042 Poster Session (Board #34), Sun, 8:00 AM-11:30 AM

Is androgen receptor useful to predict the efficacy of anti-estrogen therapy in advanced breast cancer? *First Author: Andrea Rocca, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*

Background: The androgen receptor (AR) is widely expressed in breast cancers but its role in estrogen receptor (ER)-positive tumors is still controversial. However, the AR/ER ratio may impact prognosis and the response to antiestrogen endocrine therapy (ET). **Methods:** We assessed whether AR in primary tumors and/or matched metastases is a predictor of efficacy of first-line ET in advanced breast cancer (ABC). We evaluated patients treated with first-line ET (2002–2011), excluding those receiving concomitant chemotherapy or trastuzumab or pretreated with > 2 lines of chemotherapy. ER, progesterone receptor (PgR), Her2, Ki67 and AR expression was determined by immunohistochemistry. A cut-off of < 1% immunostained cells was used to categorize AR expression. AR expression was analyzed in relation to the other conventional biomarkers (ER, PgR, Her2 and Ki67), best response (CR, PR, SD, PD), and time to progression (TTP) (months). TTP was estimated using the Kaplan-Meier method and compared with the log-rank test. Hazard ratios and their 95% confidence intervals (95% CI) were estimated using the Cox regression model. The Chi-square test was used to evaluate correlations between categorical variables and best response. p values < 0.05 were considered statistically significant. **Results:** Of the 102 evaluable patients (93% were treated with an aromatase inhibitor), biomarkers were assessed in primary tumors in 70 cases, in metastases in 49 and in 17 in both). Median TTP was 17 months (95% CI 14-21.5, median follow-up 75 months). The overall concordance rate between primary tumors and metastases was 64.7% (95% CI 42%-87.4%) for AR expression. Differences in TTP according to AR status were not statistically significant. AR/PgR ≥ 0.96 was associated with a significantly shorter TTP (HR = 1.65, 95% CI 1.05-2.61, p = 0.030). AR status in primary tumors or metastases was not associated with PD as best response. In contrast, Ki67 > 20% and PgR < 10% showed a significant association with PD as best response. Using a cut off of ≤10% for AR expression, results did not change. **Conclusions:** AR expression does not appear to be useful to predict the efficacy of ET in ABC. Ki67 and PgR exert a greater impact on the efficacy of hormone therapy than AR.

1043 Poster Session (Board #35), Sun, 8:00 AM-11:30 AM

Evaluation of tumor and circulating cell free (cf) DNA mutations in women with hormone refractory metastatic breast cancer (MBC) enrolled in a phase I study of Z-endoxifen (MC093C). *First Author: Matthew P. Goetz, Mayo Clinic, Rochester, MN*

Background: In estrogen receptor (ER) positive MBC, mutations (e.g. *ESR1*), identified from tumor biopsies or cfDNA, confer resistance. The concordance between mutations observed in tumor and cfDNA and the implications for response to Z-endoxifen, a potent anti-estrogen, are unknown. **Methods:** We previously conducted a phase I trial of Z-endoxifen in endocrine refractory, ER positive MBC. Seven dose levels were considered ranging from 20 to 160 mg/day followed by expansion cohorts (EC) of 40, 80, and 100 mg/day. Pretreatment blood samples (all pts) and fresh tumor biopsies (EC) were collected prospectively. Tumor and cfDNA were evaluated by targeted NGS. **Results:** 41 pts (38 evaluable) were enrolled. Prior endocrine therapy included aromatase inhibitors (37/38, 97%), fulvestrant (22/38, 58%) and tamoxifen (26/38, 68%). Substantial endoxifen exposure without DLTs at doses above 80 mg/day led to a halt in dose escalation and opening of the EC. Overall clinical benefit (stable > 6 months [7 pts.] or partial response by RECIST criteria [3 pts.]) rate was 26.3% (95%CI: 13.4-43.1%). cfDNA was obtained from 36 pts and mutations were identified in 13 (36%) including *ESR1* [*Y537N* or *D538G*] (5), *PIK3CA* [*H1047R* or *E542K*] (8), *TP53* [*K132R*, *R248Q*, *R267Q*, or *H179Y*] (4), *AKT* (*Q79K*) (1), and *KRAS* (*G12D*) (1). In 5 pts with cf *ESR1* mutations, 4 had additional cfDNA mutations including *PIK3CA* (3), and *TP53* (1). PFS was shorter in pts with cfDNA mutations relative to those without (median: 61 vs.132 days; log-rank p = 0.021). Discordance was observed between tumor and cfDNA mutations where 3/7 *PIK3CA* tumor mutations were detected by cfDNA, 1/2 *TP53* tumor mutations were detected by cfDNA, and 0/1 *AKT* tumor mutations were detected by cfDNA. Conversely, 2 pts had cfDNA mutations (either *ESR1*, *TP53* or *AKT*) undetected in tumor. **Conclusions:** The absence of cfDNA mutations in patients with endocrine resistant, MBC treated with Z-Endoxifen was associated with significantly longer PFS. Given the discordance between tumor and cfDNA sequence data, future studies must determine which approach maximizes prognosis and prediction of benefit for estrogen-targeted therapy. Clinical trial information: NCT01327781.

1044 Poster Session (Board #36), Sun, 8:00 AM-11:30 AM

Safety and efficacy of the BCL2 inhibitor venetoclax in estrogen receptor (ER) and BCL2-positive metastatic breast cancer: The mBEP study. *First Author: Geoffrey John Lindeman, The Royal Melbourne Hospital, Parkville, Australia*

Background: The anti-apoptotic protein BCL2 is overexpressed in ~85% of ER^+ breast cancer (BC). Venetoclax (ABT-199), a BCL2 inhibitor approved for CLL (400 mg/day), synergizes with tamoxifen in preclinical patient derived xenograft models by increasing apoptosis. In the first study to evaluate venetoclax in solid tumors, we tested the safety and efficacy of this combination in ER^+BCL2^+ metastatic BC. **Methods:** A '3+3 design' dose escalation phase 1b study enrolled women with ER^+ (> 1%), $BCL2^+$ (> 10%, mod-high) and HER2 non-amplified metastatic BC. Patients received escalating doses of venetoclax 200, 400, 600 or 800 mg/day with tamoxifen 20 mg/day. The primary objective was to determine dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) over 4 weeks. There was no limit to the number of prior lines of therapy. **Results:** Fifteen patients were enrolled (mean age 62 years, range 44-78; previous tamoxifen, 10 pts). Mean lines of prior therapy for metastatic BC was 2.5 (median 2, range 0-6) and included tamoxifen (6 pts). *ESR1* mutations were present in ctDNA of 4 patients. Treatment was well tolerated, with no DLT observed. MTD was not reached; 6 patients received the maximal planned dose (800 mg). The most common adverse event (AE) was lymphopenia (67% Grade 1-2; 13% Grade 3; No Grade 4), followed by nausea (46%, Grade 1-2), which was readily managed. Of 13 women with measurable disease (RECIST v1.1), 4 (31%) had a partial response and 5 (38%) had stable disease (clinical benefit rate, 69%). For patients with a partial response, tumor regression was rapid (evident at first restaging) and occurred in the 400-800 mg dose levels. Two patients with non-measurable bone-only disease had clinically stable disease (1 ongoing > 64 weeks). The median duration of response has not yet been reached (range, 12 to > 64 weeks). **Conclusions:** We demonstrated the safety of tamoxifen and venetoclax in ER^+BCL2^+ metastatic BC, with preliminary evidence of clinically relevant activity. A dose expansion study including serial biopsy, ctDNA and PET scans is ongoing at the 800 mg/day recommended phase 2 dose. Sponsor: Royal Melbourne Hospital Clinical trial information: ISRCTN98335443, ACTRN12615000702516.

1045 Poster Session (Board #37), Sun, 8:00 AM-11:30 AM

Efficacy and safety in elderly patient subsets across studies investigating endocrine monotherapy versus combination therapy in patients with HR+/HER2−advanced breast cancer. *First Author: Rachel A. Freedman, Dana-Farber Cancer Institute, Boston, MA*

Background: Combination of endocrine therapy and targeted agents in 1st and 2nd-line therapy prolong progression-free survival (PFS) in patients with hormone receptor–positive (HR+), HER2− advanced breast cancer (ABC). However, a greater risk of adverse events (AEs) and a greater possibility of drug-drug interaction, associated with combination therapy, present challenges in older patients. **Methods:** This study reviewed PFS and safety data in age-stratified subsets from Phase II or III clinical trials comparing endocrine monotherapy vs combinations of endocrine or targeted therapy in patients with HR+, HER2−ABC. **Results:** Among 9 identified studies, combination therapy that included ribociclib, palbociclib, and everolimus significantly reduced risk of disease progression vs monotherapy in older and younger patient subsets (Table). For combination therapy that included ribociclib or palbociclib, frequency of discontinuations due to AEs was similar between the subsets; more frequent discontinuations due to AEs were noted in the ≥70-year subset with everolimus. **Conclusions:** Combination endocrine therapies involving CDK4/6 or mTOR inhibitors have similar efficacy but vary in tolerability among older and younger patients with HR+, HER2− ABC.

Efficacy and tolerability of combination therapy in age-stratified patient subsets.

Trial	Difference in PFS, mo[a]	Risk reduction with combination therapy, %[b]	Discontinuation due to AE, %
2nd-Line			
BOLERO-2 (eve + exe vs exe)			
< 65 y, < 70 y	5, 4	62, 56	NR, 6 vs 4
≥65 y, ≥70 y	3, 5	41, 55	NR, 17 vs 0
PALOMA-3 (palbo + ful vs ful)			
< 65 y		65	
≥65 y		56	
SOFEA (ana + ful vs ful)			
50-64 y		0[c]	
≥65 y		0[c]	
NCT01381874 (exe + abi vs exe)			
Age < median	3[d]	28[c]	
Age > median	-1[d]	-22[c]	
1st-Line			
MONALEESA-2 (ribo + let vs let)			
< 65 y		48	7 vs 1
≥65 y		39	9 vs 3
PALOMA-2 (palbo + let vs let)			
< 65 y		43	
≥65 y		43	
PALOMA-1 (palbo + let vs let)			
< 65 y	11	69	13 vs 3
≥65 y	14	50	16 vs 3
NCT00075764 (ana + ful vs ful)			
< 65 y		21[c]	
≥65 y		21[c]	
NCT00083993 (tem + let vs let)			
≤65 y	3	25	
> 65 y	-2	-21[c]	

NR, not reported. aCalculated as PFScombination minus PFSmonotherapy. bCalculated as 1 minus hazard ratio. cUpper limit of hazard ratio 95% confidence interval ≥1. dPFS 95% confidence intervals overlap.

1046 Poster Session (Board #38), Sun, 8:00 AM-11:30 AM

Tumor genomics and response to CDK 4/6 inhibitors for patients with hormone receptor-positive (HR+) metastatic breast cancer (MBC). *First Author: Laura Spring, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: The combination of endocrine therapy with a cyclin-dependent kinase (CDK) 4/6 inhibitor, such as palbociclib, has changed the treatment paradigm of HR+ MBC, particularly as 1stline therapy. However, there are no predictive biomarkers at present, and little is known about the impact of tumor genomics on outcomes. For example, mutations in TP53 could impact the ability of p53 to negatively regulate p21, thereby promoting cell cycle progression despite CDK 4/6 inhibition. The aim of this study was to evaluate the association between tumor genomics, particularly PIK3CA and TP53 mutations, and response to CDK 4/6 inhibitors in HR+ MBC. **Methods:** All HR+/HER2- MBC patients at our institution receiving a CDK 4/6 inhibitor in the second line or beyond were identified. Tumor genomics were analyzed utilizing the institutional tumor genotyping next generation sequencing (NGS) assay known as "Snapshot-NGS assay" on DNA isolated from the tumor, covering key oncogenic driver mutations and tumor suppressor genes. The log-rank test was used for statistical analysis. **Results:** A total of 83 patients with HR+/HER2- MBC were identified, of which 61 had available tumor genotyping results available (52 metastatic specimens). The median line of therapy was three. Median progression-free survival (PFS) on CDK 4/6 inhibitor-based therapy, as second line or beyond, was 9.2 months (mo) overall. No significant difference in PFS was seen among patients with PIK3CA (n = 31) mutations (7.1 vs. 9.7 mo; p = 0.28) or with any alteration in the PI3K/Akt/mTOR (n = 36) pathway (8.2 vs. 9.3 mo; p = 0.40). The presence of a p53 mutation (n = 9) or complex tumor genomics (n = 14) demonstrated a trend towards shorter PFS (5.5 vs. 9.2 mo; 5.5 vs. 9.5 mo, respectively), although statistical significance was not reached due to small numbers (p = 0.76; p = 0.31). In a multivariable analysis adjusting for age and prior lines of therapy, similar results were observed. **Conclusions:** This study suggests patients with HR+ MBC harboring p53 mutations or complex tumor genomics may experience shorter PFS on CDK 4/6 inhibitor-based therapy in the second line and beyond, and these novel findings require validation in additional studies.

1047 Poster Session (Board #39), Sun, 8:00 AM-11:30 AM

First-line ribociclib plus letrozole for postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC): MONALEESA-2 safety results. *First Author: Wolfgang Janni, University of Ulm, Ulm, Germany*

Background: In the randomized, phase III MONALEESA-2 study (NCT01958021), first-line therapy with ribociclib (RIB; cyclin-dependent kinase 4/6 inhibitor; 600 mg/day; 3-weeks-on/1-week-off) + letrozole (LET; 2.5 mg/day) in postmenopausal women with HR+, HER2– ABC significantly prolonged progression-free survival vs placebo (PBO) + LET (hazard ratio: 0.556; p = 0.00000329; Hortobagyi GN *et al. N Engl J Med* 2016;375:1738–48). Here we present further safety analyses from MONALEESA-2. **Methods:** Adverse events (AEs) were characterized per CTCAE v4.03. Analyses of key AEs included time to first event, duration (time to AE resolution), and the rate of associated dose interruptions or reductions. **Results:** Safety analysis included 664 patients (pts; RIB + LET: 334; PBO + LET: 330). Neutropenia was the most common all-grade (G) and G3/4 AE in the RIB + LET arm (Table); febrile neutropenia rates were low (RIB + LET arm: 1.5%) with no associated deaths. Median time to first event for G ≥2 neutropenia in the RIB + LET arm (based on neutrophil counts) was 16 days. Other common G3/4 AEs (increased by ≥5% in the RIB + LET vs PBO + LET arm) were leukopenia (21% vs 1%), elevated alanine aminotransferase (ALT; 9% vs 1%), lymphopenia (7% vs 1%), and elevated aspartate aminotransferase (AST; 6% vs 1%). Neutropenia was the most common AE leading to dose interruptions/reductions; G3/4 neutropenia led to dose interruptions in 48% vs < 1% and reductions in 30% vs 0% of pts in the RIB + LET vs PBO + LET arm. 7.5% vs 2.1% of pts (RIB + LET vs PBO + LET) discontinued due to AEs; common AEs leading to discontinuation (> 1% pts) were elevated ALT (5% vs < 1%), elevated AST (3% vs 1%), and vomiting (2% vs 0%). **Conclusions:** First-line RIB + LET had a manageable safety profile in postmenopausal women with HR+, HER2– ABC. Neutropenia was the most common AE in the RIB arm, and was transient and reversible with dose modifications. Additional AE analyses will be presented. Clinical trial information: NCT01958021.

	RIB + LET (n = 334)		PBO + LET (n = 330)	
AE (all-G, ≥35% of pts), %	**All-G**	**G3/4**	**All-G**	**G3/4**
Neutropenia	74	59	5	1
Nausea	52	2	29	1
Infections	50	4	42	2
Fatigue	37	2	30	1
Diarrhea	35	1	22	1

1048 Poster Session (Board #40), Sun, 8:00 AM-11:30 AM

Health-related quality of life from a phase 3 randomized trial of fulvestrant 500 mg vs anastrozole for hormone receptor-positive advanced breast cancer (FALCON). *First Author: John Forsyth Russell Robertson, Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Royal Derby Hospital Centre, Derby, United Kingdom*

Background: The Phase 3 randomized FALCON trial (NCT01602380) demonstrated improved progression-free survival with fulvestrant 500 mg (F) vs anastrozole 1 mg (A) in postmenopausal women with hormone receptor-positive (HR+) locally advanced or metastatic breast cancer (BC) without prior endocrine therapy (hazard ratio [HR] 0.797, 95% confidence interval [CI] 0.637-0.999; p = 0.0486; Robertson et al. Lancet 2016). Overall health-related quality of life (HRQoL) was maintained and similar for F and A. There was no evidence of a detriment with F vs A in time to deterioration for both Trial Outcome Index (TOI; HR 0.90, 95% CI 0.70-1.15; p = 0.4008) and Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) total score (HR 0.84, 95% CI 0.66-1.07; p = 0.1594). We present additional analyses of patient (pt)-reported HRQoL outcomes from FALCON. **Methods:** Women with HR+ BC were randomized 1:1 to F (Days 0, 14, 28, then every 28 days) or A (daily) until disease progression or discontinuation. HRQoL was assessed by FACT-B questionnaire (TOI [summary of physical and functional well-being and breast cancer subscale scores] and FACT-B total score) at randomization and every 12 weeks during treatment. HRQoL data post-treatment (with or without progression) were also collected. **Results:** 462 pts were randomized (F, n = 230; A, n = 232). Compliance to FACT-B during treatment ranged from 84.6-100.0%. Mean change from baseline in TOI (scale range 0-92) and FACT-B total score (scale range 0-144) remained broadly stable (approximately ±3 points to Week 132) and similar between arms during treatment. HRQoL was also maintained in FACT-B subscales. Approximately one third of pts had improved TOI (≥ +6 points) and FACT-B (≥ +8 points) total scores from baseline up to Week 144 of treatment with F (ranges 26.4-45.0%, and 20.0-35.8%, respectively) and A (ranges 18.6-32.9%, and 22.7-37.9%, respectively). **Conclusions:** Compliance to the FACT-B questionnaire on treatment with F and A for HR+ BC in the FALCON trial was good; mean change from baseline in TOI and FACT-B total score was maintained, and similar proportions of pts had improved TOI and FACT-B total score in both arms. Clinical trial information: NCT01602380.

1049 Poster Session (Board #41), Sun, 8:00 AM-11:30 AM

Characteristics of disease activity able to identify risk categories and probability to respond to first-line endocrine therapy (ET) in HR+ve/HER2-ve metastatic breast cancer (MBC) patients (pts): Dream or reality? Evaluation of a composite risk score in a subgroup population of the GIM 13-AMBRA study. *First Author: Giorgio Mustacchi, University of Trieste, Trieste, Italy*

Background: The appropriate choice of 1st-line therapy in HR+ve/HER2-ve MBC pts is becoming more complicated since the data of front-line Fulvestrant and CDK 4/6 Inhibitors have been released. In the absence of predictive biomarkers of tumor response, one possible option is the recently proposed "composite score" (Schmid, ESMO 2016), composed by visceral tumor burden (VTB) and Disease-Free-Interval (DFI) to identify risk categories and the probability of response to ET or chemotherapy (CHT). Aim of the present analysis is to describe the choices of 1st-line treatment and the response rate, according to the mentioned score in a population of HR+/HER2-ve MBC. **Methods:** We used data of the HR+ve pts of the AMBRA study, a longitudinal cohort study, describing the choice of first and subsequent lines of treatment in HER2-ve MBC pts (SABCS 2016 P5-15-07 & P5-14-09). Using median DFI and VTB three categories of risk have been identified: Low (DFI > 24 months & VTB-), Intermediate (DFI £ 24 months & VTB- or DFI > 24 months & VTB+) and High (DFI £ 24 months & VTB+). This analysis describes the choices of 1st-line therapy and relative response rate according to these risk categories. **Results:** So far, 791/1500 pts have been registered into the AMBRA study, 673 of them (85%) with HR+ MBC and 659 (83.3%) are evaluable for this analysis. Risk categories and response to therapy are detailed in the table below. **Conclusions:** No conclusion can be done regarding the "High Risk" group because of the low number of pts treated with ET alone. Regarding the "Low" and "Intermediate" risk categories, we can conclude that the proposed "composite risk score" doesn't seem to discriminate MBC patients who could be treated with ET alone or with a more aggressive treatment, at least in terms of response rate.

	Low risk (N=264)		Intermediate Risk (N=324)		High risk (N=42)	
	ET	CHT±ET	ET	CHT±ET	ET	CHT±ET
1st-line therapy (%)	43.6%	56.4%	20.7%	79.3%	11.9%*	88.1%
Disease Control Rate (CR+PR+SD) (%)	60%	71.1%	61.2%	73.5%	na*	59.5%

*only 5 pts treated with ET

1050 Poster Session (Board #42), Sun, 8:00 AM-11:30 AM

Predictors of prolonged benefit from palbociclib (PAL) plus fulvestrant (F) in women with endocrine-resistant hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) advanced breast cancer (ABC) in PALOMA-3. *First Author: Massimo Cristofanilli, Robert H. Lurie Cancer Center of Northwestern University, Feinberg School of Medicine, Chicago, IL*

Background: PAL+F improved progression-free survival (PFS) over F + placebo (P) in patients (pts) with endocrine-resistant HR+/HER2– ABC. We examined factors predictive of long-term benefit on PAL+F. **Methods:** Pre/postmenopausal pts with HR+/HER2– ABC that progressed on prior endocrine therapy (ET) were randomized 2:1 to PAL (125 mg/d oral [3 wk on, 1 wk off]) + F (500 mg) or P+F. Characteristics of pts with prolonged benefit (treatment [tx] duration ≥18 mo for PAL+F; ≥12 mo for P+F based on median PFS and tx duration) were compared with the intent-to-treat (ITT) population. **Results:** PAL+F improved PFS vs P+F (11.2 vs 4.6 mo; hazard ratio, 0.50). By Aug 2016, 138 pts had long-term benefit: 100/347 (29%) pts on PAL+F received tx for ≥18 mo, including 70 (20%) who received > 2 y (26–39 cycles). In contrast, 38/174 (22%) pts on P+F received ≥12 mo of tx; only 16 (9%) received > 2 y (27–38 cycles). No apparent differences in baseline characteristics of pts with long-term benefit were observed between groups except that a greater proportion of those on P+F had a single site of disease involvement (40% PAL+F vs 63% P+F). Pts with long-term benefit on PAL+F had lower rates of visceral disease (42% vs 60%), liver metastases (18% vs 40%), and ≥3 disease sites (27% vs 39%) at baseline vs the ITT population; no difference in sensitivity to prior ET was observed (84% vs 79%). Objective response rate (ORR) was higher among pts with prolonged benefit on PAL+F vs ITT (36% vs 26%). **Conclusions:** PAL+F is associated with prolonged benefit in about a third of pts treated with the combination in PALOMA-3. These pts achieve higher ORR compared to other study pts and the benefit is independent of baseline site and number of metastatic recurrences and prior endocrine sensitivity. Benefit from F alone is less prolonged and appears limited to those with 1 site of disease involvement. The analysis confirms the efficacy of PAL+F in HR+ ABC with visceral recurrence. Biomarker analyses are ongoing in pts with long-term benefit to understand molecular features predictive of tx sensitivity. Funding: Pfizer. Clinical trial information: NCT01942135.

1052 Poster Session (Board #44), Sun, 8:00 AM-11:30 AM

Assessment of multiple endocrine therapies for metastatic breast cancer in a multicenter national observational study. *First Author: Olivia Le Saux, Centre Léon-Bérard, Lyon, France*

Background: For HR+/HER2– metastatic breast cancer (mBC), International guidelines recommend multiple lines of endocrine therapy (ET) before starting chemotherapy. Few studies have assessed the efficacy of such strategy on large populations. Our objective was to evaluate multiple ET activity according to clinical and biological characteristics and type of ET. **Methods:** All patients (pts) who initiated treatment for a newly diagnosed mBC between January 2008 and December 2014 in all 18 French Comprehensive Cancer Centers were included in the real life ESME database. ESME collects retrospective data using a clinical trial-like methodology. Database lock was 8 Dec 2016. Primary endpoint of the current study was progression free survival (PFS) on successive ET lines. Only pts with ET alone were assessed (pts receiving ET after chemotherapy as maintenance therapy, or combined with targeted treatment were excluded). **Results:** 9921 pts out of 16703 in ESME, had HR+/HER2- mBC (median age 62.0 years[range 23-96]). 53.9% of pts had visceral and 80.1% non visceral disease at diagnosis. Median OS of HR+/HER2- pts was 42.15 months (95% CI, 40.93-43.27). As first-line therapy, 4123 pts (41.6%) received ET alone, while 2038 received chemotherapy alone (20.5%) and 3667 received both (37%). Median PFS for first-line ET (N=4123) was 11.3 months (95% CI, 10.6-11.9). Only 668 pts (16%) received subsequent lines of ET alone. Types of ET used are described in the table below. Successive PFS will be reported at the meeting. **Conclusions:** Those data show that ET is prescribed to less than 50% of patients with HR+/HER2- mBC in first line and only to a small minority in subsequent lines. This is not in line with existing guidelines (NCCN, ABC3). Real-life median PFS for first-line ET is consistent with median PFS reported in clinical trials (Nabholtz, 2000).

Type of ET prescribed.

Endocrine therapy (ET)	First-line N=4123	Subsequent lines N=668
Non steroidal aromatase inhibitors (AI)	2868 (69.6%)	299 (44.7%)
Steroidal AI	749 (18.2%)	196 (29.3%)
Selective Estrogen Receptor Modulator	929 (22.5%)	214 (32.0%)
Selective Estrogen Receptor Degrader	562 (13.6%)	288 (43.0%)
LHRH Analogs	339 (8.2%)	33 (4.9%)
Other	33 (0.8%)	20 (3.0%)

1053 Poster Session (Board #45), Sun, 8:00 AM-11:30 AM

Palbociclib exposure-response analyses in second-line treatment of hormone-receptor positive advanced breast cancer (ABC). *First Author: Wan Sun, Clinical Pharmacology, Global Product Development, Pfizer Inc., San Diego, CA*

Background: Palbociclib (PAL) is an oral inhibitor of cyclin-dependent kinases 4 and 6 approved for ABC. Exposure-response analyses for efficacy and safety endpoints were performed to evaluate the current PAL clinical dosing regimen (125 mg daily, 3 weeks on and 1 week off) and dose modification strategy in 2nd-line ABC. **Methods:** The present analyses used data from PALOMA3, a phase 3 study comparing the safety and efficacy of fulvestrant plus either PAL or placebo in 2nd-line ABC patients (PTs). A Bayesian pharmacokinetic (PK) analysis was conducted to estimate PAL PK parameters for individual PTs. Average concentration of PAL over the entire treatment (C_{avg}) was derived from average daily dose intensity divided by post hoc estimates of clearance for each PT. Time varying C_{avg} (C_{avgt}) was also derived to account for dose modifications up to each observation point. Kaplan-Meier method and the Cox proportional hazards model were employed to explore relationship between progression-free survival (PFS) and C_{avg}, C_{avgt}, as well as other prognostic factors. A semi-mechanistic PK-pharmacodynamic (PD) model was built to quantify the relationship between PAL concentration and absolute neutrophil count (ANC). **Results:** The median PFS for low and high PAL exposure groups divided according to C_{avg} were similar (9.47 and 10.9 months, respectively) and significantly higher than that of the control arm (4.57 months). While $C_{avgt}$was found to be a significant predictor for PFS in univariate analysis (P-value < 0.05), this relationship was not significant in the multivariate analysis where other significant prognostic factors were also included. The PK-PD analysis for safety endpoint indicated higher PAL concentrations were associated with lower ANC, which is consistent with the fact that ANC profiles were well managed by dose modification strategies, i.e., dose interruption, delay and reduction. **Conclusions:** The analysis results suggested PTs were benefited similarly from fulvestrant plus PAL treatment with manageable safety profile, supporting a favorable benefit-risk profile of PAL under the current dosing regimen and dose modification strategy in 2nd-line ABC. Funding: Pfizer Inc. Clinical trial information: NCT01942135.

1054 Poster Session (Board #46), Sun, 8:00 AM-11:30 AM

Outcome of palbociclib based therapy in hormone receptor positive metastatic breast cancer patients after treatment with everolimus. *First Author: Ajay Dhakal, Roswell Park Cancer Institute, Buffalo, NY*

Background: Resistance mechanisms to CDK 4/6 inhibition are not well defined. Outcome data on hormone receptor positive (HR+) metastatic breast cancer patients (MBCP) treated with palbociclib (PA) after treatment with everolimus (EV) are lacking. The PALOMA 3 trial (P3) showing benefit of PA plus fulvestrant (FU) compared to FU in HR+ MBCP after progression on endocrine therapy excluded women previously treated with EV. The aim of our study was to investigate the outcomes of HR+ MBCP with prior EV treatment on PA based therapy. **Methods:** This is a retrospective, single institute review of HR+, HER 2 nonamplified MBCP from Jan 2014 - Nov 2016 treated with PA after treatment with EV. Women who received EV for $<$ 1 month or PA $<$ 14 days were excluded. Progression free survival (PFS) was defined as the time from the initiation of PA to the date of progression as determined by treating physician based on radiological, biochemical and/or clinical criteria. Response rates were determined based on available radiological data. Clinical benefit was defined as a complete response (CR), partial response (PR) or stable disease of at least 24 weeks. **Results:** 23 patients with mean age 67 years (42 to 81) were identified. 95% were postmenopausal, 81% had ECOG performance status 0 or 1, 83% had visceral metastases, 95% had $>$ 2 lines of prior endocrine therapy (ET), 82% shown prior sensitivity to ET, 82% received prior chemotherapy, of which 84% were in metastatic setting. Kaplan Meier estimate showed median PFS of 2.9 months (95% CI 2.0-4.2); median PFS of P3 PA cohort was 9.5 months (95% CI 9.2-11.0). Fisher's exact test comparing study cohort with P3 PA cohort showed statistically significant differences in objective response (CR or PR) rates of 0/23 (0%) vs. 66/347 (19%, p = 0.02) & clinical benefit ratio of 4/23 (17.4%) vs. 231/347 (66.5%, p = 0.00). **Conclusions:** Outcomes with PA in HR+ EV treated MBCP were worse when compared to the P3 PA cohort data. Treatment with EV may lead to resistance to CDK inhibition. Though limited by size, our data suggests that use of PA after EV is associated with low response & clinical benefit rates. Further studies are necessary to confirm the findings to determine sequencing of targeted therapies.

1055 Poster Session (Board #47), Sun, 8:00 AM-11:30 AM

The role of taxanes in HR+ve/HER2-ve metastatic breast cancer (MBC) patients (pts) from adjuvant to metastatic setting in the clinical practice: Results from GIM13-AMBRA study. *First Author: Giorgio Mustacchi, University of Trieste, Trieste, Italy*

Background: The molecular subtypes of BC have individual patterns of behavior, prognosis and sensitivity to treatment, with subsequent implications for the choice of, or indeed role, for adjuvant (Adj) and metastatic chemotherapy (CHT). Taxanes (T) play a central role in chemotherapy for BC. However, previous studies have reported that T are relatively ineffective in patients with Luminal (HR+ve) BC compared with other subtypes. Aim of the present analysis is to describe the use of T in the clinical practice in Italy in HR+ve pts. **Methods:** AMBRA is a longitudinal cohort study, aiming to describe the choice of first and subsequent lines of treatment in HER2-ve MBC pts receiving at least one CHT (SABCS 2016, P5-15-07 & P5-14-09) in the years 2012-2015. For the present analysis, we focused on the use of T from the AdJ to the metastatic setting. **Results:** So far, 791/1500 pts have been registered into the study, 651 of them (82,3%) evaluable with HR+ MBC. Main characteristics are: Mean age 52 years; pN: UK 64 (9.8%) N+=405 (62.2%); Adj CHT=397 (61 %), mean DFI=96,99 months. T were used in 60.3% of the cases in the Adj setting, alone or in combination with other drugs, mainly anthracyclines (82.6%), with a mean DFI of 56.9 months. In the metastatic setting, across 1st to 3rd line, 460 pts (70.6%) received T, alone (49.7%) or in combination with Bevacizumab (38.2%), or other CHT drugs (11.9%). Details of the use of T in MBC are described in the table below. **Conclusions:** T have been used in more than 60% of cases of Luminal tumours in the Adj setting. In this population DFS is significantly shorter as compared with the non-T treated luminal population, as previously suggested by different Authors. Re-challenge with T is very frequent across different lines for MBC. Paclitaxel is the most used T, Docetaxel the less used and Nab-paclitaxel, labelled for MBC only, shows an increasing use from 1st-to 3rd line of treatment.

Drug	1st-line %	2nd-line %	≥ 3rd-line %
Paclitaxel	79.5	60.7	44
Docetaxel	14.5	10.7	9.3
Nab-Paclitaxel	6.0	28.4	46.6

1056 Poster Session (Board #48), Sun, 8:00 AM-11:30 AM

Prospective study of UDP-glucuronosyltransferase (UGT) 2B17 genotype and exemestane (Exe) pharmacokinetics (PK) and pharmacodynamics (PD) in Asian, hormone receptor (HR) positive, metastatic breast cancer (MBC) patients. *First Author: Robert John Walsh, Department of Haematology-Oncology, National University Cancer Institute, National University Health System, Singapore, Singapore*

Background: The active metabolite of Exe, 17-dihydroexemestane (17DhExe), is glucuronidated by UGT2B17 to inactive exemestane-17-O-glucuronide (Exe17-*O*-glu). *UGT2B17*2/*2*null genotype is 7 times more common in Asians than Caucasians and leads to reduced Exe glucuronidation in vitro. We studied Exe PK and PD in MBC patients genotyped for UGT2B17. **Methods:** Eligible patients (HR+ MBC; ≥1 line of endocrine therapy) received Exe 25mg OD till progression. *UGBT2B17* genotype was correlated with day 29 (D29) steady-state PK (Exe and metabolites), change in PD biomarkers (estrone and androstenedione) at D29 *vs* baseline (BL), objective response rate (ORR) [sum of complete and partial responses], and clinical benefit rate (CBR) [response or stable disease ≥ 24 weeks]. **Results:** In 64 patients enrolled, CBR was 25%; ORR was 3%. Frequencies of *UGT2B17*2/*2, UGT2B17*1/*2* and *UGT2B17*1/*1* were 72%, 26% and 2%, respectively. PD and PK data were available for 54 and 53 patients respectively. Mean Exe17-*O*-glu AUC and C_{max} were significantly lower, and mean 17DhExe C_{max} numerically higher in patients with *UGT2B17*2/*2 vs* other genotypes (Table 1). 17DhExe C_{max} was higher in patients with clinical benefit *vs* none (5.6 *vs* 3.8 ng/ml, p=0.02). Frequency of desired PD effect (rise in androstenedione and fall in estrone at D29 *vs* BL) was 22%. Exe plasma active index (PAI) [Table 1] was higher in patients with a fall in D29 estrone *vs* those without (14.7 *vs* 9.5, *p*=0.05). **Conclusions:** *UGT2B17* genotype affects Exe PK and may have significant PD correlates. Larger studies to examine effects on clinical treatment efficacy are needed. Clinical trial information: NCT01655004.

D29 PK.

Parameter	*UGT2B17 *2/*2, n=41*	Non *UGT2B17 *2/*2, n=12*	p value
Exe C_{max} (ng/mL)	38.1 ± 3.4	34.1 ± 4.3	0.56
Exe AUC (hr*ng/mL)	100.3 ± 8.5	93.7 ± 13.7	0.71
17DhExe C_{max} (ng/mL)	4.5 ± 0.5	3.3 ± 0.4	0.08
17DhExe AUC (hr*ng/mL)	15.9 ± 1.5	13.1 ± 2.1	0.36
Exe17-*O*-glu C_{max} (ng/mL)	2.4 ± 0.3	21.5 ± 2.2	<0.001
Exe17-*O*-glu AUC (hr*ng/mL)	11.0 ± 1.5	92.4 ± 9.9	<0.001
Glucuronidation ratio $AUC_{Exe17Oglu}/AUC_{17Dh\ Exe}$	0.7 ± 0.1	7.8 ± 0.9	<0.001
PAI $(AUC_{Exe}+AUC_{17DhExe})/AUC_{Exe17Oglu}$	14.7 ± 2.1	1.2 ± 1.4	<0.001

1057 Poster Session (Board #49), Sun, 8:00 AM-11:30 AM

Choice of treatment and adherence to international ESO-ESMO (ABC) guidelines in HR+/HER2-ve metastatic breast cancer (MBC) patients (pts). *First Author: Marina Elena Cazzaniga, ASST Monza Oncology Unit, Monza, Italy*

Background: ESO/ESMO recently developed consensus guidelines for MBC treatment, potentially applicable worldwide. Aim of the present analysis is to verify the adherence to ABC recommendations for HR+ve MBC in the context of the AMBRA study. **Methods:** AMBRA is a longitudinal cohort study, aiming to describe the choice of first and subsequent lines of treatment in HER2-ve MBC pts receiving at least one Chemotherapy (CHT) (SABCS 2016, P5-15-07 & P5-14-09). For the present analysis, we selected 6 statements from the ABC1 & ABC2 Conferences, comparing them with the clinical choices of 1st-line therapy in all evaluable cases. **Results:** So far, 791/1500 pts have been registered into the study, 673 of them (85%) with HR+ MBC. Main characteristics are: N+=422 (62.2%), adjuvant chemotherapy=288 (42.4%), median DFI=70 months. 26 pts were excluded due to change into HR-ve (26; 3.8%). Endocrine Therapy (ET) was the 1st-line of treatment in 187/647 (27.8%), CHT in 310 (47.9%) and CHT followed by ET in 135 (20.8%). Viscera was the main site of disease in 328 pts (48.7%): 56 (17%) received ET, 209 (63.7%) CHT alone, the remaining CHT followed by ET. Median DFI was similar in all the 3 groups. Selected recommendations and percentages of adherence are reported in the table below. **Conclusions:** The adherence to clinical recommendation about the use of ET as 1st-line treatment in HR+ pts is very low; a potential bias could be due to the selection of the study population. Visceral disease appears to be often a key factor for selecting CHT as 1st-line treatment. In pts receiving ET, the recommendation to use AIs, TAM or F is transposed in almost all the cases.

Adherence to ABC1 & 2 Recommendations for HR+ve pts.

	n/N (% of adherence)	
1 - In HR+ pts ET is preferential	187/647 (27.8%)	
- ET, visceral relapse	56/187 (29.9%)	
2 - The preferred 1stline ET for postmenopausal pts is an aromatase inhibitor (AIs) or Tamoxifen (TAM)	100/186 (53.7%) 6/186 (3.2%)	170/186 (91.4%)
3 - Fulvestrant (F) High-Dose is also an option	65/186 (34.9%)	
4 - The addition of Everolimus to an AI is a valid option for some postmenopausal pts with disease progression after a NSAI visceral relapse	15/186 (8.1%) 5/186 (2.7%)	

1058 Poster Session (Board #50), Sun, 8:00 AM-11:30 AM

Experience of implementing a novel random sampling BICR audit for investigator (INV)-assessed progression-free survival (PFS) in the PALOMA-3 trial. *First Author: Xin Huang, Pfizer Inc., La Jolla, CA*

Background: PFS has frequently been used as a primary endpoint for evaluating efficacy of anticancer therapies in randomized clinical trials. Given high correlation between INV and independent (BICR) assessments with respect to the relative treatment effect, a pre-planned BICR audit of INV progression assessment in a random subgroup of patients (pts) instead of a BICR review of all progression assessments can be an acceptable approach to verify the INV assessments and to evaluate the potential bias in INV PFS results. **Methods:** PALOMA-3 was a randomized, double blind, placebo (PCB) controlled, Ph 3 study with the primary objective of demonstrating the superiority of palbociclib (PAL) + fulvestrant (F) over PCB + F in women with HR+, HER2- metastatic breast cancer (MBC). The primary endpoint was INV assessed PFS. BICR assessment of PFS was performed with the use of a novel audit approach involving a random sample–based BICR to verify if the INV assessed PFS was accurate. A third-party core imaging laboratory performed the blinded review for a randomly selected subgroup of pts (~40%). NIH and PhRMA methods were used to evaluate the potential for bias in the INV PFS results. **Results:** PAL + F improved PFS in patients with HR+, HER2- MBC. The observed INV HR was 0.46 (95% CI: 0.36, 0.59; stratified 1-sided $p < 0.0001$) in favor of PAL + F. The median PFS was 9.5 mo (95% CI: 9.2, 11.0) in the PAL + F arm and 4.6 mo (95% CI: 3.5, 5.6) in the PCB + F arm (Lancet Oncol. 2016; 17: 425–39). The estimated HR of the complete BICR data incorporating the information from the complete INV assessed PFS and the random sample audited BICR subgroup was 0.33 with the upper bound of the 1-sided 95% CI of 0.47. The results confirmed the INV assessed treatment effect and detected no INV bias in favor of PAL + F. **Conclusions:** PALOMA-3 is the first registrational trial to use a BICR audit and has received positive reviews from regulatory agencies. The experience of implementing the random sampling BICR audit in PALOMA-3 demonstrates that this approach can be used for randomized, double blind oncology trials with solid tumors where INV assessed PFS is the primary endpoint and a large treatment effect is targeted. Sponsor: Pfizer. Clinical trial information: NCT01942135.

1059 Poster Session (Board #51), Sun, 8:00 AM-11:30 AM

RADICAL trial: A phase Ib/IIa study to assess the safety and efficacy of AZD4547 in combination with either anastrozole or letrozole in ER positive breast cancer patients progressing on these aromatase inhibitors (AIs). *First Author: Michael Seckl, Charing Cross Hospital, London, United Kingdom*

Background: Patients with metastatic ER positive breast cancer invariably experience disease progression whilst taking AIs. Fibroblast growth factor receptor inhibitors (FGFRI) such as AZD4547 can reverse endocrine resistance in breast cancer cells. Consequently, we designed the RADICAL trial to test the safety and efficacy of AZD4547 combined with letrozole (L) or anastrozole (A). **Methods:** Patients with prior disease progression on either AI were initially recruited to a Phase Ib study which showed that L 2.5mg or A 1mg daily continuously could be safely combined with AZD4547 80mg twice daily on a 1wk on/1 wk off schedule. Pharmacokinetic data showed no significant interactions. Subsequently, 52 patients progressing on these AIs were recruited, either continuing, or, if other therapies had subsequently been given, restarting their prior AI together with AZD4547. Primary endpoint was change in tumour size (RECIST v 1.1) at 12 weeks compared to baseline. **Results:** Enrolled patients had previously received a median of 4 (range: 1-11) systemic therapies, including endocrine treatments with a median of 2 (range: 1-6). The mean tumour size change at 12 and 28 weeks was 7% (95%CI: -4%, 17%) and 8% (95%CI: -4%, 20%), respectively. Clinical benefit assessed by partial response (PR) or stable disease (SD) occurred in 36.5% (1 PR and 18 SD) and 25% (2 PR and 11 SD) of patients at 12 and 28 weeks, respectively. The median progression free survival was 3.1 months (95%CI: 2.4-5.4). Most adverse events (AEs) were G1/2 (95.3%). 11 (21%) patients developed asymptomatic AZD4547-induced retinal pigment epithelial detachment, all resolved and 1 and 6 were able to continue on study medication at full and half dose, respectively. Among 34 G3/4 AEs, only 6 were probably/possibly related to AZD4547. Out of 13 unrelated serious AEs, 2 were fatal. **Conclusions:** Combined AZD4547 with L or A appears to be safe and shows anti-tumour activity in advanced ER+ patients resistant to these AIs. Development of a biomarker to select patients for this therapy will facilitate future studies. Clinical trial information: NCT01791985.

1060 Poster Session (Board #52), Sun, 8:00 AM-11:30 AM

Estimating the effects of patient-reported outcome (PRO) diarrhea and pain measures on PRO fatigue: Data analysis from a phase II study of abemaciclib monotherapy, a CDK4 and CDK6 inhibitor, in patients with HR+/HER2- breast cancer after chemotherapy for metastatic disease—MONARCH 1. *First Author: Mark Boye, Eli Lilly and Company, Greenwood, IN*

Background: Investigators reporting treatment-emergent adverse events (TEAEs) in the 3rd line or greater abemaciclib MONARCH1 Phase 2 study observed Grade 1-3 diarrhea, fatigue, and abdominal pain in 90, 65, and 39% of the patients (n = 132). Unknown is the extent that diarrhea and overall pain add to fatigue in this setting. Using patient-reported outcome (PRO) measures, we conducted cross-sectional and longitudinal multivariate analyses to estimate these effects. **Methods:** Data came from a single-arm, open-label study of previously-treated patients with mBC. Throughout the study, the Brief Pain Inventory and the EORTC QLQ-C30 v3 were co-administered. All constructs and items from these two questionnaires – except EORTC Items 25 and 28 (memory and financial difficulties) - were used to estimate the Structural Equation Model (SEM) and the direct and indirect effects of pain and diarrhea on fatigue. Extended pattern mixture modeling (ePMM) – a latent variable modeling method that allows the explicit analysis of missing data and identifies subgroups with differential changes over time – was used to explore these relationships from screening through cycle 8. **Results:** SEM results showed that at cycle 2 of treatment, pain was a significant predictor of fatigue ($b = 0.68$; $P < 0.001$; CI 0.48 – 0.90); diarrhea was not a significant predictor of fatigue ($b = 0.06$; $P = 0.12$; CI -0.04 – 0.17). ePMM results across eight 30-day cycles found three fatigue subgroups: no change, improvement, worsening then improvement. Belonging to a similar pain subgroup predicted belonging to the corresponding fatigue subgroup (ref class was no change; improving $b = 5.03$, $P = 0.004$; worsening $b = 22.01$, $P < 0.001$); the same was not true for diarrhea and fatigue (ref class was no change; improving $b = 0.213$, $P = 0.75$; worsening $b = 0.04$, $P = 0.97$). **Conclusions:** These results suggest that for patients undergoing 3rd line or greater mBC treatment, pain is a significant predictor of fatigue early and over the course of the trial. However, diarrhea is not a significant predictor of fatigue. Clinical trial information: NCT02102490.

1061 Poster Session (Board #53), Sun, 8:00 AM-11:30 AM

Analysis of everolimus starting dose as prognostic marker in HR+ mBC patients treated with everolimus (EVE) + exemestane (EXE): Results of the 3rd interim analysis of the non-interventional trial BRAWO. *First Author: Peter A. Fasching, Universitatsklinikum Erlangen, Erlangen, Germany*

Background: BRAWO is a German non-interventional study, which enrolled more than 2400 patients (pts) with advanced/metastatic, hormone-receptor-positive and HER2-negative breast cancer treated with EVE and EXE. Main objectives are a) the impact of physical activity on efficacy and quality of life, b) prophylaxis and management of stomatitis in clinical routine, and c) the sequence of therapy when EVE is used in daily clinical practice. **Methods:** In this update on the results of the 3rd interim analysis (data cut-off 18-Oct-2016) we analyzed under real world conditions the first 1.078 patients followed up until disease progression for their progression-free survival (PFS) events. A two-stage process based on a Cox regression model was used to check the relevance of the start dose on PFS. In the first step potentially relevant covariates defined by medical experts were evaluated for relevance. In the second step start dose and all covariates showing a p-value of at most 0.1 in first step including all two-interaction of start dose with these parameters were included into the model. **Results:** Our multivariate analysis support the evidence that predictive factors, such as body mass index (BMI, p-value: < 0.001), therapeutic line (1st vs. 2nd+3rd vs. $\geq$4th; p-value: 0.013), presence of visceral metastases (p-value: < 0.001) and ECOG (Eastern Cooperative Oncology Group, p-value: < 0.001) status at the beginning of the therapy correlated significantly with the PFS. 283 patients started with 5mg and 795 Patients started with 10 mg. Starting dose had no significant impact on the PFS (neither as main effect nor within interactions, p-value: 0.44-0.88). **Conclusions:** Even though the approved and recommended starting dose for treatment with EVE is 10 mg, physicians sometimes start EVE-treatment with a lower starting dose, trying subsequently to increase the dose to the recommended dose of 10mg to allow the patient's organism to adapt to the therapeutic. As the study was not powered to detect possible differences in PFS by starting dose, the result of showing no detrimental effect of a lower start dose may be the result of limited power. Clinical trial information: EUPAS9462.

1062 Poster Session (Board #54), Sun, 8:00 AM-11:30 AM

Combination of paclitaxel and LAG3-Ig (IMP321), a novel MHC class II agonist, as a first-line chemoimmunotherapy in patients with metastatic breast carcinoma (MBC): Interim results from the run-in phase of a placebo controlled randomized phase II. *First Author: Francois P. Duhoux, Department of Medical Oncology, King Albert II Cancer Institute, Cliniques universitaires Saint-Luc and Institut de Recherche Expérimentale et Clinique (Pôle MIRO), Université Catholique de Louvain, Brussels, Belgium*

Background: IMP321 is a recombinant soluble LAG3-Ig fusion protein that binds to MHC class II molecules and mediates antigen-presenting cell (APC) activation followed by CD8 T-cell activation. The activation of the dendritic cell network with IMP321 the day after a low dose injection of a single agent chemotherapy may lead to stronger anti-tumor CD8 T-cell responses. We report initial results of the safety run-in of a randomized, placebo-controlled phase IIb trial in patients (pts) with hormone receptor positive (HR^+) MBC receiving first-line weekly paclitaxel. **Methods:** In the safety run-in phase 15 pts with MBC received weekly paclitaxel (80 mg/m^2; D1, D8, D15) in a four week cycle in conjunction with either 6 mg (n = 6; cohort 1) or 30 mg (n = 9, cohort 2) IMP321 injections s.c. (D2 and D16) for 6 cycles. Patients without progressive disease could continue with a maintenance phase of 12 additional injections of IMP321 every 4 weeks. Blood samples for pharmacokinetics and immuno-monitoring were taken in cycle 1 and 4 just before and after IMP321 injection. **Results:** In total 15 pts (median age 53 years) were enrolled between Jan 2016 and Oct 2016. No dose limiting toxicities have been reported. Cytokine release syndrome grade 1 was the only serious adverse event (SAE) related to IMP321 and occurred twice in the same patient. Grade 1 and 2 injection site reactions were the most common related AEs and occurred in 14 pts (93 %). A dose-dependent increase in serum IMP321 concentration was observed among the two dose levels with a C_{max}between 4 and 24 hours. Increased number of circulating monocytes, dendritic cells and increased activation were observed at both dose levels of IMP321, supporting the working hypothesis. **Conclusions:** The 30 mg s.c. IMP321 given every two weeks in combination with weekly paclitaxel is the recommended phase 2 dose which is used in the ongoing randomized placebo controlled phase II part of the study. Clinical trial information: NCT02614833.

1063 Poster Session (Board #55), Sun, 8:00 AM-11:30 AM

Is incomplete estradiol suppression during aromatase inhibitor treatment in post-menopausal patients with breast cancer due to insufficient systemic drug concentrations? *First Author: Daniel Louis Hertz, University of Michigan, Ann Arbor, MI*

Background: Aromatase inhibitors (AI) suppress estrogen biosynthesis and are effective treatments for estrogen receptor (ER)-positive breast cancer. In a prospectively enrolled cohort we observed a subset of post-menopausal women who exhibit high plasma estradiol (E2) concentrations during AI treatment, which could potentially contribute to treatment failure. We tested the hypothesis that incomplete E2 suppression is due to insufficient systemic AI concentrations. **Methods:** Five hundred post-menopausal women with ER-positive breast cancer were randomized to daily exemestane (Exe) 25 mg or letrozole (Let) 2.5 mg. Plasma E2 was measured using GC/MS/MS (lower limit of quantification (LLOQ) = 1.25 pg/mL) at baseline and after 3 months. Let and Exe plasma concentrations measured after 1 or 3 months were compared with the magnitude of E2 depletion using four complementary statistical procedures to assess associations of drug concentrations with: 1) a binary outcome of E2 suppression below LLOQ (logistic regression), 2) 3-month E2 concentrations (linear regression), 3) absolute change from baseline in E2 concentrations (Spearman correlation), and 4) an ordinal outcome defined by E2: decreased to below LLOQ, decreased but not to LLOQ, stayed the same, or increased from baseline (cumulative logistic regression). **Results:** 397 patients with E2 and AI concentration measurements were evaluable (Exe n = 199, Let n = 198). Thirty (7.6%) patients (Exe n = 13, Let n = 17) had E2 concentrations above the LLOQ at 3 months (range: 1.42-63.8 pg/mL). Exe and Let concentrations were not associated with achievement of unmeasurable E2 concentrations, on-treatment E2 concentrations, E2 change from baseline, or ordinal groupings of E2 change (all $p > 0.05$). In a parallel analysis there was no association of estrone-sulfate and drug concentrations (data not shown). **Conclusions:** Our results suggest that circulating drug concentrations do not explain incomplete E2 suppression in women receiving AI therapy. Additional studies are underway to determine whether age, body mass and genetic variation in the aromatase enzyme influence AI treatment response.

1064 Poster Session (Board #56), Sun, 8:00 AM-11:30 AM

Safety and tolerability of the dual PI3K/mTOR inhibitor LY3023414 in combination with fulvestrant in treatment refractory advanced breast cancer patients. *First Author: Anna M. Varghese, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Thephosphatidylinositol 3-kinase (PI3K) /mammalian target of rapamycin (mTOR) pathway is frequently activated in breast cancer. LY3023414 (LY) is an oral ATP- competitive inhibitor that selectively and potently inhibits class I PI3K isoforms, mTOR, and DNA-PK. The recommended phase 2 dose (RP2D) of LY monotherapy was previously established to be 200 mg twice daily (BID). Here we present the safety and preliminary activity data of LY in combination with fulvestrant (F) for breast cancer patients (pts) as part of a multi-cohort Phase 1 study. **Methods:** Pts with advanced HR+, HER2- breast cancer refractory to standard treatment received 200 mg LY BID + 500 mg F (day 1 and 15, then once monthly). Eligible pts had measurable disease and baseline tumor tissue available. Primary objective was to determine a RP2D. Other objectives included assessment of pharmacokinetics (PK), antitumor activity, and biomarker analysis. **Results:** 9 pts received LY + F in the breast cancer expansion cohort. All pts had multiple lines of prior systemic therapy (range 3-12), including chemotherapy. Dose limiting toxicity was observed in one pt in the form of grade (Gr) 3 oral mucositis. Common possibly related adverse events included nausea (5 pts), vomiting (4 pts), oral mucositis (4 pts), decreased appetite (3 pts), fatigue (3 pts), mucosal inflammation (2 pts), and paresthesia (2 pts). No obvious impact of LY on F PK or of F on LY PK was observed. Median duration of treatment was 15 weeks (range 3-63). In the 6 pts evaluable for tumor response, there was 1 durable partial response according to RECIST (still on treatment for $\geq$11 months) and 4 further pts had a decrease in their target lesions for a disease control rate of 56%. The median progression-free survival for this cohort is 4.2 months (90% CI 1.8, NA). Of note, the partial response was observed in a pt harboring an activating PIK3CA mutation (H1047R). Further biomarker analysis is ongoing. **Conclusions:** The RP2D of LY in combination with F is 200mg BID and may cause tumor regression or stabilization in breast cancer pts. Clinical trial information: NCT01655225.

1065 Poster Session (Board #57), Sun, 8:00 AM-11:30 AM

Genetic causes of resistance to entinostat in luminal breast cancer model systems. *First Author: Maki Tanioka, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Based on promising phase II data, the histone deacetylase inhibitor Entinostat (ENT) is in phase III trials for patients with metastatic ER-positive breast cancer. Predictors of sensitivity and resistance, however, remain unknown. **Methods:** Luminal cell lines SKBR3 (ER-/HER2+), BT474 (ER+/HER2+) and MCF7 (ER+/HER2-) were treated with or without ENT at their IC50 doses and their gene expression profiles determined. In addition, a total of 27 MMTV-Neu mouse tumors (luminal) were untreated (N = 8), or treated with ENT at 12 mg/kg for 3 weeks (N = 5), 6 weeks (N = 6), or until progression after complete response (N = 8). We investigated their gene expression profiles by microarray and copy number (CN) by arrayCGH, and utilized the Dawnrank analysis, a network-based bioinformatics tool that integrates DNA and RNA data to identify driver genes, to find predictors of resistance to ENT. **Results:** Supervised analysis of gene expression data coming from the 3 treated cell lines showed significant upregulation of multiple *MYC* gene signatures. Therefore, we constitutively overexpressed *MYC* using lentiviral *MYC* shRNA in SKBR3 and MCF7, and *MYC* overexpression made cell lines more resistant to ENT. In MMTV-Neu mice, both *MYC* gene mRNA and gene signatures were downregulated while cells responded to ENT, and became upregulated when the tumors progressed. aCGH CN analysis revealed that a large portion of mouse Chromosome 4 had DNA CN loss and low gene expression in tumors that progressed while on ENT. Within this region, *JUN* was computationally identified to be a top driver gene associated with resistance. *JUN* was next knocked down using lentiviral *JUN* shRNA in BT474 and T47D, and *JUN* knock-down repeatedly made cell lines more resistant to ENT. *MYC* gene-expression was also upregulated in *JUN*-knockdown BT474 and T47D. Finally, *JUN* CN loss was found in 22% (132/588) of luminal tumors in The Genome Cancer Atlas breast cancer, and all the *MYC* signature scores were significantly higher in JUN-deleted TCGA samples. **Conclusions:** ENT was an effective drug for all of our luminal models, both in vitro and in vivo. Using these models, we selected for resistant variants and identified *MYC* signature expression, and *JUN* CN deletion as being associated with resistance.

1066 Poster Session (Board #58), Sun, 8:00 AM-11:30 AM

Fulvestrant as maintenance therapy after first-line chemotherapy in patients with hormone receptor-positive, HER2-negative advanced breast cancer (FANCY), a prospective, multicenter, single arm phase 2 study. *First Author: Shusen Wang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Fulvestrant is potent for treatment of hormone receptor (HR)-positive advanced breast cancer (ABC); however, few data exist for this regimen as maintenance endocrine treatment after chemotherapy (CT). In our phase 2 trial, we aimed to assess efficacy and tolerability of fulvestrant 500mg as maintenance therapy in patients with disease control after first-line CT. **Methods:** Simon's two-stage design was used. We enrolled post-menopausal women with histologically confirmed HR-positive, HER2-negative ABC, who achieved disease control after four to eight cycles of first-line CT. Fulvestrant 500 mg was intramuscularly injected on day 1, 15, 29, then every 28 (±3) days subsequently, until disease progression or unacceptable toxicity. The primary endpoint was clinical benefit rate (CBR), secondary endpoint included progression-free survival (PFS) since maintenance treatment, PFS since first-line CT, objective response rate (ORR) and safety. **Results:** Between Dec 10, 2013, and Sept 30, 2015, 58 patients were enrolled. 25 (43%) patients were deemed as resistance to endocrine treatment, 36 (62%) patients had a visceral disease. Median follow-up was 21 months. After fulvestrant maintenance treatment, 36 patients remained disease stabilising for at least six months, and eight (14%, 95% CI 6-25) patients achieved a response, resulted in a CBR of 76% (95% CI 63-86), which met its primary endpoint. The median PFS since fulvestrant treatment was 16·1 months (95% CI 10·3 to not reached), and median PFS since first-line CT was 19·5 months (95% CI, 15·6 to not reached). 39 (67%) of 58 patients reported at least one adverse event (AE), of which predominantly were grade 1 or 2. The most common grade 3 AEs were increased alanine aminotransferase in two (3%) patients, increased aspartate aminotransferase in one (2%) patient, and arthralgia in one (2%) patient. No patient discontinued treatment due to AE. **Conclusions:** Fulvestrant 500mg is active in maintenance therapy in non-progrssion patients with HR-positive ABC after first-line CT. Further study is needed to assess long-term outcome of maintenance therapy. Clinical trial information: NCT02000193.

1067 Poster Session (Board #59), Sun, 8:00 AM-11:30 AM

Treat ER$^+$ight: Canadian prospective observational study in post-menopausal HR$^+$HER2$^-$ advanced breast cancer women—First interim analysis (IA). *First Author: Cristiano Ferrario, Segal Cancer Centre, Jewish General Hospital, McGill University, Montreal, QC, Canada*

Background: Treat ER$^+$ight is the first Canadian real-world study enrolling patients (pts) previously exposed to NSAI therapy and currently receiving endocrine therapy (ET) alone or in combination with targeted therapy (ET+TT). **Methods:** This first planned IA describes baseline parameters and adverse event (AE) prevention strategies adopted by 16 centers since Feb 2016 upon enrolling pts initiating ET or ET+TT. **Results:** See Table. **Conclusions:** This IA suggests that pts initiating ET+TT are younger, have a better ECOG status, mostly visceral disease and receive more prophylactic/proactive AE prevention therapies. Insights into real-world dosing and sequence will be presented. Clinical trial information: NCT02753686.

Baseline characteristics	Overall (n=72)	ET (n=34)	ET+TT (n=38)
Age, median yrs (range)	69.0 (37.0 – 88.0)	71.5 (37.0 – 88.0)	65.0 (39.0 – 80.0)
Family history of BC, n (%)	26 (36.1)	11 (32.4)	15 (39.5)
ECOG 0-1, n (%)	46 (63.9)	19 (55.9)	27 (71.1)
Time from diagnosis, median yrs (range)	-	-	-
Primary	5.1 (0.1-37.4)	5.0 (0.5-37.4)	5.3 (0.1-18.8)
Metastatic	1.0 (0.1-16.1)	1.4 (0.1-16.1)	0.9 (0.1-7.7)
Sites of metastases, n (%)	-	-	-
Bone-only	24 (33.3)	13 (38.2)	11 (28.9)
Visceral-only	36 (50.0)	16 (47.1)	20 (57.1)
Prior lines of metastatic therapy, n (%)	-	-	-
0	16 (22.2)	7 (20.6)	9 (23.7)
1	29 (40.3)	13 (38.2)	16 (42.1)
2	27 (37.5)	14 (41.2)	13 (34.2)
Therapy at enrollment, n (%)	-	-	-
Anastrozole	2 (2.8)	2 (5.9)	-
Everolimus + exemestane	28 (38.9)	-	28 (73.7)
Exemestane	7 (9.7)	7 (20.6)	-
Fulvestrant	10 (13.9)	10 (29.4)	-
Letrozole	3 (4.2)	3 (8.8)	-
Palbociclib + fulvestrant	1 (1.4)	-	1 (2.6)
Palbociclib + letrozole	8 (11.1)	-	8 (21.1)
Tamoxifen	12 (16.7)	12 (35.3)	-
Unknown	1 (1.4)	-	1 (2.6)
AE prevention at therapy initiation, n (%)	-	-	-
Patient education	-	-	-
Treatment risks/benefits	61 (84.7)	28 (82.4)	33 (86.8)
AE management	55 (76.4)	24 (70.6)	31 (81.6)
Patient-tailored information / kit provided	22 (30.6)	5 (14.7)	17 (44.7)
Anastrozole	-	1 (20.0)	-
Everolimus + exemestane	-	-	12 (70.6)
Fulvestrant	-	3 (60.0)	-
Letrozole	-	1 (20.0)	-
Palbociclib + fulvestrant/letrozole	-	-	5 (29.4)
Enrollment in patient support call-back program	11 (15.3)	4 (11.8)	7 (18.4)
Prophylactic/proactive prescription for AE prevention	16 (22.2)	1 (2.9)	15 (39.5)

1069 Poster Session (Board #61), Sun, 8:00 AM-11:30 AM

Overall survival (OS) of men and women with breast cancer according to tumor subtype: A population-based study. *First Author: Julieta Leone, Grupo Oncologico Cooperativo del Sur (GOCS), Neuquén, Argentina*

Background: The outcomes of male breast cancer (MBC) and female breast cancer (FBC) according to tumor subtype are poorly known. Our group previously reported the prognostic significance of tumor subtypes in MBC. The aim of this study was to analyze differences in OS between MBC and FBC according to tumor subtype compared with other factors. **Methods:** We evaluated men and women with microscopically confirmed invasive breast cancer between 2010 and 2013 with known estrogen receptor (ER) and progesterone receptor (PR) (together hormone receptor [HR]) status and human epidermal growth factor receptor 2 (HER2) status reported to the SEER program. Patients (pts) with other primary either before or after breast cancer were excluded. Pt characteristics were compared between MBC and FBC. Univariate and multivariate analyses were performed to determine the effect of each variable on OS. **Results:** We included 1,187 MBC and 166,054 FBC pts. Median age for MBC was 65 years (range 26-97) and for FBC was 60 years (range 18-108). Median follow-up was 21 months (range 1-48) for both groups. OS at 3 years for MBC and FBC was 85.6% and 90.4%, respectively ($p = 0.0002$). MBC pts were more frequently ductal, had higher grade, presented with more advanced stage and were more often HR+/HER2- (all $p < 0.0001$). MBC had worse OS than FBC in HR+/HER2- (Hazard ratio [HaR] 1.5; $p = 0.0005$), HR+/HER2+ (HaR 2.8; $p < 0.0001$) and triple negative (TN) (HaR 4.3; $p < 0.0001$) (p for interaction < 0.02). MBC had significantly worse OS than FBC in stage I and II, but similar OS in stage III and IV (p for interaction < 0.01). In multivariate analysis adjusted for age, race, grade, stage, surgery, radiation and marital status; HR+/HER2+ was the only subtype with significant differences in OS between MBC and FBC (HaR 2.0; $p = 0.002$). **Conclusions:** In this cohort, we observed significant differences in the distribution of tumor subtypes between MBC and FBC. OS was significantly different in both groups. Men had worse OS in stage I and II while similar OS in stage III and IV. There were significant differences in OS according to tumor subtype; compared with women, men with HR+/HER2+ tumors had twice the risk of death.

1070 Poster Session (Board #62), Sun, 8:00 AM-11:30 AM

Prognostic significance of tumor subtypes in women with breast cancer according to stage: A population-based study. *First Author: Jose Pablo Leone, University of Iowa, Iowa City, IA*

Background: Tumor subtypes (TS) are an important prognostic tool in breast cancer patients (pts). However, with contemporary therapies the prognosis of different subtypes is unclear. Recently, the AJCC proposed to incorporate TS among other variables in the 8th edition of the staging manual. The aim of this study was to analyze differences in overall survival (OS) by TS according to stage compared with other factors. **Methods:** We evaluated women with microscopically confirmed invasive breast cancer between 2010 and 2013 with known estrogen receptor (ER) and progesterone receptor (PR) (together hormone receptor [HR]) status and human epidermal growth factor receptor 2 (HER2) status reported to the SEER program. Pts with other primary either before or after breast cancer were excluded. Pt characteristics were compared between TS. Univariate and multivariate analyses were performed to determine the effect of each variable on OS. **Results:** We included 166,054 pts. Median age was 60 years (range 18-108). Median follow-up was 21 months (range 1-48). TS distribution was: 72.5% HR+/HER2-, 10.8% HR+/HER2+, 4.8% HR-/HER2+ and 12% triple negative (TN). Pts with HR+/HER2- tumors were older, had lower grade and presented with earlier stage (all $p < 0.0001$). OS at 3 years for each subtype according to stage is shown in the table (p for interaction < 0.0001). These differences in OS by TS continued to be significant for each stage in multivariate analysis adjusted for age, race, grade, histology and marital status. **Conclusions:** In this cohort, we observed significant differences in pt characteristics according to TS. Although HR+/HER2- tumors had better clinicopathologic features, the HR+/HER2+ group had the best OS in most stages. OS was significantly different by TS in each of the 4 stages and these results remained significant in the multivariate model. Pts with TN stage 1 tumors had similar OS as pts with HR+/HER2+ stage 2 tumors. Our results support the incorporation of TS as part of the staging variables in breast cancer.

	Stage 1	Stage 2	Stage 3	Stage 4
HR+/HER2-	97.2%	93.6%	85.5%	46.6%
HR+/HER2+	97.1%	94.5%	87.8%	54.8%
HR-/HER2+	96.4%	90.8%	79.5%	46.2%
TN	94.7%	85.9%	60%	14.7%
p	< 0.0001	< 0.0001	< 0.0001	< 0.0001

1071 Poster Session (Board #63), Sun, 8:00 AM-11:30 AM

Retrospective-prospective blinded evaluation predicting efficacy of epirubicin by a multigene assay in advanced breast cancer within a Danish Breast Cancer Cooperative Group (DBCG) cohort. *First Author: Anna Sofie Kappel Buhl, Department of Oncology, Herlev Hospital, Herlev, Denmark*

Background: Epirubicin remains a cornerstone in the treatment of primary and advanced breast cancer. This study evaluated the predictive effect of a multigene mRNA-based Drug Response Predictor (DRP) in the treatment of advanced breast cancer (ABC). We applied a mathematical method combining *in vitro* sensitivity with gene expression patterns in tumors. Previously the DRP has been broadly validated[1, 2] including retrospective validation of epirubicin[3]. **Methods:** Among 838 consecutive patients from a DBCG cohort 137 patients were treated with epirubicin between May 1997 and November 2016 at one of the participating sites. Patients were examined every 9 to 12 weeks by CT scan and clinical evaluation. After patient informed consent, mRNA was isolated from formalin fixed paraffin embedded tumor tissue from diagnostic biopsies and analyzed using Affymetrix arrays. Blinded predictions of epirubicin efficacy were compared to clinical data collected retrospectively from patients' medical records. Statistical analysis was done using Cox proportional hazards model adjusted for treatment line. Primary endpoint was progression free survival (PFS). **Results:** Median time to progression was 9.3 months (95% CI: 7.2-13.2). Of the 137 patients, four received epirubicin more than once. Scoring the DRP as a continuous covariate demonstrated that the DRP was significantly associated to PFS (p = 0.02). The estimated hazard ratio was 0.56 (90% CI: 0.35-0.89) comparing two patients with DRP score differing by 50 percentage points. The estimated median time to progression for a patient with a DRP value of 25% was 7 months versus 13 months for a patient with a DRP value of 75%. No interaction with previous adjuvant chemotherapy was observed (p = 0.98). **Conclusions:** The current study demonstrates a potential clinical value by being able to select patients that benefit from epirubicin against patients predicted not to benefit sparing the last patients unnecessary toxicity. Studies evaluating the predictor in an adjuvant setting will follow. [1] Knudsen et al PLoS ONE 9(2): e87415; [2] Buhl et al PLoS ONE 11(5): e0155123; [3] Wang et al JNCI 105(17): 1284-91

1072 Poster Session (Board #64), Sun, 8:00 AM-11:30 AM

Characterization of bone only metastasis (BOM) patients (pts) with respect to tumor subtypes (TS). *First Author: Amanda Marie Parkes, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Metastatic breast cancer (MBC) pts with BOM are a unique population with limited characterization. Our goal was to characterize the TS of BOM pts, evaluating differences in sites and types of bone metastases (BM), treatment, and survival. **Methods:** We identified pts followed at MD Anderson Cancer Center from 01/01/1997 to 12/31/2015 for at least 6 months with a BOM diagnosis as first site of metastasis (met). TS was assessed by initial biopsy immunohistochemistry (IHC) (Table 1) with hormone receptor (HR) + defined as ER or PR >10%. **Results:** We identified 1445 pts with BOM, 1049 with initial biopsy IHC available to group into TS (Table 1). Among BOM pts, the majority had multiple BM at diagnosis (1141/79%), most in both the axial (Ax) and appendicular (App) skeleton (53%). Of the 808 pts with BM categorized on imaging at diagnosis, the majority were lytic (389/48%), with 21% sclerotic, 18% mixed, and 12% blastic. Time from breast cancer diagnosis to first met differed significantly by TS, $\chi^2(3) = 94.33$, $P < .0001$, with median time to met longer for pts with blastic (3.08 years; 95% CI 2.03, 4.24) versus lytic lesions (1.75 years; 95% CI 1.27, 2.17). **Conclusions:** BOM patients are a unique MBC subpopulation, more commonly found in luminal TS patients. Our study demonstrates prognostic differences in BOM pts specific to TS and emphasizes the need for further study of BOM patients.

Tumor Subtype *n = 1049*	# BM at Diagnosis	BM Location at Diagnosis	Treatment	Median Time from Diagnosis to First Met *years (95% CI)*	Median OS *years (95% CI)*
Luminal A-like HR+ HER2- *(826/79%)*	Multiple: 80% Single: 19% Unk: 1%	App: 12% Ax: 32% Both: 56% Unk: 1%	NAC: 21% AC: 37% AH: 20%	1.92 (1.58, 2.17)	9.42 (8.33, 9.95)
Luminal B-like HR+ HER2+ *(118/11%)*	Multiple: 81% Single: 19%	App: 8% Ax: 44% Both: 47%	NAC: 19% AC: 42% AH: 36%	0.65 (0.15, 1.47)	8.08 (6.31, 9.78)
Triple negative HR- HER2- (72/7%)	Multiple: 79% Single: 19% Unk: 1%	App: 10% Ax: 39% Both: 53%	NAC: 19% AC: 49% AH: 10%	1.13 (0.61, 1.37)	4.03 (3.31, 6.65)
HER2 positive HR- HER2+ *(33/3%)*	Multiple: 76% Single: 24%	App: 9% Ax: 42% Both: 45% Unk: 3%	NAC: 15% AC: 39% AH: 3%	0.44 (0.05, 1.05)	5.78 (4.39, 10.45)

NAC = Neoadjuvant chemotherapy; AC = Adjuvant chemotherapy; AH = Adjuvant hormonal therapy; Unk = Unknown

1073 Poster Session (Board #65), Sun, 8:00 AM-11:30 AM

NCI Breast Cancer Steering Committee Working Group (WG) report on meaningful and appropriate endpoints for clinical trials (CT) in metastatic breast cancer (MBC). *First Author: Andrew David Seidman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There is significant heterogeneity in the natural history of MBC. Several recent randomized CT have yielded statistically significant advantages for the experimental arm, but neither led to regulatory approval nor practice change. Formal guidance for industry on CT endpoints provided by the US FDA in 2007 was not disease-specific. Patient-focused drug development is mandated by Prescription Drug User Fee Act V. Our WG sought to create specific consensus on endpoints for MBC CT focusing on subtype and line of therapy, with sensitivity to various stakeholders. **Methods:** A WG composed of medical oncologists, statisticians, advocates, FDA and NCI liaisons performed a systematic literature review of MBC natural history, CT endpoints by subtype (HR+/HER2-, HR+/HER+, HR-/HER2-, HR-/HER2+), and line of therapy (n = 146 papers). External expertise was obtained on industry perspectives, big data and real world evidence (RWE), and patient reported outcomes (PROs). WG members voted anonymously on statements and positions generated from deliberation. **Results:** The WG reached consensus on definitions relevant to contemporary CT endpoints. WG recommendations on the appropriate choice of OS or PFS are sensitive to expected post progression survival (PPS), and proportional and absolute gains. Currently, for HR-/HER2- MBC, OS is preferred as the optimal primary endpoint regardless of line of therapy; PFS is preferred in settings where expected PPS is longer. Toxicity can outweigh modest gains in PFS; scant data exist to gauge how patients value PFS gain vs toxicity. Where new agents may prolong PFS without impacting OS, exploring/validating graphic approaches that capture grade and timing of toxicity and PROs is warranted. An overview of WG Consensus Statements will be presented in detail. **Conclusions:** CT design for MBC should be sensitive to natural history (PPS), availability of other effective agents, PROs and toxicity burden. As unique subtypes (e.g. AR+) and novel therapies (e.g. immunotherapy) emerge, reassessment of relevant benchmarks is indicated. Rigorous big data approaches providing insights from RWE may inform CT endpoints in the future.

1074 Poster Session (Board #66), Sun, 8:00 AM-11:30 AM

Primary surgery versus no surgery in synchronous metastatic breast cancer: Patient-reported outcomes of the ABCSG 28 Posytive trial. *First Author: Vesna Bjelic-Radisic, Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria*

Background: The ABCSG 28 Posytive trial compared primary surgery versus primary systemic therapy without surgery in synchronous metastatic breast cancer. The primary aim of the study was to investigate whether immediate resection of the primary tumor followed by standard systemic therapy improves median survival compared with no surgical resection (NCT01015625). This report describes quality-of-life (QoL) results. **Methods:** Patients were randomized between 2011 and 2015. Patients completed the EORTC QLQ-C30 and EORTC QLQ-BR 23 before treatment and every 6 months during follow-up. **Results:** 90 patients (45 with surgery, 45 with primary systemic therapy without surgery) from 15 centers were included in the QoL analysis. At 6 months patients after surgery reported more insomnia, breast symptoms and arm symptoms than patients without surgery, but these differences were no longer present at later follow-up visits. In the univariate and multivariate analysis the global health status and physical functioning scales of EORTC QLQ C30 were statistically significant predictors for OS and TTP ($p < 0.05$). Over a 24-month follow-up, patients > 60 years showed more QoL impairments than those < 60 years, independent of treatment. Patients < 60 years had better physical functioning and less fatigue, appetite loss, constipation and breast symptoms than older patients. There were no differences in QoL between patients with bone metastases vs those with visceral ± bone metastases. **Conclusions:** In patients with primary metastatic breast cancer primary surgery does not appear to improve QoL. Global health status and physical functioning scales of EORTC QLQ-C30 appears to be a predictive factor for OS and TTP. Clinical trial information: NCT01015625.

1075 Poster Session (Board #67), Sun, 8:00 AM-11:30 AM

Trop2 gene expression (Trop2e) in primary breast cancer (BC): Correlations with clinical and tumor characteristics. *First Author: Neelima Vidula, Massachusetts General Hospital, Boston, MA*

Background: Trophoblast antigen 2 (Trop2) is a glycoprotein expressed by many cancers. A phase I study of the trop2 antibody drug conjugate (ADC) IMMU-132 has shown promising activity in triple negative (TN) BC. We studied associations of primary BC trop2e with clinical characteristics, outcomes, and selected genes in publically available databases. **Methods:** Trop2e was evaluated with microarray data from the neoadjuvant I-SPY 1 (n=149), METABRIC (n=1992) & TCGA (n=817) databases. Associations with clinical features were assessed with the Kruskal-Wallis test (all). Correlations with chemotherapy response were evaluated with the Wilcoxon rank sum test (I-SPY 1) & with recurrence free survival (RFS) by the Cox proportional hazard model (I-SPY 1 & METABRIC). Pearson correlations were used to study associations between trop2e & selected genes (all). **Results:** In all 3 datasets, trop2 was detectable and had a wide range of expression in all BC subtypes. In I-SPY 1, trop2e did not vary by hormone receptor (HR) & HER2 or intrinsic subtype; in METABRIC & TCGA trop2e was lower in HER2+ than HR+/HER2- & TNBC (METABRIC p=0.03, TCGA p=0.007) & in HER2+ enriched and luminal B BC ($p < 0.001$, METABRIC & TCGA). Trop2e was higher in grade I vs. II/III BC in METABRIC ($p < 0.001$). No association with chemotherapy response was seen (I-SPY 1) or with RFS (I-SPY 1 & METABRIC). The table below shows significant ($p<0.05$) gene correlations with trop2e in ≥2 datasets. **Conclusions:** Trop2e is seen in all BC subtypes, particularly luminal A and TNBC. Trop2e correlates with the expression of genes involved in cell epithelial transformation, adhesion, and proliferation and inversely with immune genes, which may contribute to tumor growth. These findings support the use of trop 2 directed ADC in all BC subtypes.

	ISPY-1 (n=149)	METABRIC (n=1992)	METABRIC TN (n=320)	TCGA (n=817)
POSITIVE Correlations (r)				
Epithelial & adhesion				
VTCN1	0.41	0.25	0.29	0.29
GRHL1	0.26	0.26	0.18	0.35
MUC1	0.37	0.39	0.51	0.33
Proliferative				
PI3KCA	0.35	0.13	NS	NS
KIT	0.20	0.12	0.13	0.14
FGFR2	0.23	NS	NS	0.08
STAT5A	0.22	NS	NS	0.10
AKT1	NS	0.08	NS	0.19
INVERSE Correlations (r)				
Immune				
CTLA4	-0.26	-0.16	-0.19	NS
PDCD1	-0.22	-0.17	-0.16	NS
HAVCR2	NS	-0.22	-0.22	-0.08

NS: non-significant

1076 Poster Session (Board #68), Sun, 8:00 AM-11:30 AM

The Metastatic Breast Cancer (MBC) project: Accelerating translational research through direct patient engagement. *First Author: Nikhil Wagle, Dana-Farber Cancer Institute, Boston, MA*

Background: The Metastatic Breast Cancer Project is a nationwide research study, launched in Oct 2015 in collaboration with patients (pts) and advocacy groups, that directly engages pts through social media and seeks to empower them to share their experiences, clinical information, and samples to accelerate research. **Methods:** MBC pts enroll by providing their information at mbcproject.org. Pts are sent a saliva kit and asked to mail back a sample which is used to extract germline DNA. We contact pts medical providers and obtain medical records (MRs) and stored tumor samples. Pts may also submit a blood sample, used to extract cell free DNA (cfDNA). Whole exome sequencing (WES) is performed on tumor, germline, and cfDNA; transcriptome sequencing is performed on tumor. Clinical and genomic data are used to generate genomic landscapes in pt subgroups and to identify mechanisms of response and resistance to therapies. Data are shared widely through public databases. Pts receive regular study updates. **Results:** In 12 months, 2908 MBC pts from 50 states enrolled. 95% completed the 16-question survey about their cancer, treatments, and demographics. 1730 (60%) completed the online consent form. 100-200 pts continue to enroll monthly. To date, 1539 saliva kits were mailed and 1120 samples were received (73%). 992 unique treating institutions were reported by pts, including 733 institutions reported by only 1 pt each and 5 institutions reported by more than 40 pts each. We have obtained MRs from 253 patients (67% yield) and tumor samples from 85 pts (67% yield). WES was successfully completed for 79 tumors of 88 attempted (90%). WES has been performed on initial cfDNA samples. **Conclusions:** A direct-to-patient approach enabled rapid identification of thousands of MBC pts willing to share MRs, saliva, and tumor samples, including many with rare phenotypes. Remote acquisition of MRs, saliva, tumor, and blood for pts located throughout the US is feasible. We estimate that for ~33% of consenting patients, we can obtain medical records, saliva, and tumor tissue. Genomic analysis of tumor and cfDNA from subgroups including young pts, pts with extraordinary responses, and pts with de novo MBC will be presented.

1077 Poster Session (Board #69), Sun, 8:00 AM-11:30 AM

The role of high-dose chemotherapy (CT) and stem-cell support in high-risk stage II, locally advanced, and responding stage IV breast cancer (BC): The Israeli experience with 20 years median follow-up. *First Author: Idit Peretz, Rabin Medical Center, Petah Tikva, Israel*

Background: Lately, updated data led the medical community to reconsider the use of intensive CT with stem-cell support for selected groups of BC patients (pts). Herein, we provide an update on a study investigating the efficacy, feasibility, and toxicity of high-dose CT with stem-cell support in pts with high-risk stage II, chemosensitive stage III and IV BC. **Methods:** The protocol offered adjuvant/neoadjuvant/induction doxorubicin-based CT, 75-90 mg/m^2 X 4 courses followed by high-dose CT (cyclophosphamide 6000 mg/m^2, carboplatin 800 mg/m^2, and thiotepa 500 mg/m^2) and autologous stem cell support with growth factors. Post-transplant local radiotherapy was delivered. Pts who were hormone receptor (HR) positive received Tamoxifen. **Results:** From 2/1994 to 11/1998, 292 BC pts were referred to the study from all Israeli oncology centers. Median follow-up from transplant was 20 (range, 18-22) years; 119 had stage 2 disease (42 with 4-9 positive nodes, 77 with ≥10 positive nodes); 87 had stage 3 disease, of whom 50 had locally advanced/inflammatory BC treated with neoadjuvant CT; and 86 had chemosensitive stage IV BC. Two acute transplant-related deaths and one death due to late transplant-related toxicity were reported. Median age at transplant was 45 (range, 24-63) years. Overall survival (OS) by HR status is presented in the table. In total, 167 of the 292 pts died (based on death status data retrieved from the Registry of the Ministry of the Interior), representing OS of 42%. The OS rates for stage II, III, and IV were 55%, 45%, and 23%, respectively. **Conclusions:** Long-term accurate follow-up of pts receiving well-defined treatments remains an important tool in cancer research. High-dose CT with stem-cell support could represent a therapeutic/curative option in select BC patients in all disease stages. Reintroduction of this approach should be re-examined.

	N (HR+/HR-)	OS: All pts, n/n (%)	OS: HR+ pts, n/n (%)	OS: HR-neg pts, n/n (%)	Missing data, n
Stage 2	119 (74/45)	66/119 (55%)	40/66 (60%)	26/66 (40%)	-
Stage 3	87 (36/33)	39/87 (45%)	14/39 (36%)	17/39 (43%)	18 (8 alive)
Stage 4	86 (49/29)	20/86 (23%)	14/20 (70%)	4/20 (20%)	8 (2 alive)

1078 Poster Session (Board #70), Sun, 8:00 AM-11:30 AM

Evolution of overall survival according to year of diagnosis (2008-2014) and subtypes, among 16703 metastatic breast cancer (MBC) patients included in the real-life "ESME" cohort. *First Author: Suzette Delaloge, Institut Gustave Roussy, Villejuif, France*

Background: Real-life data may help checking that public investments match closely medical needs. During the last decade, several drugs have been released on the market for MBC on the basis of a potential impact on overall survival (OS). Based on the large real-life ESME cohort, we aimed to describe the time evolution of MBC OS according to main phenotypes. **Methods:** ESME is a unique MBC national cohort including all consecutive patients (pts) who initiated treatment for MBC between 1/01/08 and 31/12/14 in the 18 French comprehensive cancer centres. ESME collects retrospective data using clinical trial-like methodology including quality assessments. Database lock was 8/12/2016. Primary objective was the impact of year of MBC diagnosis on OS. Multivariate Cox regressions were used with adjustment for main prognostic covariates. **Results:** 15170 out of 16703 pts in ESME had full IHC data allowing their classification as HR+HER2- (N=9922), HER2+ (N=2863), or HR-HER2- (N=2321) cases. Median FU and OS for the whole cohort are 4.05 yrs [95 CI: 3.98-4.12], and 3.1 yrs [95 CI: 3.03-3.18] respectively. In the adjusted multivariate analysis, year of MBC diagnosis, age at MBC, subtype (using HER2+ as reference), disease-free interval (DFI), visceral involvement, and number (nbr) of metastatic sites are significant OS predictors (table) although with low effect for the first item. Age at MBC, DFI, visceral involvement, and nbr of metastatic sites remained significant prognostic variables in subtypes. Year of diagnosis was no longer significant in HR+HER2- nor HR-HER2- cases (HR=0.997, p=0.71 and HR=0.997, p=0.84), while it was highly significant in HER2+ cases (HR=0.91, $p<0.0001$). **Conclusions:** Although OS of MBC has slightly improved over the past decade, this remains mostly confined to HER2+ cases, highlighting the need for new strategies for the luminal and triple negative populations.

	HR (95% CI)
Year of diagnosis	0.982 (0.969-0.994)
Older age	1.014 (1.012-1.016)
HR+ HER2-	1.179 (1.11-1.252)
HR- HER2-	3.122 (2.909-3.35)
Shorter DFI	0.975 (0.971-0.979)
Visceral metastasis	1.237 (1.171-1.306)
Nbr of metastatic sites	1.253 (1.226-1.281)

1079 Poster Session (Board #71), Sun, 8:00 AM-11:30 AM

Pharmacogenetics revisits bevacizumab in breast cancer patients: An ancillary analysis of the UCBG trial COMET—A French multicentric prospective study from R&D UNICANCER. *First Author: Gerard A. Milano, Oncopharmacology Unit, Centre Antoine Lacassagne, Nice, France*

Background: Bevacizumab (Beva) is no longer unanimously recommended in the management of breast cancer (BC). Given the absence of faithful predictors of Beva treatment outcome, we made the hypothesis that constitutional gene polymorphisms could play a role in this context. We report the pharmacogenetic ancillary study of the prospective COMET trial conducted in advanced BC patients (pts) receiving first-line Beva associated with paclitaxel. **Methods:** Relevant targeted gene polymorphisms were analyzed (blood) in 203 prospective pts (mean age 55.3, median follow-up 24 months). VEGFA at positions -2578C > A (rs699947), -1498T > C (rs833061), -634G > C (rs2010963), and 936C > T (rs3025039) were analyzed by PCR-RFLP. VEGFR1 319A > C (rs9582036), VEGFR2 at positions 604C > T (rs2071559), 1192C > T (rs2305948), 1416T > A (rs1870377), IL8 251T > A (rs4073), CYP2C8 139C > T (rs1572080), 399T > C (rs10509681) and ABCB1 at positions 1199 C > TA (rs2229109), 2677G > TAC (rs2032582) were analyzed by Mass-Array Agena. ABCB1 1236C > T (rs1128503) and 3435T > C (rs1045642) were analyzed by pyrosequencing. All fitted HWE. **Results:** Median progression-free survival (PFS) was 10.8 months. VEGFR1 319A allele was associated with longer PFS (p = 0.03). The VEGFA-1498T allele was significantly associated with both longer overall survival (OS) (p = 0.005) and PFS (p = 0.065). The VEGFA -2578C allele was associated with greater OS (p = 0.002) and PFS (p = 0.071). These two VEGFA polymorphisms were in linkage disequilibrium ($p < 0.0001$). Multivariate Cox analysis showed that VEGFA -2578 (p = 0.001) and VEGFR2 1416 (p = 0.025) were significant predictors of OS: the score of favorable alleles (VEGFA -2575C and VEGFR2 1416T) was highly associated with OS (p = 0.0003), with median survival at 24 months being 30% for score 0 (95%CI 15-61), 65% for score 1 (95%CI 55-75) and 90% for score 2 (95%CI 67-90). **Conclusions:** Application of an easy-to-perform low-cost genotyping test may identify strong predictors of Beva outcome in metastatic BC pts. In the current era of precision medicine, a pharmacogenetic-based personalized Beva therapy deserves to be prospectively validated in BC pts. Clinical trial information: 2012-A00244-39.

1080 Poster Session (Board #72), Sun, 8:00 AM-11:30 AM

Distribution of receptor tyrosine kinase (RTK) nsSNPs in breast cancer (BC) patients (pts) using next-generation sequencing (NGS). *First Author: Lindsay Kaye Morris, College of Medicine, The University of Tennessee Health Science Center, Memphis, TN*

Background: Non-synonymous SNPs (nsSNPs) discovered by NGS occurring in RTKs' conserved topology in pts with BC may promote oncogenic signaling and hence may be actionable. **Methods:** We analyzed BC pts for nsSNPs in 29 RTKs identified by tumor profiling with NGS from Caris during 2013-2015. Mutations were classified by location including the tyrosine kinase domain (TKD), extracellular domain (ECD), transmembrane domain (TM), juxtamembrane domain (JM) and carboxy-terminal (CT) regions. nsSNPs underwent *in silico* analysis using PolyPhen-2 (Harvard) to determine pathogenicity. **Results:** 79 pts were identified with a median age of 58 years (range 32-83); 99% female; 60% white, 38% black and 2% other. 77 pts were classifiable with 8 (10%) triple-positive, 35 (46%) ER+/PR+/HER2- (ER/PR+), 10 (13%) ER-/PR-/HER2+ (HER2+) and 24 (31%) triple-negative. 78 nsSNPs and 1 Caris-reported pathogenic substitution of *ERBB3* (TKD S846I) were found. 52/79 (66%) pts had ≥1 RTK nsSNP (range 0-4); 28/29 RTKs had ≥1 nsSNP with median of 2 (range 0-15). In 28 pts (35%), 40% of nsSNPs were predicted to be damaging (pnsSNP) and 3 pts had 2 pnsSNPs. 17/29 RTKs had pnsSNPs, median 1 (range 0-9). The most commonly mutated RTKs were *ROS1* (9/15 variants were pnsSNPs), *ALK* (3/4), *EPHA5* (3/3), *FLT4* (2/5), *cKIT* (2/4) and *ERBB4* (2/3). *ROS1* and *ALK* nsSNPs were most-frequently seen in ER/PR+ (9/15 pnsSNPs), triple-positive (3/3) and HER2+ (0/2) pts; no triple-negative pts had such variants. 100% triple-positive pts (6/8 pnsSNP), 69% ER/PR+ (18/35), 60% HER2+ (2/10) and 58% triple-negative (3/24) had RTK nsSNP. nsSNP were spread in all 5 RTK regions: 58% localized to the ECD (20/45 pnsSNPs), 17% TKD (8/13), 9% CT (2/7), 9% TM (1/7) and 8% JM (1/6) lesions were found. Of 9 *ROS1* pnsSNPs, 7 were ECD, 1 CT and 1 TKD. **Conclusions:** 35% of BC pts had pnsSNP in RTKs across various phenotypes including frequent mutations in potentially actionable genes such as *ROS1* and *ALK*. 26% of ER/PR+ pts had pnsSNPs in *ROS1* or *ALK*. nsSNPs in the ECD or TKD were most likely to be damaging.

1081 Poster Session (Board #73), Sun, 8:00 AM-11:30 AM

Immune microenvironment in brain metastases of breast cancer. *First Author: Rin Ogiya, Tokai University School of Medicine, Isehara, Japan*

Background: In patients with brain metastasis (BM) of melanoma or lung cancer, significant activity of immune checkpoint inhibitors has been reported. However, details of the immune microenvironment in BM has not been unveiled. In this study, we used immunohistochemistry (IHC) to compare primary breast tumors and BM tumor samples with respect to tumor infiltrating lymphocytes (TILs) and tumor characteristics related to the immune system. **Methods:** We retrospectively identified 107 patients with breast cancer, diagnosed with BM, who had undergone surgery between 2001 and 2012 at 8 institutions. We collected 191 samples which included both BM samples alone and pair-matched samples (primary and BM). Hematoxylin and eosin (H&E) stained slides were evaluated for stromal TILs in 10% increments (0–1%, > 1– < 10%, 10%–100%). IHC was performed using the following primary antibodies: CD4, CD8, Foxp3, PD-L1, PD-L2 and HLA class I. The cells positive for each antibody signal were counted automatically using ImageJ (NIH). The expression of PD-L1, PD-L2, and HLA on the tumor cells was scored as 0 (negative), 1 (weak or focal), or 2 (strong). **Results:** The median category of TILs of BM tumors was > 1– < 10% (range: 1–30%). Forty-six pair-matched samples were analyzed and the percentage of TILs in the primary breast tumor was significantly higher than that in BM samples (paired t-test, $P < 0.01$). The number of CD4/CD8/Foxp3 positive cells in primary breast tumor was also significantly higher than in BM samples (paired t-test, $P < 0.05$ for all categories). The negative/positive conversion occurred with the expression of HLA/PD-L2 on tumor cells (paired t-test, P = 0.03/0.06, respectively). No significant difference was observed in the overall survival (OS) of patients, from initial BM, based on high or low TILs (log-rank test, P = 0.131). However, triple negative breast cancer patients with low TILs had significantly shorter OS compared with patients with high TILs (log-rank test, P = 0.04). **Conclusions:** We demonstrated that TILs in BM tumors was significantly lower as compared to primary breast tumors. The expression of immune related molecules on tumor cells was converted in BM tumors.

1082 Poster Session (Board #74), Sun, 8:00 AM-11:30 AM

A phase II, multicenter, randomized trial of eribulin plus gemcitabine (EG) vs. paclitaxel plus gemcitabine (PG) in patients with HER2-negative metastatic breast cancer (MBC) as first-line chemotherapy (KCSG BR13-11, NCT02263495). *First Author: Kyung Hae Jung, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*

Background: PG chemotherapy is one of the preferred chemotherapeutic regimens for patients with MBC. Eribulin mesylate is a non-taxane inhibitor of microtubule dynamics of the halichondrin class. A recent pooled analysis with eribulin showed improved overall survival (OS) in various patient subgroups. Furthermore, eribulin may have rational benefit compared with paclitaxel in terms of neurotoxicity. **Methods:** This study was a prospective randomized phase 2, open-label, two-arm, multi-center study comparing EG with PG chemotherapy for patients with HER-2 negative MBC as first-line treatment. Histologically confirmed breast cancer patients, at least 19 years of age, with no prior history of chemotherapy for MBC with evaluable lesions were included. Prior hormonal therapy as a treatment of Hormone Receptor (HR)-positive MBC was allowed. This design was hypothesized that EG chemotherapy would not be inferior to PG chemotherapy. The primary endpoint was Progression-Free Survival (PFS). Estimated 6 mo. PFS rate for each arm was 70%. The secondary endpoints were: Time to Treatment Failure (TTF); OS; neuropathic scale; toxicity; clinical benefit rate. **Results:** A total of 118 patients (median age: 50, 24-66) were enrolled between 2015 and 2016, and were randomly assigned to PG (n = 59) or EG (n = 59) chemotherapy. Mean number of metastatic sites was 3 (1-8). Six month PFS rates for both arms were 72% for EG and 73% for PG arm (p = 0.457). PFS in PG arm tends to be longer than in EG group (median PFS 12.6 for PG *vs.* 9.6 months for EG) without statistical significance. In addition, there was no significant difference in OS between the two groups (not reached *vs.* 21.2 months, p = 0.223). The median numbers of chemotherapy cycles of both groups were 8 for EG and 10 for PG (range 2-32). CBRs were 44% for EG and 45% for PG arm. Major toxicities were neutropenia and neurotoxicity. Grade II or more neurotoxicity was more common in PG than in EG group (40% *vs.*25%). **Conclusions:** EG chemotherapy showed similar clinical benefit with PG chemotherapy in terms of PFS but, more favorable neurotoxicity than PG chemotherapy. Clinical trial information: NCT02263495.

1083 Poster Session (Board #75), Sun, 8:00 AM-11:30 AM

A phase I trial of mifepristone (M), carboplatin (C), and gemcitabine (G) in advanced breast and ovarian cancer. *First Author: Erica Michelle Stringer, University of Alabama at Birmingham, Birmingham, AL*

Background: Glucocorticoid receptor (GR) activity inhibits chemotherapy-induced apoptosis, and GR antagonism with m enhances chemotherapy sensitivity in GR+ breast (B) and ovarian cancer (OC) cells. C+G is a commonly used regimen for B and OC. We report the results of a phase I trial of the GR antagonist m plus C+G in patients with advanced B and OC. **Methods:** A standard "3+3" dose escalation phase I study was performed. Objectives were to assess the safety and tolerability of the regimen, and to determine the recommended phase 2 (RP2D) dose of M+C+G. C+G was administered on days 1 and 8 of a 21 day cycle, and m was administered the day prior to and the day of chemotherapy. The starting dose level (DL) was 1, with additional DLs as follows in the table. **Results:** 31 patients (pts) with a median age of 54 years (range 32-76) were enrolled. 18 pts had BC (3 ER+, 15 triple-negative), and 13 had high grade serous OC (11 platinum-sensitive, 2 platinum-resistant). The median number of prior therapies for advanced BC was 1 (range 0-5) and for OC was 2 (range 1-3). Dose de-escalation was necessary due to the DLT of neutropenia. After DL -3, prophylactic G-CSF (PGF) was instituted. The RP2D was C AUC 2, G 600 mg/m2, m 300 mg with PGF administered on day 9. Of the BC pts, 2 had a complete response (CR), 2 had a partial response (PR), 8 had stable disease (SD), 4 had progressive disease (PD). Of the OC pts, there was 1 CR (CR2 lasted > 27 mos; CR1 lasted only 8 mos), 1 PR, 6 SD, and 3 PD. 4 pts were inevaluable for response. **Conclusions:** These data suggest that M+C+G is safe and tolerable, and the most common DLT is neutropenia. This was easily managed with the institution of PGF. Studies correlating tumor GR expression with response are ongoing, and may help identify patients who are most likely to benefit from this combination. Clinical trial information: NCT02046421.

	Dose				
DL	Carboplatin	Gemcitabine	Mifepristone	Pts Enrolled	Dose-limiting Toxicities (DLTs)
1	AUC 2	1000 mg/m2	300 mg	4	Neutropenia (2)
-1	AUC 2	800 mg/m2	300 mg	3	Neutropenia (2) ALT elevation (1)
-2	AUC 2	600 mg/m2	300 mg	8	Neutropenia (1) Rash (1)
-3	AUC 2	400 mg/m2	300 mg	7	Neutropenia (1) Thrombocytopenia (1)
-1a*	AUC 2	800 mg/m2	300 mg	3	Neutropenia (2)
-2a*	AUC 2	600 mg/m2	300 mg	6	Neutropenia (1)

*Prophylactic G-CSF administered on day 9

1084 Poster Session (Board #76), Sun, 8:00 AM-11:30 AM

A phase 2 study of napabucasin with weekly paclitaxel in previously treated metastatic breast cancer. *First Author: William Jeffery Edenfield, Greenville Health System Cancer Institute, Greenville, SC*

Background: Napabucasin is a first-in-class cancer stemness inhibitor, identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells (Li et al PNAS 112 (6):1839, 2015). Napabucasin has shown potent synergistic preclinical anti-tumor activity with paclitaxel (PTX). In a phase Ib dose escalation study in patients (pts) with advanced solid tumors, Napabucasin plus weekly paclitaxel was well tolerated. A phase II expansion cohort was opened for pts with previously treated metastatic breast cancer (MBC). **Methods:** Pts with metastatic MBC for whom weekly PTX was a reasonable treatment option received Napabucasin 240, 480, or 500 mg orally, twice daily in combination with paclitaxel 80 mg/m2 IV weekly on 3 of every 4 weeks. Adverse events were evaluated using CTCAE v4.03 and objective tumor assessments were obtained every 8 weeks per RECIST 1.1 criteria. **Results:** A total of 50 pts were enrolled including 34 with triple-negative disease (negative for estrogen receptor [ER], progesterone receptor [PR], and Her2 and no prior history of positive receptor status). There were 9 pts positive for ER, PR, or Her2 and refractory to targeted agents, and 7 pts with conversion to triple-negative disease from pathology previously positive for ER, PR or Her2. Pts were heavily pre-treated, having received a median of 5 prior lines of systemic therapy. All but 3 patients had received previous systemic treatment with a taxane. Napabucasin + PTX was well tolerated. Grade 3 AE occurring in ≥ 5% patients was diarrhea (n = 4), and 1 pt had grade 4 diarrhea. The objective response rate (ORR), disease control rate (DCR), median progression free survival (mPFS), and median overall survival (mOS) for all pts and for each sub-group are summarized in the table. **Conclusions:** Napabucasin (BBI-608) plus weekly paclitaxel has demonstrated safety, tolerability, and encouraging signs of anti-cancer activity in pts with pretreated metastatic breast cancer. Further clinical evaluation of this combination regimen in controlled trials is warranted. Clinical trial information: NCT01325441.

	n	ORR	DCR (at 8 weeks)	mPFS (months)	mOS (months)
All MBC	50	20%	50%	2.5	9.1
Triple-Negative	34	18%	47%	2.3	7.2
Receptor Positive	16	25%	56%	5.5	not reached

1085 Poster Session (Board #77), Sun, 8:00 AM-11:30 AM

Extracellular matrix (ECM) protein fragments in serum and outcomes in two metastatic breast cancer cohorts. *First Author: Nicholas Willumsen, Nordic Bioscience, Herlev, Denmark*

Background: Extracellular matrix (ECM) is the non-cellular component of all tissues. Increased ECM formation and matrix metallo-protease (MMP) mediated ECM degradation are parts of tumorgenesis. The altered ECM remodeling generates specific ECM fragments that are released into the circulation. We evaluated the association of specific ECM/collagen fragments measured in serum with outcomes in two independent metastatic breast cancer (MBC) cohorts. **Methods:** C1M (MMP-degraded type I collagen), C3M (MMP-degraded type III collagen), C4M (MMP-degraded type IV collagen), and PRO-C3 (pro-peptide reflecting truetype III collagen formation) were measured by ELISA in pre-treatment serum from a phase III randomized clinical trial of 2nd-line hormone therapy (HR+, n= 153), and a 1st-line trastuzumab-treated cohort (HER2+, n=64). In both cohorts, all sites of metastases were included. The collagen-fragments were evaluated on continuous and categorical (75th percentile cut-off) bases by univariate Cox-regression analysis for their association with time-to-progression (TTP) and overall survival (OS). **Results:** In the HR+ cohort, Pro-C3 measured as a continuous variable was significantly associated with TTP; C1M, C4M and Pro-C3 were associated with OS. On a categorical basis, C1M and C3M were associated with TTP; all fragments were associated with OS (Table). In the HER2+ cohort, continuous measurements of all fragments were associated with TTP and OS. On a categorical basis (Table), all fragments were associated with TTP; C4M and Pro-C3 were associated with OS. **Conclusions:** ECM remodeling quantified in pre-treatment serum was associated with shorter TTP and OS in two independent MBC cohorts receiving systemic therapy. If validated, quantification of ECM remodeling in serum has potential as prognostic and/or predictive biomarkers in MBC.

	HR+ MBC			HER2+ MBC		
Biomarker	HR	95% CI	p-value	HR	95% CI	p-value
TTP						
C1M	1.59	1.04-2.42	0.032	3.07	1.52-6.18	0.002
C3M	1.51	0.99-2.29	0.056	2.63	1.29-5.35	0.008
C4M			ns	1.96	1.03-3.73	0.041
Pro-C3			ns	1.95	1.02-3.72	0.042
OS						
C1M	2.34	1.52-3.59	<0.0001			ns
C3M	1.64	1.04-2.55	0.03			ns
C4M	1.75	1.11-2.73	0.015	1.89	0.95-3.74	0.069
Pro-C3	1.95	1.22-3.09	0.005	3.37	1.67-6.80	0.001

1086 Poster Session (Board #78), Sun, 8:00 AM-11:30 AM

Association between insulin-like growth factor-1 receptor (IGF1R) expression in circulating tumor cells (CTCs) and prognosis in patients with metastatic breast cancer (MBC). *First Author: Alessandra Gennari, E.O. Galliera, Genova, Italy*

Background: CTCs are strongly associated with prognosis in MBC. In a recent metanalysis on 1944 patients, a CTC count > 5/7.5 ml was associated with a 2-fold increased risk of progression and death. Little evidence is available on the prognostic role of phenotypic CTC assessment, however. In this study, nested in a randomized clinical trial of Ist line chemotherapy ± metformin, we evaluated the prognostic role of IGF1R expression in CTCs, given its potential growth promoting effect. **Methods:** CTCs were isolated from blood samples of enrolled patients; an automated sample preparation and analysis system (CellSearch) was customized for detecting IGF1R positive CTCs. The prognostic role of total CTCs, IGF1R positive (+ve) and negative (-ve) CTCs was assessed by fitting different PFS and OS multivariate Cox's models. **Results:** CTC evaluation at baseline was performed in 72 of 126 patients, of whom 30 (42%) had CTCs ≥5/7,5ml and 41 (57%) had at least one IGF1R+ve CTC. In univariate analysis the prognostic role of total CTCs was confirmed: PFS (< 5 vs ≥5) HR = 1.69, 95%CI 1.01-2.69, p 0.042 and OS HR = 2.80, 95%CI 1.47-5.30, p 0.002).However, when total CTCs were split in IGF1R+ve and IGF1R–ve, a striking difference was seen in the prognostic effect of these cell types.While no association was detected between an increasing number of IGF1R+ve CTCs and PFS or OS (p = 0.56 and p = 0.99), the number of IGF1R-ve CTCs (< 4 vs ≥4) was strongly associated with an increased risk of progression and death: HR 1.93 (95%CI 1.15-3.23, p 0.013) and 3.65 (95%CI 1.88-7.09, p 0.001). In multivariate analysis, adjusted for metformin, the prognostic role of the number of IGF1R-ve CTCs was confirmed, while no residual prognostic role of total CTCs or number of IGF1R+ve cells was found (p = 0.55 and p = 0.64 for PFS; p = 0.86 in both cases for OS). **Conclusions:** In our study, the loss of IGF1R expression in CTCs exhibited a significant adverse prognostic effect, whereas no significant effect of total CTCs and IGF1R+ve CTCs was observed. This finding supports the biological characterization of CTCs as a critical step for further definition of their prognostic significance.

1087 Poster Session (Board #79), Sun, 8:00 AM-11:30 AM

Paclitaxel plus carboplatin versus paclitaxel plus epirubicin as first-line treatment for metastatic breast cancer: Efficacy and safety results of a randomized, phase III trial. *First Author: Zhongsheng Tong, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: Paclitaxel/carboplatin combinations are highly active in metastatic breast cancer (MBC). We conducted a randomized, phase III, non-inferiority trial comparing paclitaxel/carboplatin (TP) with paclitaxel/epirubicin (TE) as first-line therapy for MBC. Progression-free survival (PFS) was the primary efficacy endpoint. Secondary endpoints included response rate, overall survival, tolerability, and quality of life (QoL). **Methods:** From June 2009 to January 2015, 231 patients were randomly assigned, 115 of whom were randomized to TP and 116 to TE. Baseline characteristics were relatively well-balanced in the two treatments. **Results:** After a median follow-up of 29 months, no significant difference was observed between the two treatments in objective response rate (ORR) (38.3% vs. 39.7%, respectively). Both the progression-free survival (p=0.158) and overall survival (p=0.369) were very similar between the two treatments. Both regimens were well tolerated. The main toxicities were myelosuppression, gastrointestinal reactions, and alopecia. TP showed higher grades 3–4 alopecia and higher nausea ($p<0.05$). TE showed higher incidence of myelosuppression than TP ($p<0.05$) (Table). Those patients whose epirubicin cumulative dose was more than 1000 mg/m^2 did not suffer worse cardiotoxicity. **Conclusions:** Our study suggests that TP arm is an effective therapeutic alternative for patients with MBC, especially in those previously exposed to epirubicin in the adjuvant setting. TP has some advantages, such as less cost and less side effects (myelosuppression and fatigue). Clinical trial information: NCT02207361.

Summary of adverse events per patient.

	TP (n=115)		TE (n=116)		
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4	p value*
Neutropenia	32	12	56	17	0.045**
Leukopenis	41	15	65	18	0.037**
Anemia	9	2	8	1	0.983
Thrombocytopenia	7	2	6	0	0.715
Lymphocytopenia	4	1	6	1	0.392
Vomiting	34	6	27	6	0.287
Nausea	59	8	35	5	0.012**
Diarrhea	8	1	6	5	0.710
Alopecia	94	63	81	39	0.021**
Cardiotoxicity	6	0	8	1	0.289
Hypersensitivity reaction	1	0	0	0	—
ALT increase	34	3	27	1	0.527
Peripheral neurotoxicity	39	1	39	0	0.896

* Overall p values for the comparison of grades 1–4 are given. ** $p < 0.05$

1088 Poster Session (Board #80), Sun, 8:00 AM-11:30 AM

Phase 2 study of pembrolizumab as first-line therapy for PD-L1–positive metastatic triple-negative breast cancer (mTNBC): Preliminary data from KEYNOTE-086 cohort B. *First Author: Sylvia Adams, NYU Langone Medical Center, New York, NY*

Background: Standard first-line treatment for mTNBC is chemotherapy. However, outcomes are poor, and new treatment options are needed. Cohort B of KEYNOTE-086 (NCT02447003) assessed the safety and antitumor activity of pembrolizumab as first-line therapy for patients (pts) with PD-L1–positive mTNBC. **Methods:** Men and women with centrally confirmed mTNBC, no prior systemic anticancer therapy for metastatic disease, ECOG PS 0-1, and a tumor PD-L1 combined positive score (CPS) ≥1% received pembrolizumab 200 mg Q3W for 24 mo or until disease progression, intolerable toxicity, or investigator or pt decision. Tumor imaging was performed Q9W for 12 mo and Q12W thereafter. Clinically stable pts with PD could remain on pembrolizumab until PD was confirmed on subsequent assessment. Primary end point was safety. Secondary end points included ORR, DOR, and PFS (RECIST v1.1, central review). Planned enrollment was 80 pts. This analysis included all pts who had ≥18 wk of follow-up as of Nov 10, 2016. **Results:** 79 of the first 137 pts with PD-L1–evaluable tumors (58%) had PD-L1 CPS ≥1%. Of the first 52 pts enrolled, 100% were women, median age was 53 y, 40% had elevated LDH, 69% had visceral metastases, and 87% received prior (neo)adjuvant therapy. After a median follow-up of 7.0 mo (range 4.4-12.5), 15 (29%) pts remained on pembrolizumab. Treatment-related AEs occurred in 37 (71%) pts, most commonly fatigue (31%), nausea (15%), and diarrhea (13%). 4 (8%) pts experienced 5 grade 3-4 treatment-related AEs: back pain, fatigue, hyponatremia, hypotension, and migraine (n = 1 each). No pts died or discontinued pembrolizumab due to an AE. ORR was 23% (95% CI 14%-36%). Best overall response was CR in 4%, PR in 19%, SD in 17%, PD in 58%, and not assessed in 2%. Median time to response was 8.7 wk (range 8.1-17.7). Median DOR was 8.4 mo (range, 2.1+ to 8.4), with 8 (67%) responses ongoing at cutoff. Median PFS was 2.1 mo (95% CI, 2.0-3.9); estimated 6-mo PFS rate was 29%. **Conclusions:** Data from the first 52 pts enrolled in KEYNOTE-086 cohort B suggest that pembrolizumab monotherapy has a manageable safety profile and promising antitumor activity as first-line therapy for PD-L1–positive mTNBC. Clinical trial information: NCT02447003.

1089 Poster Session (Board #81), Sun, 8:00 AM-11:30 AM

Overall survival (OS) in patients (Pts) with diagnostic positive (Dx+) breast cancer: Subgroup analysis from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in AR+ triple-negative breast cancer (TNBC) treated with 0-1 prior lines of therapy. *First Author: Tiffany A. Traina, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: The AR may be a novel therapeutic target for pts with AR-driven TNBC. ENZA, a potent AR inhibitor approved in men with metastatic prostate cancer, was evaluated in this phase 2 study of pts with AR+ TNBC. A genomic signature associated with AR-driven biology was identified; updated OS results in pts treated with 0-1 prior lines of therapy are presented. **Methods:** This is an open-label, Simon two-stage study (NCT01889238) of ENZA monotherapy in advanced AR+ TNBC (AR > 0% by IHC). Bone-only disease and unlimited prior regimens were allowed; CNS metastases or seizure history were exclusionary. The primary endpoint was clinical benefit rate at 16 weeks (CBR16) in evaluable pts (AR > 10% and ≥1 postbaseline assessment). OS was an exploratory endpoint. Results in intent-to-treat (ITT) and evaluable pts were presented previously (Traina TA et al. *J Clin Oncol*. 2015;33:1003). **Results:** 118 pts were enrolled (ITT). CBR16 in 78 evaluable pts was 33.3%. Of the 118 ITT pts, 56 were Dx+ and 62 were Dx–; ≥50% received 0-1 prior lines of therapy (28 Dx+, 37 Dx–). As of 26 Nov 2016 there were 83 deaths (median follow-up 28 mo); median OS (mOS) was 13 mo (95% CI; 8-18). In the Dx+ subgroup there were 32 deaths (mOS 20 mo [95% CI; 13-29]) vs 51 deaths in the Dx– subgroup (mOS 8 mo [95% CI; 5-11]). In pts with 0-1 prior lines of therapy, there were 13 deaths in the Dx+ subgroup (mOS 29 mo [95% CI; 19-not reached] vs 28 in the Dx– subgroup (mOS 10 mo [95% CI; 7-15]). The most common adverse events (AEs) were fatigue and nausea; fatigue was the only grade 3 related AE in > 5% of pts. A multi-covariate Cox analysis identified Dx status (+ vs –) and line of therapy (0-1 vs ≥2) as the only variables significantly associated with OS. **Conclusions:** In this study, the mOS of pts with Dx+ TNBC who received 0-1 prior lines of therapy appears longer than that of unselected historic controls. ENZA may represent a therapeutic option in pts with AR+ TNBC who would otherwise receive cytotoxic chemotherapy and is currently being evaluated in ENDEAR, a phase 3 study in pts with Dx+ advanced TNBC and 0-1 prior lines of therapy. Clinical trial information: NCT01889238.

1090 Poster Session (Board #82), Sun, 8:00 AM-11:30 AM

Whole exome sequencing of metaplastic breast cancer (MpBC): Effect of mutation status on survival. *First Author: Luis Baez Vallecillo, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Metaplastic Breast Cancer (MpBC) is considered a chemorefractory, aggressive subtype that is characterized by squamous and/or mesenchymal differentiation and associated with a high rate of molecular aberrations that activate the PI3K pathway. The goal of this study was to correlate outcomes data with underlying genomic aberrations in MpBC. **Methods:** A cohort of 52 archived samples of MpBC collected from 1986 and 2016 that had clinical outcomes data available for central review underwent hybrid capture sequencing of 202 cancer-related genes (n = 52) and, when sufficient material was available, whole exome sequencing (n = 21). Relapse free (RFS) and overall (OS) survival analyses at 5 years were compared between patients having mutation vs. wild-type (WT) in the whole genome using Kaplan-Meier statistics. **Results:** The variant allele frequency (VAF) was relatively low with most mutations having a VAF of < 50%. *TP53* mutation was found in 33 tumors (63%) and was associated with improved RFS (HR = 2.4; p = 0.03) and OS (HR = 3.7; p = 0.006) compared to WT. Aberrations in the PI3K/AKT/mTOR pathway were present in 29% of tumors and associated with diminished OS (HR = 0.27; p = 0.02) but not RFS (HR = 0.67; p = 0.32). Though uncommon, the presence of an *AKT1* (6%) mutation was associated with worse RFS (HR = 0.006; p = 0.006) and OS (HR = 0.0005; p < 0.0001). **Conclusions:** Surprisingly, *TP53* mutation was associated with better prognosis in MpBC with increased RFS and OS. Mutations in *AKT1* were uncommon but associated with a significantly worse RFS and OS. Notably, all patients harboring an AKT1 mutation died within a year of diagnosis. Mutations activating the PI3K/AKT/mTOR pathway were associated with worse OS.

1091 Poster Session (Board #83), Sun, 8:00 AM-11:30 AM

Use of serial multi-template liquid biopsies in triple negative breast cancer monitoring. *First Author: Paul Y. Song, Cynvenio Biosystems, Inc., Westlake Village, CA*

Background: Triple negative breast cancer (TNBC) remains the most aggressive subtype of breast cancer in which up to 1/3 of all patients will relapse early and distantly. There remains no proven method to monitor and detect early recurrence. This study examines the utility of serial liquid biopsies using a multi-template approach (identification and analysis of cell-free DNA (cfDNA) and circulating tumor cells (CTCs)) as a solution. **Methods:** 210 patients (average 53 yrs.) with confirmed diagnosis of TNBC, within 3 years of completion of therapy (mean 25 mos.), and in full remission were enrolled. Liquid biopsies were performed quarterly to look for cancer specific genomic mutations not seen in germ line controls, but in cfDNA and CTCs using a custom 27-gene breast cancer panel. Prior validation of our gene panel demonstrated a false positive rate of 0.001-0.0007% in normal cfDNA and cell-based controls. **Results:** Each subject had on average 3.0 serial samples collected to date. 169 patients (80.4%) had evidence of mutations in at least one sample. Seventy-five percent of cfDNA and 36% of CTC samples examined have been found to bear mutations. The total number of samples with orthogonally (either between template or between draws) confirmed signal was 16.9%. Seven patients (3.3%) have developed documented evidence of recurrence, one in the axilla and the others with visceral/distant metastases. Of the patients that have recurred, all had a persistent mutation on consecutive blood draws or evidence of genomic mutations in both cfDNA and CTCs. **Conclusions:** The majority of TNBC patients in our study post-treatment were found to have genomic mutations on at least one liquid biopsy sample – either cfDNA or CTC. But, very few had a persistent presence of mutations in subsequent samples and 96.7% of our patients have remained NED. Unlike patients who remained NED, patients who recurred displayed persistent evidence of mutations on serial draws or in both cfDNA and CTC samples. To date our recurrence rate is lower than predicted. This study highlights the need for serial monitoring using a multi-template approach to better fully understand patient specific tumor biology and kinetics. The trial is ongoing. Clinical trial information: NCT02639832.

1092 Poster Session (Board #84), Sun, 8:00 AM-11:30 AM

Genome-wide copy number analysis of cell-free DNA from patients with chemotherapy-resistant metastatic triple-negative breast cancer. *First Author: Daniel G. Stover, Dana-Farber Cancer Institute, Boston, MA*

Background: Triple-negative breast cancer (TNBC) is a poor prognosis breast cancer subset characterized by relatively few mutations but extensive copy number alterations (CNAs). Cell-free DNA (cfDNA) offers the potential to overcome infrequent tumor biopsies in metastatic TNBC (mTNBC) and interrogate the genomics of chemotherapy resistance. **Methods:** 506 archival or fresh plasma samples were identified from 164 patients with mTNBC who had previously received chemotherapy. We performed low coverage sequencing to determine genome-wide copy number and estimate 'tumor fraction' of cfDNA (TFx). In patient samples with TFx >10%, we identified regions that were significantly gained or lost using GISTIC2.0. We compared CNAs of mTNBCs with primary TNBCs from a publicly-available dataset, METABRIC (TNBC n=277). **Results:** We successfully obtained high quality, low coverage whole genome sequencing data for 478 (94.5%) plasma samples from 158 patients, with 1 to 14 samples per patient. Archival samples had significantly higher average cfDNA per mL plasma and TFx than fresh samples, potentially due to later average line of therapy. Average TFx of first blood draw was significantly higher in patients with liver metastases (TFx 28.3% vs. 14.4%, p=1.1e-7). 101/158 patients (63.9%) had at least one sample with TFx >10%, our threshold for high confidence CNA calls. Most alterations significantly enriched in chemotherapy-resistant mTNBCs were chromosomal gains, including NOTCH2 and ERCC1. Median overall survival from time of first blood draw was 9 months, and TFx was highly correlated independent of metastatic line of therapy, age at metastatic diagnosis, BRCA status, and primary stage: adjusted hazard ratio between 4^{th} and 1^{st}quartiles = 4.29 (95% CI 1.66-11.1; p=0.0008). **Conclusions:** It is feasible to perform genome-level copy number analysis from cfDNA in both archival and fresh samples from patients with mTNBC. Copy number alterations enriched in mTNBC may have implications in the understanding of metastasis, therapeutic resistance, and novel therapeutic targets. 'Tumor fraction' of cfDNA is correlated with overall survival and may be an independent prognostic marker in mTNBC.

1093 Poster Session (Board #85), Sun, 8:00 AM-11:30 AM

Investigating tumoral and temporal heterogeneity through comprehensive -omics profiling in patients with metastatic triple negative breast cancer. *First Author: Christopher Szeto, NantOmics, LLC, Santa Cruz, CA*

Background: The "Intensive Trial of OMics in Cancer"-001 (ITOMIC-001; Clinicaltrials.gov ID: NCT01957514) enrolls patients with metastatic triple negative breast cancer (TNBC) who are platinum-naive and scheduled to receive cisplatin. Multiple biopsies (up to 7 metastatic sites) are performed under carefully controlled conditions prior to and upon completion of cisplatin treatment and following any subsequent therapies. Samples are chosen for DNA sequencing, RNA sequencing, and quantitative proteomics (GPS Cancer). Here we describe the -omic alterations acquired during treatment. **Methods:** We analyzed 74 biopsies from 17 patients taken at various clinical timepoints (e.g. initial diagnosis, initial trial recruitment, following cisplatin treatment, etc.) spanning 2 years on trial and over 8 years before recruitment. This dataset includes 64 whole genomes (with matched-normal blood samples), 44 RNAseq expression profiles, and 23 proteomic sets. GPS Cancer, which comprises whole genome sequencing, whole transcriptome sequencing, and targeted quantitative proteomics was used to detect somatic alterations, measure mutational burdens, and estimate expression profiles of both transcripts and proteins. PARADIGM pathway analysis was used to identify network-level changes through integration of all available data types. **Results:** While mutational profiles within patients were largely stable over time, we observed up to a 10-fold difference in the magnitude of mutational burden between patients. Following cisplatin treatment, the expression of over 300 genes were significantly perturbed, and an average of 270 mutations per patient were introduced. PARADIGM integrated pathway analysis shows differential activity in the MYC/MAX and ETS1 pathways during tumor progression. **Conclusions:** Using GPS Cancer we provide detailed characterizations of the molecular profiles of metastatic TNBC across space and over time. We demonstrate the potential for using this information to discover mechanisms underlying treatment resistance and disease progression. Our findings form the basis for molecularly informed QUILT trials for combination therapy.

1094 Poster Session (Board #86), Sun, 8:00 AM-11:30 AM

Validity of 1% hormonal positivity cutoff by American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines at Georgia Cancer Center. *First Author: Houssein Talal Abdul Sater, Georgia Regents University/Medical College of Georgia School of Medicine, Augusta, GA*

Background: Hormone Receptor Status (HS) in breast cancer (BC) is a universally accepted biomarker. ASCO/CAP 2010 guidelines set the threshold of Estrogen and Progesterone Receptor positivity to 1 %. BC with 1-9% HS expression remains controversial with recent data disputing these guidelines. The objective of this retrospective study was to validate these guidelines at Georgia Cancer Center (GCC) with high percentage of black race. **Methods:** All female patients with invasive BC diagnosed between 2005-2010 at GCC (11y follow-up) were chart reviewed. We used Cox proportional hazards model to explore survival among three HS groups (< 1%, 1-9%, ≥10%) adjusting for standard prognostic factors. Hazard ratios (HR) and 95% confidence intervals (CI) were also reported. 1-9 %, and ≥10% groups were further explored using same method to test survival difference with or without hormone therapy (HT). Fischer's Exact test was used to evaluate response to HT in these groups. **Results:** 400 patients (all stages) with mean age of 59, were 24.75% HS < 1%, 17.5% HS1-9%, and 57.75% HS≥10%. Race was 43.75% Black, and 54% White. Disease stages were 84.4% early (I-IIIA) and 15.56% late (IIIB-IV). Grades were 51.42% low (1-2) and 48.58% high (3). The 2 groups (1-9%, ≥10%) received chemotherapy (42.86%, 39.83%), and HT (58.57%, 80.52%) respectively while 70.71% of < 1% HS group had chemotherapy. Mortality in HS < 1% was significantly higher than HS ≥10% (HR 1.8, 95% CI 1.07-3.02), while mortality between HS 1-9% and HS ≥10% was not different (HR 1.05, 95% CI 0.48-2.30). Treated (HT) subjects had lower mortality than untreated subjects in the 1-9% group (HR 0.10, 95% CI 0.01-0.85). 100% of HT group had no evidence of tumor at last follow up compared to 87.5% in non-treatment group (p = 0.048). There was no significant difference in mortality between treated (HT) 1-9% and ≥10% groups. **Conclusions:** Hormone receptor expression as low as 1-9% was found to be equi-prognostic to ≥10% expression. It also predicted response to hormonal therapy. Whether other factors as lympho-vascular invasion, grade, and other parameters change the behavior of the 1-9% HS group remain to be explored.

1095 Poster Session (Board #87), Sun, 8:00 AM-11:30 AM

Phase II study of eribulin in combination with gemcitabine for the treatment of patients with locally advanced or metastatic triple negative breast cancer: ERIGE trial on behalf of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). *First Author: Antonino Musolino, Medical Oncology Unit, University Hospital of Parma, Parma, Italy*

Background: There are no well-established chemotherapy regimens for metastatic triple negative breast cancer. The combination of a microtubule inhibitor (eribulin) with a nucleoside analog (gemcitabine) may synergistically induce tumor cell death, especially in tumors like triple negative breast cancers (TNBC) characterized by high cell proliferation, aggressive tumor behavior, and chemo-resistance. **Methods:** We performed an open-label, national multicenter phase 2 study evaluating the combination of eribulin (0.88 mg/m^2) plus gemcitabine (1000 mg/m^2) on day 1 and 8, q21 as either first- or second-line treatment of locally advanced or metastatic TNBC. The Simon's optimal two-stage design was used for estimating objective response rate (ORR) as study primary endpoint. A prospective, molecular correlative study was carried out on germinal DNA of study population to assess the role of germinal DNA polymorphisms and BRCA mutations in predicting efficacy and toxicity of the combination regimen. **Results:** From July 2013 to September 2016, 83 (37 in the first stage, 46 in the second one) assessable patients were enrolled. Median age at baseline was 56 years. Sixty-six and 17 patients were in first or second-line treatment, respectively. All patients were previously treated with an anthracycline and/or a taxane. With regard to the first stage of study enrolment, patients received a median number of 6 cycles of treatment. The ORR (CR+PR) was 43.24% (90% CI 29.3-58.0) and the clinical benefit rate (CR+PR+SD) was 64.9% (90% CI: 50.1%-77.8%). The most common grade 3/4 AEs ($>$ 10% of patients) were neutropenia without febrile neutropenia and liver toxicity. Grade 1/2 AEs were fatigue, anemia, thrombocytopenia, diarrhea, alopecia, peripheral neuropathy, and oral mucositis. **Conclusions:** The combination of eribulin and gemcitabine shows promising activity and a moderate toxicity profile in metastatic TNBC. More mature toxicity and outcome data of the final study population and correlation with genome analysis will be presented at the meeting. Clinical trial information: 2012-003505-10.

1096 Poster Session (Board #88), Sun, 8:00 AM-11:30 AM

Immune gene signatures in triple-negative breast cancers characterized by varying levels of chromosomal instability. *First Author: Balazs Gyorffy, MTA TTK, Budapest, Hungary*

Background: Triple-negative breast cancer (TNBC) is generally characterized by high levels of chromosomal instability (CIN) and an intense immune infiltration. However, the link between these two hallmarks and its implications for clinical practice has not been fully elucidated. **Methods:** We generated eight immune metagenes representing various immune components: natural killer [NK], dendritic cells [DC], T-cells [TC], B-cells [BC], cytotoxic T-cells [CT], interferon [IFN], nuclear factor-κB [NF-kB], and macrophages [M]. Publicly available gene expression data from forty-two data sets, including 862 TNBC samples, were collected. TNBC tumors were clustered in three main subgroups (Basal-Like [BL1/2], Immunomodulatory [IM], and Mesenchymal/Mesenchymal Stem-Like [MS]) using transcriptomic profiling. The CIN70 signature was used to stratify TNBC patients according to the levels of CIN. Statistical analyses were performed using Mann–Whitney *U* test and Kaplan-Meier analyses. **Results:** The majority of TNBC samples showed a high level of CIN (83%), and several immune modules were differentially expressed between CIN-high and CIN-low tumors. Specifically, CT, NK, DC, M, and NF-kB signatures were overexpressed in CIN-low TNBC ($p < 1.0E-04$). We then evaluated the distribution of genomic instability among TNBC molecular subgroups. Noteworthy, the CIN-high group was composed by a comparable proportion of BL1/2 (39%) and MS (35%) tumors, while CIN-low TNBCs were consistently enriched for MS cancers (61%). Higher expression of the NK, M, and IFN metagenes lead to better survival in CIN-high tumors ($p = 1.9E-02$, $p = 2.1E-04$, and $p = 1.1E-03$, respectively). Only IFN had the same correlation to survival in CIN-low ($p = 1.4E-02$). **Conclusions:** TNBCs with low levels of CIN may principally enclose M/MSL tumors, which are characterized by an intense immune infiltration and overall good prognosis. Conversely, the TNBC CIN-high group is more heterogeneous in terms of both biological features and levels of immune infiltrates. Therapeutic strategies to promote and boost immune response in the genomically unstable TNBC subgroup warrant further investigation.

1097 Poster Session (Board #89), Sun, 8:00 AM-11:30 AM

Retinoblastoma (Rb) protein expression in triple-negative breast cancer. *First Author: Jaymin M Patel, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Expression of Rb, the protein product of the *RB* tumor suppressor gene, is required for cyclin D kinase (CDK) 4/6 inhibition in luminal breast cancers. Triple negative breast cancers (TNBC) frequently exhibit Rb loss and are thus believed to be poor candidates for CDK4/6 inhibition. However, the features associated with Rb loss in TNBC are poorly-defined. We aimed to assess whether TNBC that express the androgen receptor (AR) and resemble a more luminal subtype retain Rb more often than other TNBC. **Methods:** To assess the frequency and correlates of Rb expression in TNBC, we stained tissue microarrays (TMAs) containing 180 Stage I-III TNBC, 71 with germline *BRCA1* mutations (*BRCA1*+) and 109 without *BRCA1* mutation (sporadic), using a mouse monoclonal antibody to human Rb (clone G3-245, BD Biosciences). Assessment of tumor size, histologic type, grade, lymphovascular invasion and lymph node status were assessed on histologic review. The TMAs, containing three 0.6mm cores/tumor, had been previously stained for AR, CK5/6, CK14 and EGFR. Log-binomial regression was used to calculate risk ratios (RR). **Results:** Fifty percent of TNBC were Rb-positive (Rb+; $\geq$10% nuclei staining) of which 84.4% had $>$ 50% nuclei staining. Among TNBC that were Rb-negative, 76.6% had $<$ 1% nuclei staining for Rb. AR expression ($\geq$10% nuclei staining) was more common in Rb+ than Rb-negative TNBC (16.7% vs 4.5%; p = 0.01). In addition, Rb expression was significantly more common among sporadic than *BRCA1*+ TNBC (59.6% vs 35.2%, p = 0.001). Compared with Rb-negative TNBC, Rb+ tumors were associated with older age (mean 48.7 vs 45.7 years; p = 0.06) and lower histologic grade (grade 1 or 2: 9.2% vs 2.2%; p = 0.05). No other clinical or pathologic features were significantly associated with Rb status. In a multivariable model, both AR expression (RR, 1.65; 95% CI, 1.31-2.08) and lack of *BRCA1* mutation (RR, 1.63; 95% CI, 1.17-2.29) significantly predicted for Rb expression among TNBC. **Conclusions:** Sporadic TNBC is significantly more likely to be Rb+ than *BRCA1*+ TNBC. Among TNBC, AR expression significantly predicts for Rb expression. These results suggest clinically relevant biomarkers that may predict for Rb expression and potential targeted therapies in TNBC.

1098 Poster Session (Board #90), Sun, 8:00 AM-11:30 AM

Influence of marital status on risk of mortality for 23,493 cases of triple negative breast cancer for four mutually exclusive race/ethnicities. *First Author: Carol Parise, Sutter Institute for Medical Research, Sacramento, CA*

Background: Marital status has been associated with better breast cancer survival. However, breast cancer is a heterogeneous disease and it has not been determined whether marital status is a survival advantage for women with triple negative breast cancer (TNBC) and if this advantage holds for all race/ethnicities. The purpose of this study was to determine if being unmarried resulted in an increased risk of mortality for TNBC for four mutually exclusive race/ethnicities. **Methods:** We identified 23,493 cases of TNBC from the California Cancer Registry 2000-2014. Marital status at time of diagnosis was defined as: 1) married, 2) single, never married; 3) separated; 4) divorced; 5) widowed. Race/ethnicity was defined as white (n = 13,241), black (n = 2,775), Hispanic (n = 5,059), and Asian/Pacific Islander (API) (n = 2,418). Kaplan-Meier Survival Analysis and Cox Regression were used to assess the risk of mortality associated with marital status using married as the reference category. Marital status was considered a risk for mortality and hazard ratios (HR) and 95% confidence intervals reported if the Wald χ^2 was statistically significant ($p < 0.05$). Models were adjusted for AJCC stage, age, grade, socioeconomic status, and treatment. Separate analyses were conducted for each race/ethnicity. **Results:** For allraces, single women had statistically significantly worse unadjusted survival ($p < 0.05$) than married women. However adjusted analyses showed that single (HR = 1.13; 1.01-1.27) and widowed (HR = 1.43; 1.27-1.61) white women had increased mortality when compared with married women. Single (HR = 1.50; 1.14-1.96) and divorced (HR = 1.75; 1.23-2.48) API women had an increased risk of mortality compared with married women. For black and Hispanic women, marital status was not associated with risk of mortality. **Conclusions:** Being married at the time of diagnosis of TNBC is a survival advantage only for white and API women but not for black and Hispanic women.

1099 **Poster Session (Board #91), Sun, 8:00 AM-11:30 AM**

BRAF: An emerging target for triple-negative breast cancer. *First Author: Joan Albanell, Medical Oncology Department, Hospital del Mar, Barcelona, Spain*

Background: A series of reports demonstrating the successful use of BRAF and MEK inhibitors in clinically advanced non-melanoma cancers has recently emerged. *BRAF* alterations in metastatic breast cancer (mBC) are rare and BRAF is not currently considered a target for the disease. **Methods:** DNA was extracted from 40 microns of FFPE sections from a series of 10,428 cases of metastatic breast cancer (mBC). Comprehensive genomic profiling (CGP) was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of > 550X for up to 315 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. **Results:** 135 (1.2%) of the mBC featured alterations in *BRAF*. The median age of the 135 female patients was 66 years (range 27 to 83 years). The primary tumor was used for CGP in 50 (37%) and from metastatic sites including lymph nodes, liver, bone, lung, brain, adrenal and soft tissue in 85 (67%). Using *CDH1* mutation as the definition of lobular mBC, 126 (93%) were ductal and 9 (7%) were lobular histology. Activating *BRAF* alterations included amplifications (48%), SV mutations (39%) and rearrangements (13%). No (0%) mBC had multiple *BRAF* GA in the same case. 34% of *BRAF* SV were V600E and 66% were a wide variety of non-V600E GA. 10 (7.4%) of 135 BRAF mutated mBC featured *ERBB2* amplification with 1 (1%) having an *ERBB2* SV mutation and 1 (1%) having both *ERBB2* amplification and SV GA. Of the 115 *BRAF* GA cases with known hormone receptor status 71 (62%) were ER negative, 44 (38%) were ER positive and 63 (55%) were triple negative (TNBC). Other targetable genes enriched in mBC with *BRAF* GA included *CDK6* ($p = 0.001$), *HGF* ($p < 0.001$) and *MET* ($p < 0.001$). The median TMB was 4.5 with 17 (13%) of cases with TMB > 10 mut/Mb and 7 (5%) of cases with > 20 mut/Mb. **Conclusions:** *BRAF* alterations, although uncommon in mBC representing only 1.2% of cases, are enriched in TNBC and feature both targetable base substitutions and rare fusions. *BRAF* GA may be a rare cause of anti-HER2 therapy resistance in a subset of *ERBB2* driven mBC. Targetable genes co-altered with *BRAF* in mBC include *CDK6*, *HGF* and *MET*. The TMB in *BRAF* altered mBC is significantly higher than that for mBC in general and indicates potential role for immunotherapy for these patients.

1100 **Poster Session (Board #92), Sun, 8:00 AM-11:30 AM**

Dynamic relationship between cycling kinetics of triple-negative breast cancer and tumor infiltrating immune cells. *First Author: Ishita Choudhary, Georgia State University, Atlanta, GA*

Background: Recent studies show strong correlation between tumor infiltrating lymphocytes (TILs) and triple-negative breast cancer (TNBC) patient survival. CD8+ T cells serve as a favorable prognostic marker for TNBC. In addition, other cells such as CD4+ T cells, macrophages, B cells, and Tregs also infiltrate tumors. In this study, we delineate a strong relationship between the cycling kinetics of proliferating cells in TNBCs and antitumor immune response. **Methods:** A multi-institutional study performed by our group has previously shown that KAMS (Ki67-Adjusted Mitotic Score) provides a measure of the cycling kinetics of proliferating tumor cells and robustly stratifies TNBC patients into slow cycling (low KAMS) cyclophosphamide-methotrexate-fluorouracil (CMF)-responsive and fast cycling (high KAMS) CMF-resistant subgroups. In this study, we reviewed clinical data from 124 CMF-treated TNBC patients from Nottingham Hospital and sought correlations between cycling kinetics (High/Low KAMS) and tumor infiltrating immune cells. **Results:** We found that slow cycling TNBCs had higher mean expression of tumor infiltrating immune cells than fast cycling TNBCs. Intratumoral CD68 ($p = 0.003$), CD3 ($p = 0.006$), CD20 ($p = 0.01$), FOXP3 ($p = 0.01$), and total numbers of intratumoral and stromal CD68 ($p = 0.01$) and CD3 ($p = 0.03$) expressing cells were found to be significantly higher in low KAMS tumors than in high KAMS tumors. Of these biomarkers, CD68 was significantly associated with patients' breast cancer-specific survival (BCSS): (a) low KAMS, high CD68 TNBCs had better BCSS than low KAMS, low CD68 ($p = 0.01$) TNBCs, and (b) high KAMS, low CD68 cases had better BCSS than high KAMS, high CD68 cases. **Conclusions:** Our observation that there are more TILs in slow cycling TNBCs suggests that there may be a dynamic cross-regulation between cycling kinetics and antitumor immune response. From our surprising observation that CD68 exerts polar roles in low/high KAMS subgroups, we propose that distinctions in M1 and M2 macrophage subsets in slow and fast cycling TNBCs may correlate with distinct outcomes. In addition, metabolic competition between tumor and immune cells may determine the level and function of TILs.

1101 **Poster Session (Board #93), Sun, 8:00 AM-11:30 AM**

Beyond triple-negative breast cancer and African ancestry: Tumor phenotypes among internationally diverse patient populations. *First Author: Evelyn Mawunyo Jiagge, University of Michigan, Ann Arbor, MI*

Background: Population-based incidence rates of breast cancers that are negative for estrogen receptor (ER), progesterone receptor (PR), and HER2/*neu*(triple negative breast cancer {TNBC}) are higher among African American (AA) compared to White American (WA) women. Several studies show higher TNBC frequency among selected populations of African patients. The colonial-era trans-Atlantic slave trade resulted in shared West African ancestry between contemporary AA and Ghanaian (Gh) populations. The extent to which TNBC susceptibility is related to East African versus West African ancestry, and whether these associations extend to expression of other biomarkers such as Androgen Receptor (AR) and mammary stem cell marker ALDH1 is unknown. **Methods:** We used immunohistochemistry to assess ER, PR, HER2/*neu*, AR and ALDH1 among WA (n = 153); AA (n = 76); Ethiopian (Eth)/East African (n = 90) and (Gh)/West African (n = 286) breast cancers through an IRB-approved international research program. **Results:** Mean age at breast cancer diagnosis was 43; 49; 60; and 57 years for the Eth; Gh; AA; and WA patients, respectively. Frequency of TNBC was significantly higher for AA and Gh patients (54% and 41%, respectively) compared to WA and Eth patients (23% and 15%, respectively); $p < 0.001$. These associations were unchanged when limited to patients age 50 and younger (47% and 49% for AA and Gh, respectively; versus 18% and 16% for WA and Eth, respectively); $p < 0.001$. Frequency of ALDH1 positivity was also higher for tumors from AA and Gh patients (32% and 36%, respectively) compared to those from WA and Eth patients (23% and 17%, respectively); $p = 0.007$. Significant differences were observed for distribution of AR positivity, which was 71%; 55%; 42% and 50% for the WA; AA; Gh; and Eth cases, respectively ($p = 0.008$). **Conclusions:** We found a correlation between extent of African ancestry and risk of particular BC phenotypes. West African ancestry was associated with increased risk of TNBC and breast cancers that are positive for ALDH1. Future studies of hereditary TNBC susceptibility among women with African ancestry are warranted.

1102 **Poster Session (Board #94), Sun, 8:00 AM-11:30 AM**

Phase (Ph) 2 stage 1 clinical activity of seviteronel, a selective CYP17-lyase and androgen receptor (AR) inhibitor, in women with advanced AR+ triple-negative breast cancer (TNBC) or estrogen receptor (ER)+ BC: CLARITY-01. *First Author: Ayca Gucalp, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Seviteronel (Sevi), an oral selective CYP17-lyase and AR inhibitor that blocks testosterone and estradiol production and competitively antagonizes the AR, is in Ph 2 clinical development for BC and prostate cancer. The primary objective of this ongoing Ph 2 study (NCT02580448) is to estimate the activity of once daily Sevi in women with AR+ TNBC and ER+ BC as measured by clinical benefit rate (CBR) at 16 and 24 weeks (wk), respectively. **Methods:** Patients (pts) with ER+/HER2-normal metastatic BC following progression of ≥1 prior line of endocrine therapy or TNBC were enrolled with no limit of prior therapies in either cohort. Evaluable pts had AR ≥10% via central IHC staining (TNBC only) and 1 post-baseline scan. Sevi was administered at 450 mg oral daily. Scans were performed every 8 wk. Circulating tumor cell (CTC) enumeration was performed by EPIC CTC analysis. A Simon's 2-stage design was employed to determine activity (≥2 of 13 CBR16 in TNBC and ≥2 of 12 CBR24 in ER+ BC allow for accrual to Stage 2). **Results:** As of 4 Oct, 2016, 16 pts with AR+ TNBC (6 evaluable) and 14 pts with ER+ BC (11 evaluable) were enrolled. 67% had visceral metastases; 10% had stable brain metastases. 60% had ≥2 lines of prior therapy for advanced disease. 13 of 14 (93%) TNBC pts who underwent central AR testing had AR ≥10%. Four pts in the TNBC cohort and 8 pts in the ER+ cohort remain on therapy. CBR16 (TNBC) and CBR24 (ER+) was 2 of 6 (33%) and 2 of 11 (18%) allowing Stage 2 accrual in both cohorts. 7 of 10 evaluable pts with CTCs present at baseline had a CTC decline at C2D1, including all that met CBR (-94.3% [-27.5, -100] median [range]). The most common adverse events (≥ 25%) were fatigue (50%), nausea (43%) and decreased appetite (33%); all Grade 1/2. Updated CBR data will be presented at the time of presentation. **Conclusions:** Sevi Stage 1 activity is suggested by CBRs, along with associated CTC declines in heavily pretreated pts with high disease burden. The observed safety profile is consistent with on-target pharmacology. Stage 2 enrollment is ongoing. Sevi may provide a novel treatment option for women with AR+ TNBC or ER+ BC. Clinical trial information: NCT02580448.

1103 Poster Session (Board #95), Sun, 8:00 AM-11:30 AM

Efficacy/safety of epacadostat plus pembrolizumab in triple-negative breast cancer and ovarian cancer: Phase I/II ECHO-202 study. *First Author: Alexander I. Spira, Virginia Cancer Specialists Research Institute, Fairfax, VA*

Background: Epacadostat is an oral, potent, and selective inhibitor of indoleamine 2,3-dioxygenase 1, a tryptophan-catabolizing enzyme that induces immune tolerance via T-cell suppression and is associated with poor patient (pt) survival when overexpressed in some cancers. The ongoing, open-label, phase 1/2 (P1/2) ECHO-202/KEYNOTE-037 study is evaluating the efficacy, safety, and tolerability of epacadostat plus PD-1 inhibitor pembrolizumab (E + P) in pts with advanced/recurrent cancers. We report P1/2 study outcomes for triple-negative breast cancer (TNBC) pts and P2 outcomes for ovarian cancer (OVC; no P1) pts as of a 29OCT2016 data cutoff. **Methods:** Eligible pts were ≥18 years old with no prior checkpoint inhibitor treatment (tx); prior platinum/taxane tx was required for OVC pts. As part of P1 dose escalation, TNBC pts received E (300 mg BID) + P (200 mg Q3W). In P2, TNBC and OVC pts received E (100 mg BID) + P (200 mg Q3W). Response (RECIST v1.1) was assessed in evaluable pts. Safety and tolerability were assessed in pts with ≥1 dose of E + P. **Results:** A total of 39 pts with TNBC and 37 with OVC were enrolled. The majority of TNBC pts (56%, n = 22) and OVC pts (78%, n = 29) received ≥3 prior lines of tx. For TNBC pts, ORR (CR+PR) was 10% (n = 4; all PR) and DCR (CR+PR+SD) was 36% (n = 14; 10 SD); ORR and DCR for pts with ≤2 prior tx were 12% (n = 2) and 29% (n = 5), respectively, and for ≥3 prior tx were 9% (n = 2) and 41% (n = 9). For OVC pts, ORR was 8% (n = 3; all PR) and DCR was 35% (n = 13; 10 SD); ORR and DCR for pts with ≤2 prior tx were 13% (n = 1) and 25% (n = 2), and for ≥3 prior tx were 7% (n = 2) and 38% (n = 11). The most common TRAEs (≥15% of pts) were rash (18%), fatigue (15%), and nausea (15%) in the 39 TNBC pts, and fatigue (19%) in the 37 OVC pts. Grade ≥3 TRAEs occurred in 13% of TNBC pts (n = 5; none in > 1 pt) and 19% of OVC pts (n = 7; only rash occurred in > 1 pt [n = 3]). TRAEs led to discontinuation in 1 TNBC pt (grade 3 ascites) and 1 OVC pt (grade 2 arthralgia). **Conclusions:** E + P tx was generally well tolerated and showed antitumor activity consistent with previously reported P monotherapy in pts with advanced TNBC or OVC. Biomarker analysis is ongoing to characterize pt populations enrolled in this study. Clinical trial information: NCT02178722.

1104 Poster Session (Board #96), Sun, 8:00 AM-11:30 AM

Phase I study of olaparib (O), in combination with oral cyclophosphamide (C), in patients (pts) with metastatic triple negative breast cancer (TNBC) and recurrent high grade serous ovarian cancer (OVCA). *First Author: Chee Khoon Lee, St George Hospital, Sydney, Australia*

Background: Poly (ADP-ribose) polymerase (PARP) inhibitors can potentiate chemotherapy induced DNA damage, through synthetic lethality, leading to increased tumor death. We hypothesized that O+C would increase antitumor activity of O through increased DNA damage induced by C. This study (ANZCTRN12613000924752) evaluated the safety and activity of O+C. **Methods:** Eligible patient (pts) had performance status 0-2, with ≤3 lines of therapy (including platinum for OVCA and anthracycline and taxane for BC). Pts received O+C with a dose escalations strategy using a 3+3 design with cohort expansions once maximal tolerated dose (MTD) was determined. Dose level 1 (DL1); O, 300 mg bid continuously, C, 50mg on days 1,3 and 5 weekly, 21 day cycle. Dose level 2 (DL2); O, 300 mg bid continuously, C, 50mg days 1-5 weekly 21 day cycle. Dose limiting toxicity was evaluated during 1st two cycles. Safety was assessed by CTCAEv4.0 and efficacy with RECISTv1.1 and GCIC criteria. **Results:** Of the 32 pts (median age 56, 9 had BC (*BRCA*1 22%, *BRCA*2 44%) and 23 had HGSOC (*BRCA*1 39%, *BRCA*2 26%). 4 pts were treated at DL1 and 28 pts at DL2. DL2 was the MTD. At the time of analysis, 16 of 29 pts had 8 cycles of O+C, with 14 of 16 pts continued with O beyond the 8th cycle. One pt stopped because of adverse events (AEs) and the remaining 12 stopped due to disease progression. The median treatment duration of O+C was 4.3 months (0.7-23.5). Common AEs were nausea (Grade (Gr) 1/2: 88%, Gr 3: 3%), fatigue (Gr 1/2: 81%), constipation (Gr 1/2: 38%, Gr 3: 3%), and vomiting (Gr 1/2: 38%, Gr 3: 3 %). There were no grade (Gr) 4 or 5 AE. 50% required blood transfusion for anemia. Unconfirmed disease control rate (DCR) was 73% (N = 30; CR = 1, PR = 9, SD = 12). DCR for BC and HGSOC were 56% and 81% respectively. In the *BRCA* cohort (N = 19), DCR was 79%. GCIG CA125 response rates were 70% and 92% for all HGSOC and *BRCA* cohort respectively. **Conclusions:** In HGSOC and BC pts, the recommended phase II dose (O 300 mg bid continuously, C 50mg on days 1-5 weekly) is tolerable and active, particularly in those with germline *BRCA* mutation, supporting our hypothesis. A randomised phase II study in *BRCA* mutant HGSOC is planned. Clinical trial information: ACTRN12613000924752.

1105 Poster Session (Board #97), Sun, 8:00 AM-11:30 AM

Combined peripheral natural killer (NK) cell and circulating tumor cell (CTC) enumeration to enhance prognostic efficiency in patients (pts) with triple-negative breast cancer (TNBC). *First Author: Xiao-ran Liu, Peking University Cancer Hospital and Institute, Beijing, China*

Background: CTCs have emerged as an independent prognostic factor for metastatic breast cancer. However, the prognostic value of baseline CTCs regarding PFS in TNBC is still controversial, especially beyond first-line. We evaluated a novel combined NK cell/CTC detection system for enumeration to better understand the impact of cell count on prognosis in TNBC. **Methods:** 83 consecutive patients with metastatic TNBC were enrolled and received a new line of therapy (median=2, range: 1~5). Baseline circulating CTCs and NK cells were isolated and enumerated simultaneously prior to starting a new line of therapy using our previously published method targeting EpCAM (Bai et al. *J Mater Chem B*, 2014) and flow cytometry (antibodies against $CD3^-$, $CD45^+$, $CD56^+$) respectively. The NK cell level was expressed as the proportion of total lymphocytes (%). Patients with normal to high NK cell proportion (≥ 9.15%) and > 2 CTC/2 ml were defined as NK resistant CTC, the rest were defined as non-NK resistant CTC. **Results:** 33 out of 83 TNBCs had first-line of therapy. Pts with ≤ 2 CTC/2 ml had a significantly longer median PFS than those with > 2 CTC/2 ml (P = 0.028). The differences in median PFS were not significant (P=0.110) for the entire group of pts with TNBC receiving different lines of therapy. Pts with non-NK resistant CTCs had a significantly longer median PFS than those with NK resistant CTCs (P= 0.025), regardless of line of therapy. **Conclusions:** Including peripheral NK cell level into consideration can improve CTC prognostic efficiency in predicting PFS for TNBCs receiving different line of therapy. Further analysis of the unique biological features of NK-resistant CTCs and associated clinical consequence holds promise in guiding clinical practice.

Association of baseline CTC enumeration with PFS in 83 TNBCs.

	First-line TNBCs classified by CTC status[a] (n=33)		Total TNBCs classified by CTC status[b] (n=83)		Total TNBCs classified by NK-resistant CTC status[c] (n=62)	
	PFS (n)	P	PFS (n)	P	PFS (n)	P
Positive	6 (n=15)	0.028	6 (n=45)	0.110	5 (n=24)	0.025
Negative	25 (n=18)		9 (n=38)		9 (n=38)	

[a,b]Threshold: 2 CTC/2 mL. [c]Threshold: NK cell frequency ≥9.15% while > 2 CTC/2 mL.

TPS1106 Poster Session (Board #98a), Sun, 8:00 AM-11:30 AM

Trastuzumab emtansine (T-DM1) and ribociclib, an oral inhibitor of cyclin dependent kinase 4 and 6 (CDK 4/6), for patients with metastatic HER2-positive breast cancer: Phase 1b clinical trial. *First Author: Laura Spring, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Despite the availability of multiple effective therapies, most patients with metastatic HER2-positive breast cancer will experience disease progression and death. While traditionally the focus has been targeting the HER receptor family itself, combinations involving targets downstream of the HER2 pathway, particularly CDK 4/6, could potentially enhance therapeutic efficacy. In pre-clinical models of acquired resistance to HER2-targeted therapies, inhibition of CDK4/6 has been shown to result in tumor inhibition. Trial Design: This phase Ib, single arm, open-label clinical trialis investigating the combination of Trastuzumab emtansine (T-DM1) and the CDK4/6 inhibitor, ribociclib (LEE011). Eligible patients include patients age ≥ 18 years with HER2-positive metastatic breast cancer. Prior treatment with at least one regimen containing trastuzumab and a taxane is required. Ribociclib is given orally for two weeks of a 21-day cycle (days 8-21), with T-DM1 given at standard dose every 3 weeks on day 1. Trial Objectives: 1. To estimate the MTD and/or RP2D of ribociclib in combination with T-DM1. 2. To assess the safety and tolerability of ribociclib in combination with T-DM1. 3. To explore the clinical activity of T-DM1 and ribociclib in HER2-positive metastatic breast cancer. 4. To assess potential biomarkers of response to ribociclib in combination with T-DM1. Statistical Methods: A standard 3+3 dose escalation design is being used to evaluate various doses of ribociclib in combination with T-DM1 to determine the maximum tolerated dose (MTD) and/or recommended phase-2 dose (RP2D). Once MTD/RP2D is determined there will be a dose-expansion cohort (N = l5) to confirm the safety profile and evaluate preliminary evidence of efficacy, including objective response rate (ORR) by RECIST 1.1 and progression-free survival (PFS). Clinical trial information: NCT02657343.

TPS1107 Poster Session (Board #98b), Sun, 8:00 AM-11:30 AM

A randomized, double-blinded, controlled study of tucatinib (ONT-380) vs. placebo in combination with capecitabine (C) and trastuzumab (Tz) in patients with pretreated HER2+ unresectable locally advanced or metastatic breast carcinoma (mBC) (HER2CLIMB). *First Author: Carey K. Anders, University of North Carolina, Chapel Hill, NC*

Background: Tucatinib (ONT-380) is a highly selective small molecule inhibitor of HER2 kinase with nanomolar potency. Unlike dual HER2/EGFR agents, it does not inhibit EGFR at clinically relevant concentrations, decreasing the potential for EGFR-related toxicities (severe skin rash and diarrhea). In preclinical studies, tucatinib demonstrated synergistic activity with Tz, and was active in HER2+ models of brain metastases (mets). In a Phase 1b study, tucatinib was combined with C and Tz in pts with HER2+ MBC previously treated with trastuzumab emtansine (T-DM1) and Tz. Objective responses were seen, including in pts with brain mets. The combination was well tolerated, with low rates of Gr 3 diarrhea at the recommended dose (300 mg PO BID, equivalent to the single agent MTD). Based on these data, tucatinib is now being evaluated in a study in combination with C and Tz (HER2CLIMB). **Methods:** The primary study objective is to assess the effect of tucatinib vs. placebo given with C + Tz on progression-free survival (PFS) based on independent central review. Additional objectives include PFS in patients with brain mets, overall survival, ORR, duration of response, clinical benefit rate, and safety. The study population includes adult patients with progressive HER2+ locally advanced or MBC who have had prior treatment with a taxane, Tz, pertuzumab and T-DM1. Patients with brain mets, including untreated or progressive brain mets, may be enrolled. 480 patients will be enrolled in North America, Europe, Israel, and Australia. Patients are receiving C (1000 mg/mg^2 PO BID for 14 days of a 21-day cycle) and Tz (6 mg/kg IV once every 21 days), and are being randomized in a 2:1 ratio to tucatinib 300 mg PO BID or placebo. Patients with isolated CNS progression may continue on study treatment after undergoing local CNS therapy. An independent Data Monitoring Committee is monitoring patient safety. Clinical trial information: NCT02614794.

TPS1109 Poster Session (Board #99b), Sun, 8:00 AM-11:30 AM

A phase II randomized study to compare abemaciclib plus trastuzumab with or without fulvestrant to standard of care chemotherapy plus trastuzumab in hormone receptor positive, HER2-positive advanced breast cancer (monarcHER). *First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Boston, MA*

Background: Inhibition of CDK4 in preclinical models, demonstrated efficacy in HER2+ breast cancer and enhanced activity of HER2-targeted therapy suggesting a crosstalk between HER2 signaling and the cyclin D/CDK4 signaling pathway in which CDK4 & CDK6 inhibitors may re-sensitize resistant tumors to HER2 blockade.Abemaciclib is a selective inhibitor of CDK4 & CDK6 inhibitor that demonstrates single-agent anti-tumor activity on a continuous dosing schedule in women with hormone receptor positive (HR+) advanced breast cancer. Triple regimens with abemaciclib have been tolerable. **Methods:** monarcHER is an ongoing Phase 2, open-label, study in postmenopausal women with HR+, HER2+ locally advanced or metastatic breast cancer. Eligible patients (pts) are those previously treated with ≥2 HER2-directed therapies in advanced disease setting; T-DM1 and a taxane in any disease setting; no prior treatment with fulvestrant or any CDK4 & CDK6 inhibitor or with ECOG PS ≤1; LVEF ≥50%; no visceral crisis and no CNS metastases that are untreated, symptomatic or requiring steroids. Pts are randomized 1:1:1 to Arm A (abemaciclib [150mg PO Q12H] plus trastuzumab [IV infusion Q3 weeks] plus fulvestrant [IM injection on D1, 15, 29 then Q4 weeks]), Arm B (abemaciclib plus trastuzumab), or Arm C (trastuzumab plus SOC single-agent chemotherapy of physician's choice); stratified based on number of prior systemic regimens (excluding single agent endocrine therapy) and disease status (measurable vs nonmeasurable). The primary objective evaluates investigator-assessed progression-free survival (PFS). Secondary objectives include overall survival, objective response rate, duration of response, disease control rate, clinical benefit rate, safety and tolerability, efficacy, health outcomes and pharmacokinetics. Analysis is planned at 165 PFS events, providing ≥80% power to detect superiority of Arm A and Arm B over Arm C, assuming a hazard ratio of 0.67 at a one-sided alpha of 0.10. First pt visit occurred in May 2016; with a target enrollment of 225 pts. Contact information: 1-877-CTLILLY (1-877-285-4559) Clinical trial information: NCT02675231.

TPS1110 Poster Session (Board #100a), Sun, 8:00 AM-11:30 AM

A pilot study of palbociclib in patients with HER2-positive breast cancer with brain metastasis. *First Author: Cesar Augusto Santa-Maria, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: HER2+ breast cancers have the propensity to metastasize to the CNS. Most systemic therapy does not cross the blood-brain barrier (BBB) effectively, limiting treatment options. Palbociclib is a small molecule inhibitor of cyclin dependent kinases (CDK) 4 and 6, which has been studied in hormone positive breast cancers and found to have significant anti-tumor activity. Preclinical models demonstrate HER2+ tumors require cyclin D1 and CDK4 for progression and maintenance, and palbociclib has been found to have single agent activity in transgenic HER2+ models. Preclinical studies have also found that palbociclib crosses the BBB and exerts anti-cancer effects; indeed, clinical trials investigating its activity in primary brain tumors are ongoing. The summary of these data provide rationale for investigation of palbociclib in patients with HER2+ breast cancer and brain metastasis. **Methods:** A single arm study of palbociclib in patients with metastatic HER2+ breast cancer with brain metastasis was designed. The primary objective is to determine overall radiographic response rate in the CNS using modified RANO-BM criteria. Secondary objectives include PFS, OS, systemic response rates, safety, and tolerability. Exploratory objectives include assessment of mutational profiles in tissue and ctDNA, and quality of life endpoints using FACT-Cog and FACT-Br. Eligible patients must have metastatic HER2+ breast cancer with measurable brain metastasis (at least 1 lesion > = 5mm). Patients with rapidly progressive symptoms or with leptomeningeal disease are excluded. Concurrent therapy with trastuzumab is allowed. Eligible patients are treated with palbociclib 125mg PO (21 days on, 7 days off) until progressive disease or unacceptable toxicity. Available archival tissue will be obtained, ctDNA/FACT-Cog/Br will be assessed at baseline, 2, and 4 months. A total of 20 patients will be enrolled. To detect a radiographic response rates increase from 23% to 40%, a Bayesian posterior probability will be calculated after the response status in 20 patients has been assessed. The goal is that there is at least an 80% probability that the response rate exceeds 40%. Clinical trial information: NCT02774681.

TPS1111 Poster Session (Board #100b), Sun, 8:00 AM-11:30 AM

A phase 3 study of alpelisib (ALP) plus fulvestrant (FUL) in men and postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) ABC progressing on or after aromatase inhibitor (AI) therapy: SOLAR-1. *First Author: Hope S. Rugo, University of California San Francisco Comprehensive Cancer Center, San Francisco, CA*

Background: Patients (pts) with HR+ breast cancer (BC) often havedysregulatedphosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway, which further leads to resistance to endocrine therapy (ET). In a phase 1 study, alpelisib (BYL719), a PI3Kα-specific inhibitor in combination with fulvestrant (FUL) has demonstrated antitumor activity in pts with estrogen receptor-positive, HER2– advanced BC (ABC) with *PIK3CA*-altered tumors. SOLAR-1 (NCT02437318) aims to assess the efficacy of ALP + FUL in *PIK3CA*-mutant and non-mutant tumors in HR+, HER2– ABC setting. **Methods:** SOLAR-1 is a phase 3, randomized, double-blind study conducted in men and postmenopausal women with HR+, HER2– ABC. Pts are randomly (1:1) allocated to oral alpelisib/placebo (300 mg qd) and intramuscular FUL (500 mg) until disease progression or treatment (tx) discontinuation. Stratification factors are presence of liver and/or lung metastases and prior use of CDK4/6 inhibitors. The eligibility criteria for the targeted BC patient population are shown in the Table. The primary endpoint is progression-free survival (PFS; RECIST v1.1; local assessment), while overall survival (OS) is a key secondary endpoint in the *PIK3CA*-mutant cohort. Other secondary endpoints are PFS and OS in the *PIK3CA* non-mutant cohort, the association between PFS and baseline *PIK3CA*status in ctDNA, overall response rate, clinical benefit rate, and safety. Recruitment of the planned 560 pts is currently ongoing. Clinical trial information: NCT02437318.

Inclusion criteria	Exclusion criteria
• Locally advanced or metastatic HR+, HER2− BC • Recurrence or progression on or after AI therapy • Identified PI3K mutational status • ≥1 measurable lesion (RECIST v1.1) or predominantly lytic bone lesion • ECOG-PS ≤1	• Ineligibility for ET due to symptomatic visceral disease or other disease burden • Prior tx with FUL, chemotherapy (except [neo] adjuvant), or PI3K/AKT/mTOR inhibitors • Premenopausal status

TPS1112 Poster Session (Board #101a), Sun, 8:00 AM-11:30 AM

A randomized phase II trial of fulvestrant with or without ribociclib after progression on aromatase inhibition plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer. *First Author: Kevin Kalinsky, Columbia University Medical Center, New York, NY*

Background: CDK4/6i, including palbociclib and ribociclib (R), have demonstrated remarkable benefit in progression free survival (PFS) in patients (pts) with HR+, HER2- MBC with anti-estrogen therapy. Switching between anti-estrogen therapies at disease progression is standard of care in the treatment of HR+ MBC. We evaluate the strategy of switching anti-estrogen therapy to fulvestrant (F) and maintaining CDK4/6 inhibition with R in pts with HR+, HER2- MBC who have progressed on an AI + CDK4/6i. **Methods:** Trial Design Phase II, multi-center, randomized, double-blind, placebo-controlled trial to evaluate F +/- R in pts with HR+, HER2- MBC who have previously progressed on any AI + CDK4/6i: Screened at 2 different scenarios: Scenario 1: Before receiving any CDK4/6i Scenario 2: Time of progression of disease (POD) while being treated with an AI + CDK4/6i Intervention At randomization, pts assigned 1:1 to either a) F + R or b) F + placebo, with treatment given in 4-week cycles. Major Eligibility Criteria 1, Metastatic BC, 2. HR+ HER2-, 3. Measurable or unmeasurable disease Specific Aims Primary: PFS. Secondary: Objective response rate, clinical benefit rate, overall survival, and duration of response. Biomarker assessment: amplification of cyclin D1 and cyclin E, phosphoRb and TK1 expression, Rb1 and p16 loss, and ctDNA for ESR1 and PIK3CA mutations. Statistical Methods Assuming a median PFS of 3.8 months with F alone, we predict that F + R will lead to a median PFS of at least 6.5 months. A one-sided log-rank test with a sample size of N = 120 and alpha = 0.025, achieves 80% power to detect a difference in PFS of 2.7. With a 10% dropout, n = 132. Clinical trial registry number NCT02632045.

TPS1113 Poster Session (Board #101b), Sun, 8:00 AM-11:30 AM

Phase Ib study to assess the safety, tolerability, and clinical activity of gedatolisib in combination with palbociclib and either letrozole or fulvestrant in women with metastatic or locally advanced/recurrent breast cancer (B2151009; NCT02684032). *First Author: Andres Forero-Torres, University of Alabama at Birmingham, Birmingham, AL*

Background: Hormone receptor positive (HR+) disease is the most common subset of both early and late stage breast cancer (BC). The majority of women with HR+ metastatic BC (MBC) ultimately develop resistance to endocrine therapy, with a median survival of ~2-3 years. A new standard-of-care strategy to treat HR+ metastatic disease involves the combination of hormone therapy and cyclin-dependent kinase (CDK) 4/6 inhibition, which has demonstrated improved progression-free survival (PFS) in both the first- and later-line metastatic setting. More recently, preclinical data with the dual phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor gedatolisib (PF-05212384) suggest synergy with the combination of hormone therapy, CDK 4/6 inhibition, and inhibition of the PI3K/mTOR pathway. **Methods:** This phase Ib study includes a dose escalation portion to evaluate dose-limiting toxicities (primary endpoint) and determine the recommended phase II dose for triplet therapy with gedatolisib combined with palbociclib/letrozole or palbociclib/fulvestrant in women with HR+ HER2-negative MBC or locally advanced/recurrent BC, in the first- and later-line setting. Thereafter, a 3-arm expansion for early signals of efficacy will investigate objective response rates (primary endpoint) with gedatolisib combined with palbociclib/letrozole (n = 26), palbociclib/fulvestrant in patients without prior CDK 4/6 inhibition (n = 28), and palbociclib/fulvestrant in patients who have previously received palbociclib (n = 27). The rates of objective response will be compared to historical controls. Secondary endpoints include safety, tumor response, PFS (expansion portion only), pharmacokinetics, and biomarker correlations associated with the PI3K/mTOR pathway. This trial is now recruiting. Clinical trial information: NCT02684032.

TPS1114 Poster Session (Board #102a), Sun, 8:00 AM-11:30 AM

A phase I/II dose escalation and expansion study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK525762 in combination with fulvestrant in subjects with ER+ breast cancer. *First Author: Joseph A. Sparano, Montefiore Medical Center, Bronx, NY*

Background: Advanced or metastatic ER+BC (estrogen receptor positive breast cancer) is an incurable illness that will prove fatal for most afflicted women. Current standards of care include endocrine, targeted, and chemotherapy. Preclinical data suggest that reducing expression of the estrogen receptor (ER) as well as other ER-responsive genes may provide therapeutic benefit for women for whom endocrine therapy alone has proven inadequate. The bromodomain (BRD) and extra-terminal (BET) family of proteins (BRD2, BRD3, BRD4 and BRDT) bind to acetyl-histone residues and epigenetically control transcription of genes driving cell survival and proliferation. In preclinical models, BET proteins reduce ER expression and down regulate ER-dependent gene expression and may be a novel therapeutic target in multiple tumors e.g. ER+BC. GSK525762 is a pan-BET inhibitor showing strong synergistic activity with fulvestrant in killing ER+BC cells in vitro and in xenograft models. The combination of BET agents with endocrine therapy may provide therapeutic benefit and restore sensitivity to ER targeting agents like fulvestrant. **Methods:** The study is a Phase I/II dose-escalation, expansion (Phase I) and randomized control (Phase II) study with oral administration of GSK525762 in combination with fulvestrant in advanced or metastatic ER+BC subjects, whose disease has progressed on prior treatment with $\geq$ 1 line of endocrine therapy. Phase I of the study is designed as parallel single arms to determine the recommended Phase 2 dose based on safety, tolerability, PK, and efficacy profiles in two distinct populations of ER+ BC: 1. Subjects with disease that progressed on anti-estrogen and/or $\geq$ 1 AIs, OR. 2. Subjects with disease that progressed on CDK4/6 inhibitor plus letrozole. Phase I will employ a Bayesian predictive adaptive design. Phase II of the study is a randomized, double-blind, placebo-controlled study, the composition of which will be selected at the end of Phase I. Patients must have received $<$ 3 lines of anticancer therapy ($\leq$1 line of chemo), measurable disease, and PS 0-1. Funding: GSK. Clinical trial information: NCT02964507.

TPS1115 Poster Session (Board #102b), Sun, 8:00 AM-11:30 AM

A randomized, open-label, multicentre, phase IV study evaluating palbociclib plus endocrine treatment versus a chemotherapy based treatment strategy in patients with hormone receptor positive/HER2-negative metastatic breast cancer in a real world setting. *First Author: Sibylle Loibl, German Breast Group, Neu-Isenburg, Germany*

Background: Although endocrine based therapy is recommended as first-line treatment in metastatic breast cancer (MBC) in patients with an HER2-/HR+ tumour up to 50% of the patients receive chemotherapy. Palbociclib (P) a CDK4/6 inhibitor improves PFS by 42% in endocrine sensitive and resistant HER2-/HR+ MBC when added to an endocrine therapy (ET). Patients included in clinical trials are often criticised not to be representative for real world breast cancer patients. **Methods:** Patients with first-line HER2-/HR+ MBC who are candidate for mono-chemotherapy will be eligible to be randomised 1:1 to receive either P plus ET per label or mono-chemotherapy per investigator´s choice with or without maintenance ET. In both study arms, treatment will be given until disease progression, unacceptable toxicity, withdrawal of consent of the patient or change of initial treatment plan (either planned six chemotherapy cycles followed by maintenance ET or chemotherapy until disease progression). Primary objective is to compare the time-to-treatment failure (TTF), defined as time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity and death. Secondary objectives are progression free survival, overall survival at 36 months, amongst other time to event endpoints; investigator assessed overall clinical response; toxicity and compliance; patient well-being and health care utilization by daily monitoring treatment impact. Aim: 360 patients will be accrued to show an improved TTF for P in combination with ET. Recruitment will start in QII/2017 and is planned for approximately 18 months in 100 sites in Germany, Spain, Poland, Italy, France, UK and Canada. Conclusions: The aim of the trial is to demonstrate that an endocrine based strategy consisting of ET plus P is superior to a chemotherapy based strategy as first-line therapy in women with HER2-/HR+ breast cancer in a real world setting.

TPS1116 Poster Session (Board #103a), Sun, 8:00 AM-11:30 AM

Phase 1/2, multicenter, non-randomized, open-label, multiple-dose first-in-human study of U3-1402 (anti-HER3 antibody drug conjugate) in subjects with HER3-positive metastatic breast cancer. *First Author: Takahiro Kogawa, National Cancer Center Hospital East, Chiba, Japan*

Background: There is a need for effective late-line treatments in metastatic breast cancer. HER3 overexpression in breast cancer is associated with poor prognosis, but there is as yet no approved targeted treatment against HER3. U3-1402 is a novel antibody-drug conjugate (ADC) comprised of a fully humanized anti-HER3 antibody (patritumab) covalently conjugated via a cleavable peptide linker to a derivative of the topoisomerase I inhibitor exatecan. After U3-1402 binds to HER3 on the tumor cell surface, it is internalized and leads to apoptosis via inhibition of topoisomerase I. This ADC achieves a high drug-to-antibody ratio of ~8:1. **Methods:** This is a Phase 1/2, multicenter, non-randomized, open-label, multiple-dose, first-in-human study in subjects with HER3-positive metastatic breast cancer. The study consists of 3 parts: Dose Escalation, Dose Finding, and Phase 2. In Dose Escalation, safety and tolerability of U3-1402 are evaluated and the maximum tolerated dose is determined using the modified continuous reassessment method with escalation with overdose control. In Dose Finding, the recommended phase 2 dose (RP2D) of U3-1402 is determined using continued assessment of safety and efficacy as well as pharmacokinetic data of U3-1402. Efficacy and safety of the RP2D are further evaluated in Phase 2 part. Patients with locally advanced or metastatic breast cancer who have disease refractory to standard treatment, who cannot tolerate standard treatment, or for whom no standard treatment is available, will be enrolled. Key inclusion criteria include HER3-positive tumor, ECOG performance status 0–1, and measurable disease based on RECIST version 1.1. HER3 expression in tumor tissue will be evaluated with immunohistochemistry at a central laboratory. Prior chemotherapy regimens are restricted to 6 or fewer in Dose Finding and Phase 2, but not in Dose Escalation. Patients will receive U3-1402 intravenously every 3 weeks until unacceptable toxicity or disease progression. Enrollment of an estimated 80 patients is ongoing. Clinical trial information: 02980341.

TPS1117 Poster Session (Board #103b), Sun, 8:00 AM-11:30 AM

An open-label, phase II study of rucaparib, a PARP inhibitor, in HER2- metastatic breast cancer patients with high genomic loss of heterozygosity: RUBY. *First Author: Anne Patsouris, Institute of West Cancerology Paul Papin, Angers, France*

Background: *BRCA1* and/or *BRCA2* mutations confer sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi). In addition to BRCA1/2, alterations of other genes (PALB2, RAD51C….) implicated in homologous recombination repair (HRR) pathways leads to a BRCAness phenotype that is also associated with PARPi sensitivity. Rucaparib, a potent oral PARP-1, -2 and -3 inhibitor, has shown activity in a phase 1 study of patients (pts) with homologous recombination deficient (HRD) breast cancer (Kristeleit, RS. J Clin Oncol 32:5s, 2014 [suppl; abstr 2573]). This single arm, open-label, multicenter phase II study (NCT02505048) is evaluating the efficacy and safety of rucaparib in pts with HER2- metastatic breast cancer (MBC) associated with a BRCAness phenotype determined by "high tumor genomic LOH" score and/or a somatic *BRCA*mutation. **Methods:** Pts with HER2- MBC exhibiting a BRCAness phenotype will receive oral rucaparib 600 mg BID continuously in 21-day cycles until disease progression. The primary endpoint is clinical benefit rate (CBR), defined by complete and partial response and stable disease lasting for at least 16 weeks and, if CBR is significant, the objective response rate (ORR). Secondary endpoints include progression-free survival, overall survival, safety, and the prognostic value of the BRCAness signature. Targeted enrollment is 41 pts using a Simon two-stage design. Eligibility: Women with HER2- MBC with a BRCAness phenotype who received 1-4 prior chemotherapy regimens are eligible. ECOG PS 0-1 and adequate organ function is required. The BRCAness phenotype is defined by high tumor genomic LOH (LOH cutoff of 18%) that can identify HRD tumors, including both known *BRCA1* methylation and unknown genetic/epigenetic mechanisms and somatic *BRCA1/2* mutations. Pts with a known *BRCA1* and/or *BRCA2* germline mutation are excluded. "high tumor genomic LOH" score will be generated from the CytoScan HD SNP array, which is available from the SAFIR02 protocol or other molecular programs. To date, 13 pts have been enrolled, with enrollment ongoing. This trial design is intended to establish proof-of-concept that rucaparib can improve ORR in HER2- MBC with HRD. Clinical trial information: NCT02505048.

TPS1118 Poster Session (Board #104a), Sun, 8:00 AM-11:30 AM

A phase 2 study of investigational TORC1/2 inhibitor TAK-228 with fulvestrant in women with ER+/HER2–advanced or metastatic breast cancer (mBC) that has progressed during or after aromatase inhibitor (AI) therapy. *First Author: Jose Angel Garcia Saenz, Hospital Clínico San Carlos, Madrid, Spain*

Background: Antiestrogen therapy, including AI, is standard for ER+ tumors in the adjuvant and metastatic setting; however, resistance is common. These tumors may respond to alternative second-line anti-estrogen therapies such as fulvestrant but response durations are often short. Preclinical and clinical studies suggest that simultaneous inhibition of ER and PI3K/mTOR could prevent/delay the emergence of hormone-independent cancer cells, thereby improving patient (pt) outcomes. This study will test whether fulvestrant plus TAK-228, a dual TORC1/2 inhibitor, can overcome endocrine therapy resistance in ER+ mBC. This is an open-label, randomized, phase 2 study of continuous once-daily TAK-228 (4 mg) or once-weekly TAK-228 (30 mg) plus fulvestrant (per label), vs fulvestrant alone, in pts with ER+/HER2– advanced or mBC that has progressed during/after AI therapy (EudraCT 2015-003612-20). **Methods:** 153 pts will be randomized 1:1:1 and stratified (presence or absence of visceral metastasis, prior hormonal therapy sensitivity, and prior exposure to CDK 4/6 inhibitors). Pts will receive study drug(s) until progressive disease (PD), unacceptable toxicity, or consent withdrawal. Pts with histological confirmation of ER+/HER2– advanced or mBC with measureable disease, ECOG 0–1, PD during/after prior AI therapy (progression $\leq$12 mos after discontinuation of adjuvant therapy or $\leq$1 mo after discontinuation in the metastatic setting) and adequate organ function, but not prior therapy with mTOR, PI3K, dual PI3K-mTOR or AKT inhibitors, or fulvestrant, $>$ 1 prior line of chemotherapy for mBC or recurrent or progressive disease on $>$ 2 endocrine therapies for mBC are eligible. This study aims to determine the efficacy (primary endpoint: PFS; secondary endpoints: OS, TTP, ORR), safety and tolerability of TAK-228 plus fulvestrant vs fulvestrant alone. The primary hypothesis (TAK-228 plus fulvestrant can improve median PFS to 8 mos [hazard ratio, HR 0.5] vs fulvestrant-alone median PFS of 4 mos) is to be tested at the 0.10 significance level (2-sided; dropout rate 10%). To date, 24 pts have been enrolled. Clinical trial information: EudraCT 2015-003612-20.

TPS1119 Poster Session (Board #104b), Sun, 8:00 AM-11:30 AM

SANDPIPER: Phase III study of the PI3-kinase (PI3K) inhibitor taselisib (GDC-0032) plus fulvestrant in patients (pts) with estrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer (BC) enriched for pts with *PIK3CA*-mutant tumors. *First Author: Jose Baselga, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: As one of the most frequent genomic alterations in BC, *PIK3CA* mutations occur in ~40% of ER-positive, HER2-negative breast tumors. *PIK3CA* mutations may mediate resistance to endocrine therapies and promote growth and proliferation of tumors in BC. Taselisib is a potent and selective PI3K inhibitor that preferentially degrades mutant versus wild-type PI3Kα via a unique mechanism not seen with alpelisib and pictilisib. In *PIK3CA*-mutant BC cell lines, taselisib had enhanced activity. Confirmed partial responses were reported in pts with *PIK3CA*-mutant BC treated with taselisib either as a single agent or in combination with fulvestrant. **Methods:** SANDPIPER is a double-blind, placebo-controlled, randomized, phase III study, designed to evaluate the efficacy and safety of taselisib plus fulvestrant in pts with ER-positive, HER2-negative, *PIK3CA*-mutant locally advanced or metastatic BC. Postmenopausal pts will be randomized 2:1 to receive either taselisib (4 mg qd) or placebo in combination with fulvestrant (500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each subsequent 28-day cycle). Pts must have had disease recurrence or progression during or after aromatase inhibitor treatment. Randomization will be stratified by visceral disease, endocrine sensitivity, and geographic region. SANDPIPER enriches for pts with *PIK3CA*-mutant tumors and a centrally assessed, valid cobas PIK3CA Mutation Test result in tumor tissue is required prior to enrollment; pts with *PIK3CA*-mutant tumors are randomized separately from those with non-mutant tumors. The primary efficacy endpoint is investigator-assessed progression-free survival in pts with *PIK3CA*-mutant tumors (estimated by Kaplan–Meier methodology). Other endpoints include overall survival, objective response rate, clinical benefit rate, duration of objective response, safety, pharmacokinetics, and patient-reported outcomes. Enrollment is open for pts with *PIK3CA*-mutant tumors. Target enrollment is 600 pts and $>$ 300 patients have been enrolled. Clinical trial information: NCT02340221.

TPS1120 Poster Session (Board #105a), Sun, 8:00 AM-11:30 AM

ATTAIN: Phase 3 study of etirinotecan pegol (EP) vs treatment of physician's choice (TPC) in patients (pts) with metastatic breast cancer (MBC) who have stable brain metastases (BM) previously treated with an anthracycline, a taxane, and capecitabine (ATC). *First Author: Debu Tripathy, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: EP is a next generation topoisomerase I inhibitor-polymer conjugate that provides continuous exposure to SN-38, the active metabolite. A BM mouse model showed high penetration and retention of SN-38 in CNS lesions, resulting in decreased size of CNS lesions and improved survival (OS) at concentrations achieved at the recommended dose in pts (Adkins BMC Cancer 2015). A Phase 3 trial (BEACON) of EP vs TPC in 852 pts with advanced BC did not meet its primary endpoint of OS (HR 0.087; p = 0.08); a subset of 67 pts with stable BM showed improved OS (HR 0.51 [95% CI 0.30-0.86]; $p < 0.01$) (Perez Lancet Oncol 2015). The current Phase 3 trial (ATTAIN) was designed for this subpopulation of pts having high unmet medical need. **Methods:** Pts with MBC with locally treated stable BM will be randomized 1:1 to EP vs TPC in an open-label, randomized Phase 3 study. Eligibility includes ECOG PS 0 or 1; adequate organ function who received prior ATC (in neo/adjuvant or locally advanced/MBC setting); pts must have had ≥1 prior cytotoxic regimen for MBC (triple negative BC); ≥2 prior cytotoxic regimens and either 1 prior hormone therapy (HR+ BC) or 1 prior HER2 targeted therapy (HER2+ BC). Pts must have undergone definitive local therapy of BM (whole brain radiation [RT]; stereotactic RT or surgical resection as single-agent or combination); signs/symptoms of BM must be stable with steroids unchanged or decreasing for ≥7 days prior to randomization. Primary endpoint is OS. Key secondary endpoints: ORR and PFS by RECIST v1.1 and RANO-BM, clinical benefit rate (ORR+SD ≥ 6 months) and QoL. Pts randomized to TPC will receive 1 of 7 IV cytotoxic agents. Pts are stratified by region, PS and receptor status. 350 pts will be randomized to obtain number of events required at 90% power to detect a statistically significant improvement in OS (hypothesizing HR = 0.67); 1 interim analysis at 50% of deaths (130 events) will be performed. PK sampling and UGT1A1 testing will be performed in the EP arm; plasma ctDNA will be assessed for potential predictive markers of efficacy. Enrollment will begin early 2017. Clinical trial information: NCT02915744.

TPS1121 Poster Session (Board #105b), Sun, 8:00 AM-11:30 AM

An open label, phase II trial of continuous low-irradiance photodynamic therapy (CLIPT) using verteporfin for the treatment of cutaneous breast cancer metastases. *First Author: Steven J. Isakoff, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Cutaneous metastases occur in approximately 20% of patients (pts) with metastatic breast cancer (mBC) and can be highly symptomatic and distressing. Radiation is frequently offered, but progression often occurs quickly. Photodynamic therapy is a promising approach with encouraging results in small studies. Here we will evaluate a novel Continuous Low-Irradiance Photodynamic Therapy (CLIPT) system that emits 690nm LED via a handheld powerpack attached to a single-use sterile light patch to deliver a total energy level of 10J/cm2. Verteporfin (Visudyne) is a photosensitizer approved for ophthalmological use that when combined with CLIPT generates activated oxygen species which can destroy tumor cells with limited normal tissue reaction. **Methods:** This open label, phase 2 study will evaluate the efficacy and safety of CLIPT with verteporfin in 15 pts with cutaneous lesions from mBC. Pts will receive a single IV injection of verteporfin on day 1. The 9x9cm patch with an adhesive border is placed over the treatment site and attached to the CLIPT portable power pack. The pt turns the device on at home 6 hours after the verteprofin injection and it automatically turns off after 24 hours. The pt will remove the patch and return to clinic on day 3. The primary endpoint is objective response rate (RR) at 3 weeks following CLIPT using a modified RECIST which accounts for nodular or diffuse plaque-like lesions. Secondary endpoints include RR at 2, 8 and 12 weeks, toxicity, and quality of life (using FACT-B, a Participant Symptom Scale, and Brief Pain Inventory). Pts who derive clinical benefit may be retreated up to 3 times to the same or different region. Eligible pts will have: cutaneous metastases from mBC with measurable disease by protocol defined modified RECIST 1.1, ≥ 1 line of prior systemic or local therapy for mBC, ≥ 14 days from prior systemic therapy or 60 days from radiation to target lesion, and no expectation for systemic therapy for ≥ 14 days after CLIPT. RR will be reported with 95% CI. If ≥ 3 responses (RR ≥ 20%) are observed, the null hypothesis of RR ≤ 5% will be rejected. At the time of abstract submission, 1 patient has been accrued. Clinical trial information: NCT02939274.

TPS1122 Poster Session (Board #106a), Sun, 8:00 AM-11:30 AM

A randomised phase 2 study of 3 weekly cabazitaxel vs weekly paclitaxel chemotherapy in the first-line treatment of HER2 negative metastatic breast cancer. *First Author: Amit Bahl, University Hospitals Bristol NHS Foundation Trust - Bristol Haematology and Oncology Centre, Department of Oncology, Bristol, United Kingdom*

Background: Breast cancer (BC) represents 25% of all cancers in women. Whilst the majority have early stage disease approximately 30% will develop metastatic breast cancer (MBC). In HER2 negative MBC, palliative chemotherapy is one of the main treatment options. It remains to be seen whether the use of adjuvant taxane chemotherapy leads to an increase in taxane resistance at the onset of MBC, although for patients with a relatively short disease free interval this may be the case. Cabazitaxel (CBZ) is a novel taxoid selected for development from preclinical evidence in cell lines resistant to docetaxel and paclitaxel including activity in a HER-2 positive BC tumour xenograft, with innate resistance to docetaxel. Clinically CBZ is licensed for metastatic castration-resistant prostate cancer following progression during or after docetaxel chemotherapy. A phase 3 RCT in this patient group showed a 3 month overall survival benefit for patients receiving CBZ and prednisolone compared with mitoxantrone and prednisolone. **Methods:** CONCEPT is an open label randomised phase 2 trial of first line chemotherapy in patients with HER-2 negative MBC where paclitaxel would be considered the standard treatment. Patients are randomised to cabazitaxel 25 mg/m^2 every 21 days for 6 cycles or paclitaxel 80 mg/m^2 weekly for 18 weeks. Eligibility includes patients who are PS 0 or 1 who may have received prior docetaxel in the adjuvant setting or be taxane-naïve. The primary endpoint is progression free survival (PFS), defined as the time between the date of randomisation and progression (according to RECIST version 1.1) or death from any cause. Secondary end-points include safety, overall survival and assessment of quality of life factors by FACT-B and EQ-5D-5L. For the current phase 2 study 90 patients will be recruited, with a 1:1 randomisation, proceeding to phase 3 of 160 patients, if the interim analysis does not show futility. To date 38 patients have been recruited from 10 centres. The IDMC met in Oct 2016 and recommended the study continue recruitment.

TPS1123 Poster Session (Board #106b), Sun, 8:00 AM-11:30 AM

Phase II study of apatinib plus vinorelbine, a novel combination of all-oral regimen in heavily pretreated patients with metastatic HER2-negative breast cancer. *First Author: Anjie Zhu, Chinese Academy of Sciences and Peking Union Medical College, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Beijing, China*

Background: Antiangiogenic therapy in combination with chemotherapy is effective in control advanced breast cancer(ABC). Apatinib is an oral, highly potent tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2(VEGFR-2). Phase II clinical trials of Apatinib single agent had presented objective response and manageable toxicity in heavily pretreated, metastatic breast cancer. The median progression free survival (PFS) and median overall survival (OS) of single agent in both triple-negative and non-triple-negative breast cancer were 3.3-4.0 months and 10.3-10.6 months, respectively. The overall response rate and disease control rate (DCR) reached 16.7% and 66.7%, respectively. This all-oral phase II study aims to investigate the efficacy and safety of the oral vinorelbine-Apatinib combination in pre-treated metastatic breast cancer(MBC). **Methods:** This single arm prospective study enrolled patients with HER2(Human epidermal growth factor receptor-2) negative advanced breast cancer, pretreated with anthracycline and taxanes, and who failed in the metastatic setting at least one prior chemotherapy regimen. The estimated Enrollment was 40 patients. The primary end point of this study was PFS. Secondary end points included objective response rate (ORR), DCR, OS and safety. Patients were treated with apatinib 500/425mg daily plus oral vinorelbine 60-80 mg/m2 day1,8,15 every 3 weeks/cycle. Starting doses of Apatinib were chosen according to age, weight and patient status. Patients eligible were evaluated by CT or MRI scan at baseline and every 2 cycles (6 weeks) there after until disease progressed. Adverse events (AEs) were assessed and graded in accordance with the Common Terminology Criteria for AEs, version 4.0. Clinical trial information: NCT02768415.

TPS1124 Poster Session (Board #107a), Sun, 8:00 AM-11:30 AM

Phase II trial of pembrolizumab in combination with nab-paclitaxel in patients with metastatic HER2-negative breast cancer. *First Author: Maryann J. Kwa, New York University Cancer Institute, New York, NY*

Background: Immunotherapy has shown therapeutic promise in several cancers, including breast cancer. Monotherapy with anti-PD-1/anti-PD-L1 antibodies has demonstrated durable responses in patients with metastatic triple-negative breast cancer (mTNBC) (Nanda et al, JCO 2016) and metastatic estrogen receptor-positive (mER+)/HER2-negative breast cancer (Rugo et al, SABCS 2015). Furthermore, response rates have been increased with combination approaches with chemotherapy (Adams et al, ASCO 2016). Based on these results, we seek to study the anti-tumor efficacy and safety of pembrolizumab (anti-PD-1 antibody) and nab-paclitaxel, the impact of therapy on the tumor microenvironment, and predictive markers of response. **Methods:** This is an ongoing single-arm open-label multi-cohort phase II study of pembrolizumab and nab-paclitaxel in patients treated with ≤2 prior lines of therapy for metastatic HER2-negative breast cancer (n = 50) (ClinicalTrials.gov: NCT02752685). Thirty patients with mTNBC and 20 patients with mER+/HER2-negative breast cancer will be enrolled. Enrollment of patients with metaplastic breast cancer is encouraged. Patients will receive pembrolizumab 200 mg IV on day 1 plus nab-paclitaxel 100 mg/m^2 IV on day 1 and 8 (21-day cycle). Prior taxane therapy given > 3 months before cycle 1 is allowed. Primary objective is treatment efficacy, as determined by overall response rate (RECIST 1.1). Secondary objectives include safety, progression-free survival, overall survival, and duration of response. Serial tumor biopsies will be performed to assess changes in the tumor microenvironment from baseline with chemotherapy alone (cycle 1) and then with chemoimmunotherapy (cycle 2 and subsequent cycles). Mutational and neoantigen load, TILs by histopathological assessment, TCR by immunosequencing, and immune gene profiles in tumors will be evaluated. PD-L1 expression in tumor tissue is not required for enrollment but will be assessed as a predictive marker. The potential role of the gut microbiome in modulating the immune response will also be evaluated by 16S rRNA. An initial safety run-in with 12 subjects has been completed with no unexpected toxicity. Clinical trial information: NCT02752685.

TPS1125 Poster Session (Board #107b), Sun, 8:00 AM-11:30 AM

LCCC 1525: Combination immunotherapy with cyclophosphamide plus pembrolizumab in patients with advanced triple negative breast cancer (TNBC). *First Author: Benjamin Garrett Vincent, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: Immunotherapy is a promising strategy to treat advanced TNBC, an aggressive subtype of BC lacking expression of estrogen and progesterone receptors and HER2. TNBC response to antibodies targeting programmed cell death protein 1 (PD-1) or its ligand (PD-L1) are modest (< 20%); high expression of PD-L1 is associated with enhanced response. The presence of intratumoral regulatory T cells (Tregs), potent suppressors of the immune response, dampens response to checkpoint inhibitors. The capacity of cyclophosphamide (Cy), a cytotoxic with known activity in BC, to deplete Tregs is well-established. Preclinical mouse models of TNBC illustrate Treg depletion with improved outcome when Cy is administered prior to PD-1 inhibition. We are testing the hypothesis that a single dose of Cy given prior to pembrolizumab (pembro) will improve progression free survival (PFS) beyond historical control in advanced TNBC. **Methods:** This phase II, single-arm, multicenter study will evaluate pembro 200 mg IV every 3 weeks following a single priming dose of Cy 300 mg/m2 IV in patients (pts) with advanced TNBC who have received ≥1 prior therapy in the metastatic setting. The primary objective is to estimate PFS for Cy + pembro in advanced TNBC pts. A co-primary objective is to describe reduction in circulating Tregs. Secondary objectives include overall response rate (ORR, RECIST 1.1), duration of response (DOR), disease control rate (DCR) and overall survival (OS). Determination of ORR based on immune response criteria (irRECIST) and association of immunogenomic features with PFS are exploratory. Statistical considerations: A sample size of 36 pts has an 80% power to detect change in median PFS from 1.9 (null) to 2.9 (alternative hypothesis) months at a 0.05 significance level. Assuming 10% dropout rate, we will enroll 40 pts. We will also be able to detect a 67% reduction in Tregs with 80% power and one-sided alpha = 0.05. Correlative studies: Archival primary and/or metastatic tissues are required of all pts to evaluate molecular subtype, gene signature expression, T and B cell receptor repertoires, and PD-1 and PD-L1 expression; correlations with outcome will be performed. Clinical trial information: NCT02768701.

TPS1126 Poster Session (Board #108a), Sun, 8:00 AM-11:30 AM

A phase 1b study of safety and immune response to PVX-410 vaccine alone and in combination with durvalumab (MEDI4736) in HLA-A2+ patients following adjuvant therapy for stage 2/3 triple negative breast cancer. *First Author: Steven J. Isakoff, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Stage 2-3 triple negative breast cancer (TNBC) remains at high risk for recurrence despite modern adjuvant therapy. An important role for the immune system in TNBC has recently emerged. Tumor infiltrating lymphocytes (TILs) are correlated with improved prognosis and several PD-1/PD-L1 checkpoint inhibitors, including Durvalumab (DUR), demonstrated activity in metastatic TNBC. Vaccines are a promising approach to further enhance the immune response in many cancers including TNBC. PVX-410 (PVX) is a novel tetra-peptide vaccine against XBP1 (2 splice variants), CD138 and CS1 that was safe and induced immune responses in a phase 1b study in smoldering myeloma. XBP1 and CD138 are also over-expressed in TNBC. **Methods:** This Phase 1b multi-center, single arm study will enroll 20 HLA-A2+ female patients (pts) following completion of all adjuvant therapy for stage 2-3 TNBC. Pts will receive 6 doses of 800ug PVX (emulsified in Montanide (SC) and co-administered with Hiltonol (IM)) at 2-week intervals, and 2 doses of DUR 1500mg IV at the 4th and 6th vaccine visits. Eligible pts must be between 1-6 months from completing adjuvant therapy, have no prior autoimmune disease, and have residual disease if neoadjuvant therapy was used. The primary objective is to determine the safety and tolerability of the combination, and the key secondary objective is to determine the immune response to PVX + DUR. If ≤1 pt in the first 6 has a protocol defined dose limiting toxicity within 4 weeks after the first DUR dose, accrual will continue to 20 pts. Immune response will be assessed at baseline, pre-dose 4 PVX/dose 1 DUR, and 4 weeks after completing protocol therapy. Paired data in 20 pts provides 90% power to see a shift of 0.75 standardized units from baseline to 4 weeks post treatment with the signed rank test. Immune response will be determined by a FACs based assay of antigen specific CD3+CD8+ T lymphocyte response and IFN-γ production (intracellular staining) in patient PBMCs. Additional correlative studies, including T-cell PD-1 and tissue PD-L1, XBP1, and CD138, are planned. Currently 4 pts are enrolled. Clinical trial information: NCT02826434.

TPS1127 Poster Session (Board #108b), Sun, 8:00 AM-11:30 AM

Phase Ib study of heat shock protein 90 inhibitor, onalespib in combination with paclitaxel in patients with advanced, triple-negative breast cancer (NCT02474173). *First Author: Robert Wesolowski, The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH*

Background: Heat shock protein 90 (HSP90) is a molecular chaperone which is necessary for proper folding and stabilization of proteins. Client proteins of HSP90 include many oncogenic proteins known to be over-activated in triple negative breast cancer such as AKT, EGFR, members of RAS/MAPK signaling pathway and androgen receptor. High expression of HSP90 in breast cancer has been associated with poor outcome. In addition, over-expression of HSP90 client proteins such as AKT and c-RAF has been implicated in paclitaxel resistance. Onalespib (AT13387) is a synthetic non-ansamycin small molecule that acts as an inhibitor of HSP90 by binding to the amino terminal of the protein and has dissociation constant (Kd) of 0.71 nM. **Methods:** Patients with inoperable or metastatic, triple negative or < 10% hormone receptor positive breast cancer are treated with onalespib and paclitaxel on days 1, 8, 15 every 28 days. Paclitaxel is given at a standard dose of 80 mg/m2 while the dose of onalespib is gradually increased using standard 3+3 design (see table). In order to assess the effect of each drug on pharmacokinetics of the other drug, onalespib is given on day -7 prior to cycle 1 and skipped on day 1 of cycle 1 during which paclitaxel is administered alone. The primary objective of the study is to determine recommended phase II dose and assess the toxicity profile of the combination. The secondary objectives include pharmacokinetic of each agent. Overall response rate, response duration and progression-free survival will also be assessed. The study is currently enrolling patients to dose level 2. Clinical trial information: NCT02474173.

Dose escalation schedule.

	Dose	
Dose Level	**Onalespib (mg/m^2 IV on days 1, 8, 15)**	**Paclitaxel (mg/m^2 IV on days 1, 8, 15)**
Level -1	100	80
Level 1	120	80
Level 2	150	80
Level 3	200	80
Level 4	260	80

1500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Enrichment of germline DNA-repair gene mutations in patients with colorectal cancer. *First Author: Saud H Aldubayan, The Broad Institute of MIT and Harvard, Cambridge, MA*

Background: Twin studies showed that 30% of all colorectal cancer (CRC) patients have an inherited genetic susceptibility. Several CRC predisposition genes have been described to date. However, mutations in these genes explain the risk in only 5-10% of CRC cases. In this study, we hypothesized that some of the CRC heritability may be explained by excess disruptive germline mutations in DNA repair genes (DRGs). **Methods:** Exome sequencing data of 716 in the discovery cohort (CanSeq and NHS/HPFS studies) and 1609 CRC patients in the validation cohort (TCGA and NSCCG studies) were used to evaluate germline variants in a pre-selected group of 42 DRGs and 12 known CRC risk genes. Frequencies of disruptive mutations in our cohorts were examined relative to 27173 non-Finnish European cancer-free adults from the ExAC cohort to evaluate for enrichment. **Results:** Of 716 patients in the discovery cohort, 27 (3.8%) patients harbored germline mutations in *APC* (n = 11), *MSH6* (n = 2), *MUTYH* (n = 11), CHEK2 (n = 1) and *TP53* (n = 2). Interestingly, germline mutations in *ATM* and *PALB2* were significantly enriched in our CRC discovery cohort (OR = 2.7; P = 0.044; and OR = 4.8; P = 0.026, respectively). Evaluation of germline data from another 1609 CRC patients (validation cohort) also showed significantly higher rates of *ATM* mutations (5; 0.7%; OR = 2.1; P = 0.044), and a trend for enrichment of *PALB2* mutations (3; 0.4%; OR = 2.8; P = 0.056). Secondary analysis of actionable germline mutations in a highly penetrant cancer risk gene set (*ATM, BRCA1, BRCA2, BRIP1* and *PALB2*) suggest a broader enrichment trend in CRC patients for these genes (Discovery: OR = 1.7; P = 0.06; Validation: OR = 2; P = 1.96e-04). **Conclusions:** Our analysis of germline variants in 2325 CRC patients showed the first robust evidence for germline *ATM* mutations to confer a higher risk of developing CRC. We also presented evidence to support *PALB2* as a potential novel CRC risk gene. Overall, our study shows that mutations in some DRGs may explain some of the missing CRC heritability. It also indicates that a significant percentage of CRC patients, who carry mutations in highly actionable genes where cancer screening recommendations for patients and families do exist, are not captured with current testing recommendations.

1501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Germline genetic testing in unselected pancreatic ductal adenocarcinoma (PDAC) patients. *First Author: Mary Linton Bounetheau Peters, Beth Israel Deaconess Medical Center, Cambridge, MA*

Background: The aim of this study is to assess the prevalence of known heritable germline mutations in unselected PDAC patients and to determine how well current guidelines for genetic testing identify mutation carriers. **Methods:** Consecutive, unselected patients with recently diagnosed PDAC from three centers were enrolled from May to December 2016 in an ongoing prospective study. A three-generation pedigree was obtained. Germline mutations in 12 genes associated with PDAC risk (*APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, PALB2, PMS2, STK11, TP53*) and in 19 genes related to other cancer risks were screened for by NGS. American College of Gastroenterology and NCCN criteria for genetic testing for *BRCA1/2*, Lynch syndrome, and Familial Pancreatic Cancer (FPC) were assessed. **Results:** Among 183 patients, 46% are female, 79% are Caucasian and 10% are Ashkenazi Jewish, with median (IQR) age 68 (62,75) years at diagnosis. 41% of patients met [3]1 criteria for genetic testing (35.5% *BRCA1/2*, 2.7% Lynch, 9.3% FPC). Twenty patients (11%) were found to have a total of 21 pathogenic mutations (table). Mutation status was not associated with age at diagnosis, sex, or personal history of cancer (all $p > 0.05$). Six mutation carriers (30% of positives) did not meet current criteria for genetic testing. **Conclusions:** Preliminary results show that 6.6% of unselected PDAC patients carry a germline mutation in a gene known to increase PDAC risk and 4.3% have a mutation in genes not previously linked to PDAC. Existing testing criteria did not identify 30% of carriers. Continued refinement of guidelines is necessary to align genetic testing with inherited PDAC risk. Clinical trial information: NCT02790944.

			Testing Criteria Met		
Patient	Gene	Mutation	BRCA1/2	Lynch	FPC
1	*ATM*	c.1027_1030delGAAA	Y	N	N
2	*ATM*	c.1564_1565delGA	Y	N	N
3	*ATM*	c.3245_3247delATCinsTGAT	N	N	N
4	*ATM*	c.5932G > T	N	N	N
5	*ATM*	c.6027C > G	N	N	Y
	RAD50	c.1052-2A > C			
6	*ATM*	c.7630-2A > C	N	N	Y
7	*BRCA1*	c.68_69delAG	Y	N	N
8	*BRCA1*	c.181T > G	Y	N	N
9	*BRCA1*	c.5266dupC	Y	N	N
10	*BRCA2*	c.1237delC	Y	N	N
11*	*CDKN2A*	c.-34G > T	N	N	N
12	*CHEK2*	c.470T > C	Y	N	N
13	*CHEK2*	c.470T > C	N	N	N
14	*CHEK2*	c.470T > C	Y	N	Y
15	*CHEK2*	c.470T > C	Y	Y	N
16	*CHEK2*	c.1116dupC	Y	N	N
17	*CHEK2*	c.1283C > T	Y	N	Y
18	*CHEK2*	EX8_9del	N	N	N
19	*MSH6*	c.2230dupG	N	N	N
20	*NF1*	c.663G > A	N	N	Y

*No personal or family history of melanoma or other PDAC

1502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Prevalence of homologous recombination deficiency among all tumor types. *First Author: Arielle Lutterman Heeke, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Triple negative breast and ovarian cancer are known to have a high frequency of homologous recombination deficiencies (HRDef). The prevalence of HRDef among all tumors is unknown. **Methods:** Molecular profiles of 48,733 tumors obtained from pts with bladder, breast, ovarian, pancreas, prostate, thyroid, cervical, hepatobiliary, colorectal (CRC), endometrial, gastric/esophageal (GE), head/neck, renal, non-small cell lung (NSCLC), small cell lung (SCLC), GIST, glioma, melanoma, sarcoma and unknown 1° cancers were reviewed to identify somatic pathogenic mutations (mut) in HR genes *ATM, ATRX, BARD1, BLM, BRCA1/2, BRIP1, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, PTEN, RAD50, RAD51, RAD51B,* or *WRN*. Molecular profiles were generated from tumors submitted to Caris Life Sciences using multiple technologies including next generation sequencing (average read depth 500X). **Results:** Overall frequency of HR mut among all tumors is 11.61% (5658/48733). Cancer lineages with highest frequency of HR mut are endometrial (38.08%, 1956/5137), glioma (15.90%, 265/1667), ovarian (12.99%, 1151/8862), prostate (11.21%, 77/687), cervix (10.06%, 79/785) & breast (9.66%, 562/5818). Least commonly mutated lineages include GIST (1.50%, 3/200), sarcoma (3.12%, 55/1763), head/neck (3.70%, 24/648), hepatobiliary (4.72%, 39/827) & pancreas (5.05%, 102/2022). Frequencies of HR gene mutations are depicted in Table 1. **Conclusions:** HR mutations were seen in 11.61% of tumors. While the percentage of HRDef in pancreatic cancer pts is lower than what has been seen in other datasets, the percentage in breast and ovarian cancer, as well as the percentage of other tumors with HRDef, provide a path to employ HRDef-directed therapies such as platinums, but especially PARP inhibitors and newer agents such as ATRX inhibitors.

Frequency of HR gene mutations.

HR Mutation	Frequency (%)	Lineages Mutated
ATM	14.24	All except (ex) head/neck
ATRX	0.91	Breast, cervix, CRC, endometrial, GE, GIST, glioma, melanoma, SCLC, NSCLC, ovarian, sarcoma, unknown 1°
BLM	0.21	CRC, GE, melanoma, NSCLC
BRCA1	2.70	All ex GIST, renal
BRCA2	2.88	All ex renal
BRIP1	0.17	Melanoma, pancreas
NBN	0.15	Breast, hepatobiliary, CRC, GE, glioma, NSCLC, ovarian
PALB2	0.55	All ex GIST, head/neck, prostate, renal, thyroid
PTEN	6.10	All ex GIST

1503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Genetic counseling and testing in endometrial cancer: Are we capturing high-risk women? *First Author: Jessica Lee, New York University School of Medicine, New York, NY*

Background: Lynch syndrome accounts for the majority of inherited endometrial cancers and the identification of probands presents a unique opportunity to treat and prevent multiple cancers. This is now even more relevant with the potential of novel immunotherapy agents for women with germline mutations. The diagnosis of endometrial cancer (EC) can provide the indication for women with specific risk factors to undergo genetic testing (GT). We sought to evaluate genetic counseling referrals (GCR) and subsequent GT rates. **Methods:** All women with EC between 2012 and 2015 were identified. Statistical analyses were performed to evaluate risk factors including age, body mass index (BMI), positive family history defined as two or more family members with Lynch-related cancers, and tumor mismatch repair (MMR) protein expression loss. **Results:** A total of 447 women were diagnosed with EC and of these, 107 (24%) were given GCR by their gynecologic oncologist based on their discretion. Compared to non-GCR, GCR women were significantly younger (median 54 vs 65, $p < 0.0001$) and had lower BMI (median 28.2 vs 30.8, $p = 0.007$). Of the 107 GCR women, 71 (66%) underwent GT. Of the 71 GT women, 8 (11%) were found to have a germline mutation in one of the MMR genes. Table 1 lists GCR, GT and positive germline mutations among specific high-risk cohorts. Of these cohorts, 56% under 50 years of age, 28% with family history, and 61% with loss of tumor MMR proteins had GCR. **Conclusions:** Many young, thin EC women with a family history or a tumor MMR deficiency are not given GCR. Among GCR women, 66% underwent GT, despite there being a high rate of germline mutations among these women. It is imperative that high-risk women receive GCR with subsequent GT to capture the maximum number with Lynch syndrome to screen and prevent additional cancers as well as enable cascade testing in family members. Facilitated pathways may be helpful in increasing GCR, as well as GT in EC women.

Cohort	GCR / all women	GT / GCR women	Lynch syndrome / GT women
Age < 50 years	40/71 (56%)	25/40 (63%)	4/25 (16%)
BMI < 25kg/m^2	33/109 (30%)	22/33 (67%)	3/22 (14%)
Positive family history	28/101 (28%)	23/28 (82%)	6/23 (26%)
MMR protein expression loss on tumor immunohistochemistry	25/41 (61%)	17/25 (68%)	5/17 (29%)

1504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Extended follow-up in the COGENT study: A randomized study of in-person versus telephone disclosure of cancer genetic test results. *First Author: Angela R. Bradbury, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

Background: Alternative delivery models are needed in the era of Precision Medicine given a shortage of genetic providers and increasing utilization of genetic testing. Telephone disclosure (TD) of genetic test results, including multi-gene panel testing, is non-inferior to usual care in-person disclosure (IPD) for short-term distress but failed non-inferiority for knowledge. Longitudinal data including health behaviors are needed. **Methods:** 970 patients undergoing clinical genetic testing at 5 centers were randomly assigned to usual care IPD (n = 497) or TD (n = 473) of results in the COGENT Study (NCT01736345). Participants completed surveys after pretest counseling, post-disclosure and at 6 and 12 months. We used non-inferiority tests for primary analyses and T-tests and logistic regressions for secondary analyses. **Results:** TD was not worse than IPD for anxiety both post-disclosure and at 6 months, but did not reach the non-inferiority threshold for knowledge at either time point. In secondary analyses there were no significant differences in anxiety, depression, or cancer worry between arms, but there was less knowledge gain at 6 (-0.41 v. +0.11 in IPD, p = 0.05) and 12 months (-0.34 v. +0.31 in IPD, p = 0.05) in the TD arm. In the TD arm, 195 (50%) returned for clinical follow-up with a physician to discuss medical management. Not returning for follow-up varied by site and was associated with a negative result, being male and non-white. Knowledge gain at 6 months was lower for those who did not return for follow-up (-0.77) compared to those who returned (-0.17, p = 0.08). There were no significant differences by arm at 6 and 12 months in performance of mammogram, breast MRI, colonoscopy or prophylactic surgeries. **Conclusions:** Distress is not unacceptably worse with TD, but knowledge failed the test for non-inferiority. Longitudinal knowledge declined more for those who did not return for medical follow-up, but uptake of screening and risk reducing behaviors did not differ by arm. Telephone disclosure of genetic test results, even MGPT, may be a reasonable alternative to in-person disclosure for patients who agree to return to meet with a provider for medical management recommendations. Clinical trial information: NCT01736345.

1505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Effects of lifestyle and diet as modifiers of risk of breast cancer (BC) in *BRCA1* and *BRCA2* carriers. *First Author: Marina Pollan, National Center of Epidemiology, Instituto Salud Carlos III, Madrid, Spain*

Background: Mutations in the *BRCA1/2* genes confer a high lifetime risk of BC. Penetrance varies among populations and individuals suggesting that non-genetic factors may modify the inherited risk. Knowledge of modifiable factors will help to develop preventive strategies. **Methods:** Information on physical activity (PA) (current PA and in the adolescence) and smoking was collected in 892 women (W) with a *BRCA1/BRCA2* germ-line mutation (582 with BC, 45,62% *BRCA2*) from 279 families, followed at three Spanish Genetic Counseling Units, 481of these W also answered a food frequency questionnaire. Participants gave their consent and the study was approved by the ethics committee. The association between BC, lifestyle factors and dietary patterns (Mediterranean and Western) associated with BC were studied using logistic regression. Huber-White robust estimators of variance were employed to take into account correlations between family members. Age, menopausal status, specific mutated gene, BMI, parity and oral contraception were included as co-variables. BC was classified as HR+/+,- or HR-. **Results:** W who did PA daily had half the risk of BC than sedentary W (OR:0,53;p=0,043 for current PA;OR:0,40;p=0,007 for PA in the adolescent) and no differences were observed between *BRCA1* and *BRCA2* carriers. Also, W who daily exercised in both periods had a reduction of their BC risk (OR:0,22;p<0,001). The effect of PA was particularly important among premenopausal W (p-het<0,05). PA in the adolescent decreased the risk of all type of tumors. Nevertheless, alcohol intake, smoking habit and type of diet, did not significantly modify BC risk in this *BRCA* W. **Conclusions:** Our preliminary data suggest a clear reduction in BC risk among *BRCA1/2* carriers who exercise regularly, mainly during the adolescence, and could be considered as potential modifiable factor for BC prevention in these group of W.

1506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Lung cancer screening patient navigation for current smokers in community health centers: A randomized controlled trial. *First Author: Sanja Percac-Lima, Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA*

Background: Annual chest computed tomography (CT) can decrease lung cancer mortality in high risk individuals. Patient navigation (PN) has been shown to improve cancer screening rates in underserved populations. We evaluated the impact of PN on lung cancer screening (LCS) in current smokers in community health centers (CHC). **Methods:** Current smokers aged 55-77 receiving care in five CHC affiliated with an academic medical center were randomized to intervention (n = 400) or control (n = 800) groups. In the intervention arm, patient navigators (PNs) determined eligibility for LCS, provided brief smoking cessation counseling, introduced shared decision making about LCS, scheduled appointments with the primary care provider (PCP), reminded patients about appointments and PCPs to order CTs, and helped patients attend testing and follow-up any abnormal results. Control patients received usual care. The primary outcome was the proportion of patients in each group who had any chest CT during the study period. Secondary outcomes included proportion of patients receiving lung screening CTs and the number of lung cancers diagnosed in each group. **Results:** Baseline patient characteristics were similar between randomized groups. From March 2016-January 2017, PNs contacted 332 (83%) of intervention patients; 76 refused further participation. Of participating patients, 130 (51%) were eligible for LCS. Exclusions included insufficient smoking history (n = 117), competing comorbidities (n = 5), moved (n = 2), and died (n = 2). In intention-to-treat analyses, 124 intervention patients (31%) had chest CT vs. 138 control patients (17.3%, p < 0.01). Lung cancer screening CTs were performed in 94 intervention patients (23.5%) vs. 69 control patients (8.6%, p < 0.01). Eight lung cancers were diagnosed in intervention patients (2%) vs. 4 in controls (0.5%). **Conclusions:** A patient navigation program implemented in community health centers significantly increased lung cancer screening among current smokers. PNs may help underserved low-income current smokers complete LCS and improve equity in care while decreasing lung cancer mortality. Clinical trial information: 2015P002239.

1507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

High risk genetic screening program in a community hospital breast imaging center. *First Author: Anne C. Kushwaha, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The NCCN has published guidelines for screening and testing of Hereditary Breast and Ovarian Cancer (HBOC) that is typically used by the primary physician or oncologist. Little data exists on the value of genetic screening at a major health care access point: the breast imaging center (BIC). Using BICs as potential clinics to identify high risk women could increase the number of appropriate referrals for genetic risk assessment. Therefore, at our hospital-based BIC serving mostly low to middle income patients in a major metropolitan center, we developed a practical screening tool based on the HBOC guidelines and prospectively screened women receiving screening and diagnostic mammography. **Methods:** A questionnaire based on the NCCN HBOC genetic referral guidelines was added to the intake forms of all patients (pts) obtaining breast imaging at our BIC from 2012 to 2015. Forms were reviewed by the radiologists and flagged if the patient met the guidelines of the tool. Identified pts were contacted by letter and/or telephone and a nurse navigator or genetic counselor verified data, and provided information about genetic counseling to the patient prior to scheduling genetic counseling appointments. **Results:** Almost 35, 000 pts were seen during the study period. 1214 pts (3.5%) were flagged as possibly high risk, of which 189 pts. had received prior genetic testing. Of the 1025 remaining pts identified as candidates for genetic counseling, 258 (25%) made a genetic counseling appointment and 163 (16%) received genetic counseling. 106 pts. were tested for BRCA1/2. 9 pts (8.5%) tested positive for a BRCA1/2 pathogenic mutation and 8 pts (7.5%) had a Variant of Unknown Significance. **Conclusions:** Screening for HBOC syndromes at the time of annual breast imaging in a community-based middle to low income metropolitan breast imaging center is practical. Our screening tool identified women with BRCA mutations who would have been otherwise missed. This will have immediate implications for the patient and their family members in regards to increased surveillance and risk reductive surgery discussions.

1508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Survival outcomes of screening with breast MRI in high-risk women. *First Author: Min Sun Bae, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Mammography is the only imaging modality proven to reduce mortality from breast cancer. Over the past decade, magnetic resonance imaging (MRI) screening of women with increased risk of breast cancer ($>$ 20% cumulative life time risk) has been recommended. However, there is little evidence that supplemental screening with MRI improves survival. The purpose of this study was to compare survival outcomes of combined screening with MRI and mammography to screening mammography alone in women at increased risk for breast cancer. **Methods:** A total of 3,002 women at increased risk underwent at least two screening rounds between 2001 and 2005, with at least 5 years of follow-up. 1,534 women had combined screening (MRI and mammography), and 1,468 had screening mammography alone. Cancer detection yield and survival were determined in the two groups. **Results:** 60 women were diagnosed with breast cancer, 38 patients in the combined screening group and 22 in the mammography-only group. Cancer yield was 24.8 per 1000 (95% CI, 17.6-33.8) combined screening and 15.0 per 1000 (95% CI, 9.4-22.6) mammography-only. No interval cancers occurred in women undergoing combined screening, while 9 interval cancers were found in women undergoing only mammography screening. During a median follow-up of 10.8 years (range, 0.7-15.2), a total of 11 recurrences and 5 deaths (4 breast cancer cause and 1 unknown cause) were found. Of the 11 recurrences, 6 were in the combined screening group and 5 were in the mammography-only group. All deaths were in the mammography-only group. The Kaplan-Meier estimate for disease-free survival showed no statistically significant difference between the two groups (P = .325). However, patients in the combined screening group had a significantly better overall survival compared with patients in the mammography-only group (P= .002). **Conclusions:** Combined screening with MRI and mammography in women with increased risk of breast cancer resulted in not only a higher cancer detection yield but also better overall survival.

1509 Poster Discussion Session; Displayed in Poster Session (Board #167), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Variation in screening rates in a multi-ethnic population-based study in Chicago. *First Author: Brisa Aschebrook-Kilfoy, The University of Chicago, Chicago, IL*

Background: We initiated the Chicago Multiethnic Prevention and Surveillance Study (COMPASS) in 2013. Here, we present screening rates for key cancers with known disparities in risk/and or outcomes in Chicago, considering the effect health care access and race/ethnicity, and we compare the findings in COMPASS to rates reported by the CDC. **Methods:** COMPASS participant responses to a health interview were analyzed. The analysis of colorectal cancer screening (CRCS) was limited to persons 50-75, mammography screening (MS) was restricted to women ages 50-74, and cervical screening (CS) by pap smear testing was restricted to women ages 21-65. Frequency statistics and linear regression models were run to evaluate associations. **Results:** A total of 2,967 COMPASS participants were included in the analysis from 18 communities. We found ever CRCS rates in Chicago are lower than the national average (52.3% vs. 58.6%; $p < .01$) and that CRCS is lower in blacks (50.3%) and Hispanics (52.1%) compared to whites (65.8%), and that those with health insurance (HI) report a CRCS rate of 56.8% compared to 25.5% without insurance. Mammography within the last 2 years was 70.8% in COMPASS women compared to 72.4% nationally, with black women reporting higher rates of MS in the past 2 years (73.0%) compared to white women (65.4%) and Hispanic women (62.9%); and higher MS among women with HI (74.2%) compared to women without HI (47.2%). Pap screening within the last 5 years was 84.3% in COMPASS women compared to 83.0% nationally (last 3 years), with both black (85.3%) and Hispanic (83.2%) women reporting non-significantly higher CS compared to white women (80.9%) in COMPASS, and significantly higher CS among women with HI (86.2%) compared to women without HI (77.7%). **Conclusions:** Our results reinforce the fact that differences in cancer screening reflect the larger problem of access to care. We further found racial disparities in CRC screening in COMPASS to be consistent with disparities in incidence. However, our results do not support the notion that the disproportionate burden of breast and cervical cancer in black and Hispanic women in Chicago are primarily due to a lack of screening.

1510 Poster Discussion Session; Displayed in Poster Session (Board #168), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Incidence, persistence and determinants of human papillomavirus: A prospective cohort study of 10,000 HIV-negative Nigerian women. *First Author: Sally Nneoma Adebamowo, University of Maryland School of Medicine, Baltimore, MD*

Background: Cervical cancer is the second commonest cancer in Africa. Persistent High-risk HPV (HRHPV) infection is a necessary cause but little is known about the persistence and associated risk factors of HRHPV infection in African women. The aim of this study was to determine risk factors and incidence of HPV infection in Nigerian women. **Methods:** ACCME is a multicenter prospective cohort study of host germline, cervical somatic and HRHPV genomics, epigenomics, and vaginal microenvironment; and their association with HPV. From February/2014 to January/2016, 10,000 HIV-negative women were enrolled into the cohort and are being followed up every 6 months. We used SPF_{25}/$LiPA_{10}$to characterize HPV infection and defined persistent infection as 2 consecutive positive tests done at least 12 months apart. Logistic regression models were used to estimate the associations between risk factors and persistent HPV. **Results:** The mean (SD) age of the study participants at baseline was 40 (10) years and the mean (SD) vaginal pH was 5.2 (0.6). About 42% of the participants were positive for any HPV positive and 21% had persistence of any HPV infections. Some, 35% of the participants had multiple infections with any HPV. About 54% of those with persistent any HPV infections had HRHPV; HPV types 52 (25%) and 18 (15%) were the most prevalent and persistent HRHPV types. The incidence of any HPV infection was 6.6/1,000 person-months while that of HRHPV was 2.6/1,000 person-months. Age, body mass index, level of education, marital and socio-economic status and total number of lifetime sexual partners were associated with HPV infection in these women. **Conclusions:** We defined the incidence, risk factors and commonest types of HRHPV in a large cohort of women in West Africa.

1511 Poster Discussion Session; Displayed in Poster Session (Board #169), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A randomized trial of selenium and vitamin E for primary prevention of non-melanoma skin cancer: Trial results and experience from a low-resource setting. *First Author: Maria Argos, Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, IL*

Background: Selenium and vitamin E supplementation previously have shown some evidence of a beneficial effect in the secondary prevention of non-melanoma skin cancer (NMSC). More than 100 million people worldwide are at increased risk of NMSC and other cancers due to arsenic exposure from drinking water and diet – a risk that persists for several decades even after the exposure has terminated. Here, we report on the design, methods and main results of the Bangladesh Vitamin E and Selenium Trial (BEST) – a population-based chemoprevention study conducted among 7,000 adults with visible arsenic toxicity. **Methods:** BEST is a 2×2 full factorial, double-blind, randomized placebo controlled trial of 7,000 adults having manifest arsenical skin lesions evaluating the efficacy of 6-year supplementation with alpha-tocopherol (100 mg daily) and L-selenomethionine (200 μg daily) for the prevention of NMSC incidence. **Results:** Excellent compliance was maintained through the course of the trial, based on data from pill counts, self-reported compliance, and bioadherence. Among participants on treatment through the end of the 6-year intervention period, $>$ 85% were adherent to at least 80% of study supplements. More than 500 new NMSC cases were ascertained using a three-tiered biopsy protocol. No significant beneficial effects were observed on NMSC incidence during the study period for selenium or vitamin E. Among more than 500 observed deaths (including 182 cancer-related deaths), there were also no significant treatment effects on total mortality, cancer-related mortality or arsenical cancer-related mortality. **Conclusions:** This large population-based trial does not support any beneficial effect of vitamin E or selenium supplementation for the primary prevention of NMSC or mortality in an arsenic-exposed population. With the rapidly increasing burden of preventable cancers in low- and middle-income countries, efficient and feasible chemoprevention study designs and approaches, such as employed in Bangladesh, may prove impactful in conceiving large scale cancer chemoprevention trials in low-resource settings. Clinical trial information: NCT00392561.

1512 Poster Discussion Session; Displayed in Poster Session (Board #170), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Multi-gene panel testing of patients with multiple primary malignancies suspected with hereditary cancer syndrome. *First Author: Gloria HJ Chan, National University Hospital, Singapore, Singapore*

Background: Developing multiple primary cancers is an indicator of underlying hereditary cancer predisposition, but there is a paucity of data regarding the characteristics and clinical genetic testing outcome of these patients. **Methods:** We compared cancer index patients with 1 vs > 1 primary malignancy who underwent evaluation and clinical testing with multi-gene panels comprising up to 49 genes in a cancer genetics clinic in a tertiary cancer centre in Asia from 1998-2016. **Results:** Among 1191 cancer index patients, 960 (80.6%), 205 (17.2%), and 26 (2.2%) respectively had 1, 2, and ≥3 primary malignancies. Among patients with > 1 primary cancers (n = 231), the most common cancer pairs were breast-breast (35.4%), breast-ovary (12.1%), endometrium-ovary (8.2%), colon-colon (2.4%) and, colon-endometrium (2.4%). The mean age at diagnosis of the first, second and third cancers were 46.0 (21 to 87), 52.1 (21 to 89) and 57.7 (41 to 83) respectively. The mean duration between first and second cancers is 6.0 years (0 to 32). The most commonly suspected syndromes in patients with 1 vs > 1 primary cancer were hereditary breast and ovarian cancer 63.8% vs 53.6%, Lynch 24.8% vs 31.1%, Li-Fraumeni syndromes 1.8% vs 1.7%, and others 9.3% vs 13.4% (p = 0.03). Patients with > 1 primary cancer were more likely to have > 20% a priori risk of suspected hereditary cancer syndrome (42.8% vs. 26.5%; p < 0.001). 504/1191 (42.3%) patients underwent gene testing, including 394/960 (41.0%) and 110/231 (47.6%) patients with 1 vs > 1 cancer. Deleterious mutations were more likely to be identified in patients with > 1 vs 1 cancer (34.5% vs. 25.8%; p = 0.073), with causative genes being BRCA1 38.5%, BRCA2 17.9%, MLH1/MSH2/MSH6 20.5%, TP53 7.7%, and others (ATM [n = 2], MUTYH, APC, PALB2, RAD51 [n = 1 each]) for patients with > 1 cancer. VUS rates were 31.7% vs.31.8% in patients with 1 vs > 1 cancer, and were identified in genes including BRIP1, CHEK2, PALLD, POLE, PTEN, STK11, SMARCA4, and VHL. **Conclusions:** Patients with > 1 primary cancer comprised one-fifth of cancer index patients evaluated at a cancer genetics clinic, and were more likely to be found with deleterious mutations than patients with only 1 cancer on multi-gene panel testing.

1513 Poster Discussion Session; Displayed in Poster Session (Board #171), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Routine tumor next-generation sequencing (NGS) to identify rare germline lung cancer risk mutations in EGFR and ERBB2. *First Author: Ruthia Chen, Dana-Farber Cancer Institute, Boston, MA*

Background: New insights into lung cancer genomics has required a new look at genetic determinants of inherited lung cancer risk. There are now four germline mutations in lung cancer oncogenes (EGFR T790M, V843I, R776H; and ERBB2 G660D) which have been reported in kindreds with a high prevalence of lung cancer in nonsmokers. We hypothesized that routine tumor NGS could be used to find rare kindreds with inherited lung cancer risk. **Methods:** An institute-wide database of tumor NGS results was queried for cases positive for one of the reported germline risk alleles in EGFR or ERBB2. At our center, tumor NGS is performed using a hybrid-capture platform spanning exons and key introns of ~400 cancer related genes, and is available for patients (pts) with consent to a research protocol. For living pts with a mutation detected at an allelic fraction (AF) > 25%, and excluding acquired T790M, genetic counseling and CLIA germline testing was provided. For pts with EGFR T790M, testing was performed on the INHERIT EGFR study (NCT01754025; ALCMI). **Results:** 51 cases were identified from a total of 13,488 cancers with NGS results: 45 with EGFR T790M (all lung cancer), 4 with EGFR R776H (NSCLC, endometrial cancer, and 2 glioma), 2 with ERBB2 G660D (NSCLC and glioblastoma). 34 pts with T790M detected after EGFR inhibitor were excluded, leaving 17 pts of interest. Germline testing was performed on 9 living pts with > 25% AF on NGS, and was positive in 8; 6 of these had germline EGFR T790M. Additionally, germline EGFR R776H was found in a never-smoker with metastatic endometrial cancer; she had a prior a history of NSCLC, and family history was notable for multiple members with lung, breast, and colon cancer. Germline ERBB2 G660D was found in a young never-smoker with metastatic NSCLC and a family history significant for lung cancer in multiple first-degree relatives. **Conclusions:** Rare germline lung cancer risk mutations in EGFR and ERBB2 can be identified on routine tumor NGS, and may indicate a risk of inherited lung cancer. Our study includes the second known report of a germline EGFR R776H or ERBB2 G660D mutations. Commercial germline NGS assays could be expanded to cover these rare but potentially high-penetrance variants.

1514 Poster Discussion Session; Displayed in Poster Session (Board #172), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Identification of putative germline mutations in 10,288 patients undergoing circulating tumor DNA testing. *First Author: Thomas Paul Slavin, City of Hope, Duarte, CA*

Background: No studies have yet described incidental detection of germline cancer predisposition mutations using circulating cell-free DNA (cfDNA). **Methods:** Deidentified cfDNA sequencing data from 10288 advanced cancer patients (pts) undergoing clinical circulating tumor DNA testing (Guardant360, 73 genes) were included in this study. CfDNA was extracted from plasma and quantified. A DNA library was prepared and sequenced to 15,000X average read depth. Using Ingenuity Variant Analysis, point mutations and small indels suspicious for germline origin (allele fraction 40-60%) were classified following American College of Medical Genetics and Genomics guidelines. **Results:** More than 50 cancer types were studied, including lung (40%), breast (20%), CRC (8%), prostate (6%), and pancreas (3%). Average age was 63.6 years (range:18-95), 42% were male. Of 34,873 putative germline variants identified, 520 (1.5%) were pathogenic or likely pathogenic (PV), 16,939 (49%) were of uncertain significance, and 17,414 (50%) were benign or likely benign. Of the 250 pts (2.4%) with hereditary cancer syndrome gene PVs, 83 were excluded due to high level of somatic tumor burden leaving 167 (1.6%) with putative germline PVs; rates were higher in pts <50 vs >50 overall (3.3% vs 1.4%, p=0.02) and in breast cancer pts (4.3% vs 1.5%, p=0.03). **Conclusions:** The observed frequency of incidentally identified putative germline PVs is expectedly lower than the true germline rate; however, these findings illustrate that detection from cfDNA is clinically feasible. Importantly, incidental germline findings could impact oncology treatment planning (e.g. PARP inhibitors for *BRCA1/2* mutations) and could benefit families via increased surveillance/primary prevention. Further research is needed to explore how to report potential germline results to clinicians using a systems-based approach.

		PV by Cancer Type (N)						
Gene	**ALL**	**Ov**	**Panc**	**Pr**	**Breast**	**Lung**	**CRC[1]**	**Other**
BRCA2	78	3	7	18	26	17	1	6
BRCA1	38	11	1		9	12	1	4
TP53	16				4	8	2	2
CDKN2A	10		1		3	2		4
ATM	5		1		2	2		
KIT	4				1	2	1	
NF1	4			1		1		2
RET	4		1			2		1
APC	4						1	3
RB1	2							2
MLH1	1						1	
SMAD4	1						1	
TOTAL	167	14	11	19	45	46	8	24
# pts	10288	205	328	577	2047	4136	830	2165
% of pts	1.6%	6.8%	3.4%	3.3%	2.2%	1.1%	1.0%	1.1%

[1]Lynch genes not sequenced except for MLH1 exon 12

1515 Poster Discussion Session; Displayed in Poster Session (Board #173), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Effects of gene penetrance on adherence to breast cancer screening recommendations (BCSR) among high-risk women. *First Author: Jacqueline Talea Desjardin, University of California, San Francisco, San Francisco, CA*

Background: Adherence to cancer screening depends on the interplay between risk perception and convenience. For instance, high perceived risk is likely what motivates high-risk mutation carriers (HRMC) to adhere well to rather inconvenient BCSR. While the NCCN offers BCSR for moderate-risk genes, adherence in moderate-risk mutation carriers (MRMC) and non-carriers with negative multigene panels (NC) is unknown. **Methods:** Screening behavior was examined in 120 women (15 HRMC, 20 MRMC, 85 NC) 20-65 years old (y) without cancer who received genetic testing and counseling. The groups did not differ in age or family history (fhx). Medical records were reviewed pre- and post-testing to determine adherence. Average follow up was 15 months. Data were analyzed by Chi-squared test. **Results:** Prior to genetic testing, 93% of women were adherent to general population BCSR, and 58% were already screening in accordance with post-test counseled BCSR. Testing altered adherence to counseled BCSR for HRMC (p<0.01), but not for MRMC (p=0.21) or NC (p=0.86). HRMC had better post-test adherence than MRMC (p<0.05). **Conclusions:** MRMC are often told to follow similar BCSR to HRMC, namely annual mammogram and MRI, but MRMC may be less motivated to adhere to these BCSR due to lower risk perception. We found adherence was high in HRMC, likely due to high risk perception; intermediate in NC, likely due to manageable BCSR; and comparably low in MRMC, possibly because their risk perception was insufficient to motivate biannual imaging studies. Understanding how genetic testing influences adherence is essential to ensuring proper surveillance in high-risk women.

	NC		MRMC *CHEK2, PALB2, ATM, NBN, CDH1, MRE11A*		HRMC *BRCA1/2*	
	Pre-Testing	**Post-Testing**	**Pre-Testing**	**Post-Testing**	**Pre-Testing**	**Post-Testing**
General	77/85	74/85	19/20	20/20	15/15	15/15
Population BCSR[a] Adherence	91%	87%	95%	100%	100%	100%
Counseled	61/85	62/85	7/20	11/20	2/15	13/15
BCSR[b] Adherence	72%	73%	35%	55%	13%	87%

[a]Annual mammogram starting at 40y; [b]Counseling based on NCCN guidelines: a) annual mammogram advised—starting at 30y (HRMC) or fhx-based (MRMC/NC); b) annual breast MRI advised for all carriers and 6/85 NC—starting at 25y (HRMC) or fhx-based (MRMC/NC)

1516 Poster Discussion Session; Displayed in Poster Session (Board #174), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Knowledge and understanding of genetic test results in men undergoing multigene testing for inherited prostate cancer. *First Author: Veda N. Giri, The Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA*

Background: Genetic counseling (GC) for prostate cancer (PCA) risk is an emerging field, with limited insights regarding needs of males considering genetic testing (GT). Genetic Evaluation of Men is a prospective multigene testing study to identify inherited mutations linked to PCA, with testing following GC. We surveyed men pre-GT and post-GT on knowledge of cancer risk and genetics (KCRG) and understanding of personal GT results to identify GC needs. **Methods:** Eligibility for males affected or high-risk for PCA encompass age, race, family history (FH), and PCA stage/grade. Demographic, clinical, and FH data were obtained from participants and medical records. Pre-GT survey included questions on KCRG (15 items) and health literacy/numeracy (6 items). Post-GT survey additionally included understanding of GT results (9 items). Personal and FH were categorized into three hereditary cancer syndromes (HCS) linked to PCA. Factors associated with baseline KCRG were assessed by univariable models followed by multivariable linear regression. McNemar's test was used to assess concordance of understanding GT results vs. actual results. **Results:** Among 109 men (mean age 63 years, 81% White, 59% PCA diagnosis) who completed pre- and post-surveys, factors associated with higher pre-test KCRG included meeting HCS criteria ($p = 0.006$) and higher numeracy ($p = 0.025$). On multivariable analysis, HCS remained significantly predictive of higher KCRG ($p = 0.040$). However, of 101 men who responded definitively regarding understanding of personal GT results, 13 responded incorrectly on mutation status indicating significant disagreement with actual results (McNemar's $p < 0.001$). Of these 13 men, 12 had $> = 1$ variant of uncertain significance (VUS). Additionally, 6 men were unsure whether they carried a mutation when their GT results found VUS but no mutations. **Conclusions:** This is the first report of knowledge and understanding of genetics and cancer risk in the context of multigene testing for PCA. While personal/FH of HCS was associated with higher KCRG, understanding of personal GT results was lacking, and warrants tailored GC strategies for multigene testing for inherited PCA.

1517 Poster Discussion Session; Displayed in Poster Session (Board #175), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Optimizing somatic genomic reporting and physician interpretation with web-based, interactive technologies. *First Author: Stacy W. Gray, City of Hope, Duarte, CA*

Background: The increased availability of tumor genomic profiling is revolutionizing oncology. However, the promise of precision care will not be realized if providers misinterpret complex genomic data. **Methods:** We created web-based, interactive reports with enhanced data visualization elements and embedded decision support for $>$ 300 gene panels. We conducted a randomized vignette-based survey study to determine whether exposure to the interactive reports, as compared to static reports, improves physicians' genomic understanding and report-based satisfaction. Overall comprehension and satisfaction scores were calculated across three vignettes (possible range 0-18 and 1-4 respectively, higher score correspond to improved endpoints). **Results:** 105 physicians at a major cancer center participated (29% participation rate); 67% medical, 20% pediatric, 7% radiation and 7% surgical oncology; 37% female. Prior to viewing the case-based vignette reports, 34% of physicians reported that they found it difficult to make treatment recommendations based on the standard report in their routine practice. After viewing the case-based vignettes, physicians' overall comprehension scores did not differ significantly by report type (mean score interactive 11.6 vs. static 10.5, difference = 1.1, 95% CI -0.3, 2.5, $p = 0.13$). However, physicians who viewed the interactive report were more likely to correctly assess sequencing quality ($p < 0.001$) and understand when reports needed to be interpreted with caution (e.g., if low tumor purity, $p = 0.02$). Overall satisfaction scores were significantly higher in the interactive group than the static group (mean score 2.5 vs. 2.1, difference = 0.4, 95% CI 0.2, 0.7, $p = 0.001$). Of the 92 physicians who endorsed the need for additional genomic support for providers, 66% reported that interactive genomic reports would be helpful. **Conclusions:** Interactive, genomic reports may improve physicians' ability to accurately assess genomic data and increase physician satisfaction. To advance the field, further research in representative provider populations is warranted and efforts to integrate interactive genomic reports into electronic health records are needed.

1518 Poster Discussion Session; Displayed in Poster Session (Board #176), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Multigene hereditary cancer testing in sarcoma patients. *First Author: Sarah A. Jackson, Genedx, Inc., a Wholly-Owned Subsidiary of Opko Health, Inc., Elmwood Park, NJ*

Background: In multi-gene hereditary cancer testing, multiple syndromes may be interrogated simultaneously, increasing the likelihood of detecting an underlying cancer predisposition. We characterized the yield and distribution of pathogenic or likely pathogenic variants (PV/LPV) in patients with a personal history of sarcoma undergoing panel testing through our clinical diagnostic laboratory. **Methods:** We retrospectively reviewed panel test results, demographic data, and personal/family history information from patients reporting a personal history of sarcoma. Patients included in this study underwent panel testing (NGS and del/dup) of up to 61 genes at this laboratory and concurrent or prior *TP53* analysis at this or an outside laboratory. Chi-square and Fisher's exact tests were used to compare groups. **Results:** Among 374 sarcoma patients, 53 (14.2%) harbored one or more PV/LPV in 14 genes: *TP53*, *BRCA2*, *CHEK2*, *BRCA1*, *ATM*, *MSH6*, *MLH1*, *NBN*, *BAP1*, *BRIP1*, *FLCN*, *MSH2*, *PTEN*, and *RB1*. Thirty-nine (10.4%) individuals reported both a personal and family history of sarcoma; however, PV/LPV were not more likely to be detected among this group than those with personal history alone ($p = 1.0$). PV/LPV were most often detected in *BRCA1/2* (15/374, 4.0%) or *TP53* (12/374, 3.2%). Notably, four probands with *BRCA1/2* PV/LPV reported a family history of sarcoma, including one kindred in which the variant was present in two brothers, both affected with sarcoma. Additionally, seven patients were found to have PV/LPV (1.9%) in genes causative for Lynch syndrome. Among patients with PV/LPV in genes other than *TP53,* nearly half (17/41, 41.5%) met National Comprehensive Cancer Network *TP53* testing criteria. **Conclusions:** The majority of PV/LPV were identified in genes for which association with sarcoma risk is not well-established. While several of these genes have been implicated in somatic pathways related to sarcoma development, it is unclear whether these germline findings are causative, play no role, or modify sarcoma risk. Although these data do not inherently associate non-*TP53* genes with sarcoma risk, they suggest a potential clinical benefit can be gained from performing hereditary cancer risk assessment and multi-gene panel testing in sarcoma patients.

1519 Poster Discussion Session; Displayed in Poster Session (Board #177), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

The Angiosarcoma Project: Generating the genomic landscape of a rare cancer through a direct-to-patient initiative. *First Author: Corrie Painter, Broad Institute of MIT and Harvard, Cambridge, MA*

Background: Angiosarcoma (AS) is a rare soft tissue sarcoma, with an incidence of 300/yr and a 5-year DSS of 30%. The low incidence has impeded large-scale research efforts that may lead to improved clinical outcomes. To address this, we launched a nationwide study, which seeks to empower patients (pts) to accelerate research by sharing their samples and clinical information remotely. **Methods:** With pts and advocacy groups we developed a website to allow AS pts to participate across the US. Pts are mailed a saliva and blood draw kit for germline and cell free (cf) DNA analysis. We then obtain medical records and stored tumor samples. Whole exome sequencing will be performed on tumor, cfDNA and saliva samples. Transcriptome analysis will be performed on tumor samples. A clinically annotated genomic database will be generated and shared widely to identify genomic drivers and mechanisms of response and resistance to therapies. Study updates will be shared with pts regularly. **Results:** We conducted a 3-week pilot study to test the feasibility of enrolling geographically dispersed AS pts through a direct-to-patient (DTP) approach. Through social media, we identified 100+ pts willing to participate, 90 within the first day of outreach. We enrolled 15 pts from 10 states to test our ability to remotely obtain pt reported data, online consent, and samples. The average age of pts is 48, ranging 23-71 yrs. Primary locations of AS are breast 6 pts (40%), cardiac 4 pts (27%), scalp 2 pts (13%), liver 1 pt (6%), bladder 1 pt (6%), forehead 1 pt (6%). 9 pts (60%) reported being disease free, 4 pts (27%) reported having AS spread to lung, lymph, bone, and hip. Requests for medical records and tissue samples are underway, and initial saliva samples have been received. We are now opening this study to all AS pts in the USA. **Conclusions:** A DTP approach enabled rapid identification of an initial cohort of AS pts willing to share tumors, saliva, blood and medical records. We were able to obtain detailed clinical experiences and samples to perform genomic analysis. This study serves as proof of principle that DTP genomics efforts can democratize cancer research for exceedingly rare cancers, which to date have been disproportionately understudied.

1520 Poster Discussion Session; Displayed in Poster Session (Board #178), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Baseline screening and psychosocial results from the UK SIGNIFY study: A whole-body MRI screening study in *TP53* mutation carriers and matched controls. *First Author: Ros A. Eeles, The Institute of Cancer Research, Sutton, United Kingdom*

Background: In the United Kingdom, current screening guidelines for *TP53* germline mutation carriers solely recommends annual breast MRI, despite the wide spectrum of malignancies typically seen in this group. Some centres employ family specific screening with most centres having an "open-door" policy. Recent evidence suggests there may be a survival benefit with more intensive screening, including whole-body MRI. There are no published data on the psychological impact of such screening programmes. **Methods:** This study sought to investigate the role of one-off non-contrast whole-body MRI (WB MRI) in the screening of asymptomatic *TP53* mutation carriers aged over 18 years. Clinical and psychological endpoints were assessed. Scans were read by radiologists blinded to participant carrier status. The incidence of malignancies diagnosed in *TP53* mutation carriers against general population controls was calculated. The incidences of non-malignant relevant disease and irrelevant disease were measured, as well as the number of investigations required to determine relevance of findings. A series of questionnaires is used to assess the psychological impact of screening. **Results:** 44 *TP53* mutation carriers and 44 population controls were recruited. In *TP53* mutation carriers, six of 44 (13.6%, 95% CI: 5.2%-27.4%) participants were diagnosed with cancer during the study, all of which would be considered life threatening if untreated. Two were found to have two primary cancers. Two participants with cancer had abnormalities on the MRI which were initially thought to be benign (a pericardial cyst and a uterine fibroid) but transpired to be sarcomas. No controls were diagnosed with cancer. Fifteen carriers (34.1%, 95% CI: 20.5%-49.9%) and 7 controls (15.9%, 95% CI: 6.6%-30.1%) underwent further investigations following the WB MRI for abnormalities that transpired to be benign (p = 0.049). To date, there is no evidence of clinically significant adverse psychosocial effects. **Conclusions:** The cancer detection rate in this group justifies a minimum baseline non-contrast WB MRI in germline *TP53* mutation carriers. Clinical trial information: NCT01737255.

1521 Poster Session (Board #179), Mon, 1:15 PM-4:45 PM

Impact of *PIK3CA* tumor mutation on the association of aspirin or NSAID use and time to breast cancer recurrence. *First Author: Anne Marie McCarthy, Massachusetts General Hospital, Boston, MA*

Background: Aspirin or NSAID (A/N) use post diagnosis is associated with lower risk of breast cancer recurrence and mortality in cohort studies. A potential mechanism is that A/Ns may suppress cell growth and induce apoptosis in tumors driven by phosphatidylinositol 3 kinase (*PIK3CA*), the most common oncogene mutation in breast cancer. An interaction of A/Ns and *PIK3CA* mutation has been observed for colorectal cancer prognosis, but has not been studied in breast cancer. The objective was to assess time to breast cancer recurrence (TTR) with respect to A/N use and *PIK3CA* mutation. **Methods:** Patients with HR+/HER2- breast cancer treated at Massachusetts General Hospital in 2009-2014 who received tumor genotyping were included. *PIK3CA* mutations, including 8 common hotspot mutations, were assessed by a high-throughput tumor genotyping assay using DNA from formalin-fixed, paraffin-embedded tumor tissue. A/N use beginning 6 months post diagnosis through metastasis was extracted from electronic medical records using coded data and natural language processing. Patients with de novo metastatic disease or progressive disease within 6 months of primary diagnosis were excluded. TTR was estimated using Cox proportional hazards models. **Results:** Among breast cancer patients (N=212), 60 (28%) used A/Ns and 69 (33%) had *PIK3CA* mutation (see Table). After adjusting for age, stage, adjuvant endocrine therapy, radiation, and chemotherapy, A/N users had significantly longer TTR (HR=0.65 p=0.01). The association was similar for wild type (HR=0.58 p=0.01) and *PIK3CA* mutated tumors (HR=0.60 p=0.06), with no significant interaction of A/N use and *PIK3CA* (p=0.34). **Conclusions:** Among HR+ breast cancer patients, those who used A/Ns following primary diagnosis had longer TTR than non-users, regardless of tumor *PIK3CA* mutation status. The study provides a model for how tumor genomics could be integrated into secondary chemoprevention studies.

Time to recurrence adjusted for age, stage, treatment.

		N	HR	95% CI	p-value	p-interaction
A/N user		60	0.65	0.46-0.91	0.01	
***PIK3CA* mutation**		69	0.81	0.59-1.11	0.19	
A/N use	*PIK3CA* mutation					
-	-	102	Reference			0.34
+	-	41	0.58	0.38-0.88	0.01	
-	+	50	0.75	0.52-1.07	0.11	
+	+	19	0.60	0.35-1.02	0.06	

1522 Poster Session (Board #180), Mon, 1:15 PM-4:45 PM

Comparison of epigenetic aging in normal breast tissue from women with and without breast cancer. *First Author: Erin Wysong Hofstatter, Yale School of Medicine, New Haven, CT*

Background: Age is one of the most important risk factors for developing breast cancer. However, why increasing age is associated with increasing incidence of breast cancer remains poorly understood. We hypothesize that accumulated epigenetic alterations in the breast contribute to the development of breast cancer, and that such changes accumulate more rapidly in the breast during the lifetime of women who develop breast cancer as compared to their healthy peers. We therefore sought to identify an epigenetic pattern of accelerated breast tissue "aging" in women with breast cancer. **Methods:** Samples of normal breast tissue were collected from four cohorts of women: age $<$ 50 years with and without breast cancer, and age $\geq$50 years with and without breast cancer (BC). Samples were obtained from the Susan G. Komen Tissue Bank at IU Simon Cancer Center, reduction mammoplasties and adjuvant mastectomy specimens at Yale. The Illumina Human 450K BeadChip microarray was used to generate DNA methylation profiles. Data was analyzed using the "Epigenetic Clock", a published biomarker of aging based on 353 specific CpGs in the human genome. Clinical data collected for each subject included: age, height, weight, ethnicity, medical and reproductive history, tobacco and alcohol use, family history of breast cancer, current medications, and tumor characteristics. **Results:** Normal breast tissue samples from 90 subjects were analyzed (age $<$ 50 with BC = 22, age $<$ 50 without BC = 30, age $\geq$50 with BC = 15, age $\geq$50 without BC = 23). Age range was 24-82 years and 18-82 years for cohorts with and without BC respectively. In the cohort with BC, 95% of tumors were estrogen receptor-positive. Overall, DNA methylation tissue age (DNAmAge) was strongly correlated with chronologic age (r = 0.88, p $<$ 0.001). However, normal breast tissue from women with breast cancer demonstrated significantly accelerated DNAmAge as compared to healthy peers (p $<$ 0.001). **Conclusions:** Normal breast tissue from women with breast cancer demonstrates evidence of an accelerated epigenetic "aging" process. DNAmAge of normal breast tissue may prove to be a useful tool in identifying those women at highest risk, and lend insight into novel mechanisms of breast cancer prevention.

1523 Poster Session (Board #181), Mon, 1:15 PM-4:45 PM

Performance of mutation risk prediction models in a racially diverse multi-gene panel testing cohort. *First Author: Gregory Idos, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Mutation carrier prediction models are clinically useful tools for identifying candidates for genetic counseling and testing. Consensus guidelines recommend germline genetic testing for those with a carrier probability (CP) of approximately 5% or higher. However, prediction models may perform less well among racial/ethnic minorities. Our hypothesis is that pathogenic mutations (PM) are identifiable in a clinically meaningful fraction of racially/ethnically diverse patients with a CP of $<$ 5%. **Methods:** We conducted a multicenter prospective clinical trial of patients undergoing cancer-risk assessment using a 25 gene panel, which include *APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*. Patients were recruited from August 2014 to November 2016 at three centers. Patients were enrolled if they met standard clinical criteria for genetic testing or were predicted to have a $\geq$2.5% probability of inherited cancer susceptibility using validated prediction models. We evaluated the CP of patients with a PM in *BRCA1*, *BRCA2*, and/or a mismatch repair (MMR) gene using the following models: (1) BRCApro, (2) MMRpro and (3) $PREMM_{1,2,6}$. **Results:** Of 2000 patients enrolled in this cohort, 80.6% are female (n = 1612). Regarding race/ethnicity, the cohort is 40.1% Non-Hispanic White (n = 802), 37.4% Hispanic (n = 748), 11.5% Asian (n = 230), 3.9% Black (n = 78), and 7.1% Other (n = 142). Among 241 (12.1%) patients who tested positive for a pathogenic mutation, 76 (31.5%) patients had a *BRCA1* or *BRCA2* mutation. Of those, 52 (68.4%) patients had a BRCApro CP of $<$ 5%. Thirty-eight (15.8%) patients had a pathogenic mutation in an MMR gene: 19 (50.0%) had an MMRpro CP of $<$ 5%, while 13 (34.2%) had a $PREMM_{1,2,6}$ CP of $<$ 5%. The racial/ethnic distribution of *BRCA1/2* or MMR mutation carriers is similar to that of the whole cohort. **Conclusions:** In a diverse cohort of patients undergoing 25-gene multiple-gene panel testing, half or more carriers of *BRCA1/2* or MMR mutations had a CP of $<$ 5%, the consensus guideline-recommended cutoff for genetic testing. These results support a lower threshold for genetic testing guidelines. Clinical trial information: NCT02324062.

1524 Poster Session (Board #182), Mon, 1:15 PM-4:45 PM

Prevalence of incidental germline pathogenic (PV) and likely pathogenic (LPV) variants in hereditary cancer-related genes identified in matched tumor/normal sequencing of advanced solid tumors. *First Author: Ecaterina Elena Ileana Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Next-generation sequencing (NGS) for tumor molecular profiling can reveal germline incidental mutations in hereditary cancer-related genes. The American College of Medical Genetics and Genomics (ACMG) has recommended that laboratories performing clinical sequencing seek and report PV and LPV in 56 genes. We assessed the prevalence of incidental germline LPV and PV in other cancer-related genes among patients undergoing hybrid capture sequencing of 201 cancer-related genes. **Methods:** Matched tumor and germline DNA NGS of a targeted panel of 201 genes was performed in 1000 patients (pts) with advanced or metastatic solid tumors enrolled in a molecular testing protocol (NCT01772771) in a research laboratory. We previously reported germline alterations in the putative most actionable genes as designated by ACMG (PMID: 26787237). We assessed the germline LPV and PV in 54 additional cancer-related genes. **Results:** Among the 1000 patients who underwent tumor and normal DNA sequencing, 37 patients (3.7%) were found to have a germline PV or LPV in the following genes: ATM (4); BAP1 (1); CDH1 (1); CDKN2A (1); CHEK1 (2); CHEK2 (10); EGFR (1); ERCC3 (4); ERCC5 (1); HNF1B (1); HRAS (1); MLL3 (1); NF1 (3); PKHD1 (4); PTCH1 (1) and SMARCA4 (1). Eight pts (22%) had previous genetic counseling and testing for various reasons, but only 3 pts (8%) had previously identified alterations (all with NF1 mutations). After discussion in our return of germline results board, it was decided to return the findings in established hereditary cancer predisposition genes with high penetrance: BAP1 (p.Y401X), CDH1 (p.C688X), CDKN2A (p.G101W), EGFR (p.T790M) and SMARCA4 (p.S332FfsX55) after validation in a CLIA laboratory. **Conclusions:** Return of the previously unrecognized germline LPV or PV in patients with advanced or metastatic cancers who undergo somatic profiling is of great interest. The exact genes for which the germline results should be returned is controversial. Broader genomic testing is likely to identify additional incidental germline alterations with potential clinical utility to patients and their relatives.

1525 Poster Session (Board #183), Mon, 1:15 PM-4:45 PM

Expanded yield of multiplex panel testing in fully accrued prospective trial. *First Author: Gregory Idos, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Genetic testing is a powerful tool for stratifying cancer risk. Multiplex gene panel (MGP) testing allows simultaneous analysis of multiple high- and moderate- penetrance genes. However, the diagnostic yield and clinical utility of panels remain to be further delineated. **Methods:** A report of a fully accrued trial (N = 2000) of patients undergoing cancer-risk assessment. Patients were enrolled in a multicenter prospective cohort study where diagnostic yield and off-target mutation detection was evaluated of a 25 gene MGP comprised of *APC*, *ATM*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, *TP53*. Patients were enrolled if they met standard testing guidelines or were predicted to have a ≥2.5% mutation probability by validated models. Differential diagnoses (DDx) were generated after expert clinical genetics assessment, formulating up to 8 inherited cancer syndromes ranked by estimated likelihood. **Results:** 1998/2000 patients had reported MGP test results. Women constituted 81% of the sample, and 40% were Hispanic; 241 tested positive for at least 1 pathogenic mutation (12.1%) and 689 (34.5%) patients carried at least 1 variant of uncertain significance. The most frequently identified mutations were in *BRCA1* (17%, n = 41), *BRCA2* (15%, n = 36), *APC* (8%, n = 19), *CHEK2* (7%, n = 17), *ATM* (7%, n = 16). 39 patients (16%) had at least 1 pathogenic mutation in a mismatch repair (MMR) gene (*MLH1*, n = 10; *MSH2*, n = 10; *MSH6*, n = 8; *PMS2*, n = 11). 43 individuals (18%) had *MUTYH* mutations – 41 were monoallelic. Among 19 patients who had mutations in *APC* – 16 were *APC* I1307K. Only 65% (n = 159) of PV results were included in the DDx, with 35% (n = 86) of mutations not clinically suspected. **Conclusions:** In a diverse cohort, multiplex panel use increased genetic testing yield substantially: 35% carried pathogenic mutations in unsuspected genes, suggesting a significant contribution of expanded multiplex testing to clinical cancer risk assessment. The identification of off-target mutations broadens our understanding of cancer risk and genotype-phenotype correlations. Follow-up is ongoing to assess the clinical utility of multiplex gene panel testing. Clinical trial information: NCT02324062.

1526 Poster Session (Board #184), Mon, 1:15 PM-4:45 PM

NGS-based multi-gene panel analysis in *BRCA1/2*-negative breast and ovarian cancer families. *First Author: Esther Pohl, Center for Familial Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Medical Faculty, University of Cologne and University Hospital Cologne, Cologne, Germany*

Background: 24% of familial breast cancer (BC) and/or ovarian cancer (OC) cases analyzed within the framework of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) are due to pathogenic mutations in the *BRCA1* or *BRCA2* genes. The population-specific mutation prevalence of non-*BRCA1/2* genes associated with familial BC and/or OC is largely unknown and was determined in a large German cohort. **Methods:** Here, we present next-generation sequencing (NGS) data established from TruRisk (GC-HBOC-designed) or TruSight cancer gene panels. A cohort of 6,507 *BRCA1/2*-negative index cases fulfilling the inclusion criteria of the GC-HBOC for germline testing was analyzed. Illumina sequencing platforms were used and data analysis was carried out at each individual center using different analysis pipelines. Analysis of copy number variations (CNV) was not included in the present data evaluation. **Results:** By focusing on 8 confirmed BC/OC risk genes (*ATM, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D, TP53*), the 6,507 cancer patients revealed 165 different deleterious variants in 378 unrelated mutation carriers (5.8%). We found a high prevalence of *CHEK2* (n = 150, 2.3%), *ATM* (n = 89, 1.4%), and *PALB2* (n = 72, 1.1%) mutations while *RAD51C* (n = 21, 0.3%), *TP53* (n = 16, 0.2%), *NBN* (n = 15, 0.2%), *CDH1* (n = 10, 0.2%), and *RAD51D* (n = 5, 0.1%) were less frequently mutated. **Conclusions:** The high frequency of pathologic mutations in the genes *ATM, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D,* and *TP53,* together accounting for almost 6% of familial BC/OC risk, highlights the importance of these genes to be included in BC/OC routine diagnostics. The relevance of these mutations in a clinical setting for early detection of breast and ovarian cancer needs to be established.

1527 Poster Session (Board #185), Mon, 1:15 PM-4:45 PM

PALB2 mutations in high-risk women with breast or ovarian cancer. *First Author: Kelly A. Metcalfe, University of Toronto, Toronto, ON, Canada*

Background: In Canada, genetic testing for *BRCA1* and *BRCA2* is available free of charge to women who meet eligibility criteria, based on personal and family history of cancer. Less than 10% of women are identified with a *BRCA* mutation, despite features of hereditary cancer. *PALB2* has been identified as a moderate penetrance gene in various populations. In the current study, we examined the frequency of *PALB2* mutations in women with breast or ovarian cancer who met criteria for genetic testing for *BRCA1* and *BRCA2*and tested negative. **Methods:** DNA samples from women with breast or ovarian cancer, who met criteria for provincial *BRCA1* and *BRCA2* genetic testing and tested negative between the years of 2007 and 2014 were included in this study. All 13 coding exons of *PALB2* plus 20 base pairs from the exon boundaries were amplified using Wafergen SmartChip technology. The amplified DNA were paired-end sequenced at 2x250 cycles using an Illumina MiSeq sequencer. **Results:** 2,225 women with breast cancer and 429 women with ovarian cancer were tested for *PALB2* mutations. No *PALB2* mutations were found in women with ovarian cancer. Seventeen deleterious *PALB2* mutations were detected in women with breast cancer (0.8%). The frequency of *PALB2* mutations was significantly higher in women with bilateral breast cancer (2.4%) compared to women with unilateral breast cancer (0.6%) (p = 0.01). There was no significant difference in age at diagnosis between those with and without a *PALB2*mutation (50.9 years vs 53.8 years; p = 0.34). **Conclusions:** Genetic testing for *PALB2* should be considered for high-risk women with breast cancer, especially those who present with bilateral breast cancer. However, *PALB2* does not appear to contribute to ovarian cancer which has implications for counselling women who are identified with a *PALB2* mutation.

1528 Poster Session (Board #186), Mon, 1:15 PM-4:45 PM

Pathogenic germline mutations in emerging cancer genes: What happens after panel testing? *First Author: Evan Thomas Hall, Stanford University School of Medicine, Stanford, CA*

Background: Next-generation sequencing technology enables more comprehensive germline genetic testing, including genes whose cancer risks are less well-characterized (particularly among patients with less striking family histories). Little is known about patient outcomes, particularly adherence to risk-reducing recommendations and family testing. **Methods:** We attempted a phone interview ≥3 times with each adult patient who had a germline pathogenic or likely pathogenic mutation found in an emerging cancer gene (defined as any gene other than *BRCA1/2* or the Lynch Syndrome genes *MLH1, MSH2/6, PMS2*) at a single academic cancer genetics clinic from January 2013-July 2016. **Results:** Of 143 eligible patients, 53 (37%) were successfully contacted and all consented to participate. Median follow-up was 677 days (range 247–1401) and age was 52 years (21-82). Two-thirds (68%) had personal cancer history and 93% had a first-degree relative with cancer. Mutations in genes associated with named syndromes (*APC*=5, *CDH1*=3, *TP53*=3, *PTEN*=2) were found in 23% (many of whom lacked family history typical of these syndromes) whereas 77% had mutations in less well-characterized genes (*MYH*=10, *CHEK2*=10, *ATM*=6, *PALB2*=6, *NBN*=3, *RAD51C*=2, *RAD51D*=2, *SDHB*=1, *CDKN2A*=1, *MRE11A*=1, *RAD50*=1, *FLCN*=1). **Conclusions:** Two years after panel testing, patients with germline mutations in less well-characterized genes reported high rates of adherence to recommendations, family communication and testing. Limitations include a relatively low response rate and a single academic center; this may bias toward a "best-case" scenario. Larger, population-based studies will be crucial to understand the real-world outcomes of germline multiple-gene panel testing and its contribution to precision oncology.

Patient-reported experiences (N=53)	N (%)
Any risk-reducing intervention recommended (change in screening, preventive surgery, chemoprevention)	48 (84%)
Change in screening recommended	46 (81%)
Preventive surgery recommended	8 (14%)
Chemoprevention recommended	6 (11%)
Patient adhered to recommendations	45 (79%)
Patient shared genetic results with ≥1 relative	52 (91%)
≥1 relative had genetic testing based on patient's results	36 (63%)

1529 Poster Session (Board #187), Mon, 1:15 PM-4:45 PM

Pathogenicity of mutation analyzer (PathoMAN): A fast automation of germline genomic variant curation in clinical sequencing. *First Author: Vijai Joseph, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A challenge in clinical oncology is interpretation of multiplexed gene sequencing of patients at risk. The plethora of variants to be curated for pathogenicity or actionability poses a growing burden for cancer care professionals. Current guidelines by the ACMG requires the aggregation of multiple lines of genomic data evidences from diverse resources. A computational tool that automates, provide uniformity and significantly speed the interpretive process is thus necessary. **Methods:** The *Pathogenicity of Mutation Analyzer* (PathoMAN), is a tool that automates germline genomic variant curation from clinical sequencing based on ACMG guidelines. PathoMAN aggregates multiple tracks of genomic, protein and disease specific information from public sources such as ClinVar, ExAC, UniProt, 1000 genomes, dbNSFP and locus specific databases. Variant specific and gene specific annotations are used to classify variants to model the ACMG rubric. We analyzed 2500 manually curated and classified, high quality variants in 180 genes from 3 large, published studies to quantify the performance of PathoMAN; analyzing 242 pathogenic/likely pathogenic (P/LP), 1272 benign/likely benign (B/LB) and 1261 variants of uncertain significance (VUS). We report the summary of PathoMAN classifications in four categories contrasted against the manual curation. **Results:** PathoMan achieves an average of 75% concordance and 1.5% discordance for P/LP mutations and 60% and 0.1% for B/LB variants. PathoMAN is able to resolve 12% of reported VUS as either P/LP or B/LB. It loses resolution to classify 25% of P/LP and B/LB variants due to lack of information and due to inconsistencies in available data from public resources. **Conclusions:** PathoMAN provides a breakthrough in rapid classification of genetic variants by generation of robust models using a knowledgebase of diverse genetic data. It is easily accessible, web-based resource that allows the community to rapidly test a large number of variants for pathogenicity. Such bioinformatic tools are essential to reduce manual workload of a domain level experts. We propose, a new nosology for the 5 ACMG classes to facilitate better reporting to ClinVar.

1530 Poster Session (Board #188), Mon, 1:15 PM-4:45 PM

Germline mutations of PALB2 gene in a sequential series of Chinese patients with breast cancer. *First Author: Jiaojiao Zhou, Department of Surgical Oncology, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: PALB2 (Partner and Localizer of BRCA2) is recently recognized as a breast cancer predisposition gene, which plays a critical role in genome maintenance via interacting with BRCA1/2 and RAD51 when DNA break. Germline loss-of-function mutations in PALB2 lead to increased breast cancer risk. Since the germline mutation frequency of PALB2 is much less than BRCA1/2, the distinct mutation spectrum of PALB2 is still obscure. Therefore, we assessed the mutational frequency, spectrum and predictors of the PALB2 gene in a sequential series of Chinese breast cancer patients from our Research DNA Bank, to verify the utility of PALB2 genetic testing in Chinese population. **Methods:** We examined Chinese breast cancer cases (n = 2279) who agreed to participate in research DNA banking, recruited from 1990 through 2016. To identify the mutations, complete coding sequence and intron–exon boundaries of PALB2 were screened with Next Generation Sequencing. Personal and family histories were synchronously collected for mutation identification. **Results:** Among the 2279 breast cancer patients, 307 patients were familial breast cancer cases and the rest 1972 patients were sporadic breast cancer cases. PALB2 mutation carriers accounted for 7.8% (n = 24) and 4.8% (n = 95) in familial and sporadic breast cancer cohort separately. In total, 31 missense, 4 nonsense, 3 frameshift, 3 splicing and 1 codon mutations of PALB2 were identified in this study. Among the pathologic variants, PALB2 c.1744C > T, c.2748+1G > A, c.2749-1G > C, c.3114-1G > A were newly identified in sporadic breast cancer, and c.3271delC newly found in familial breast cancer. Based on in silico analysis, a total of 6 potential damaging missense variants were novelly found in this study, among which the PALB2 c.3035C > T was detected in both sporadic and familial breast cancer. **Conclusions:** Our data presents the germline mutation status of PALB2 in Chinese patients with breast cancer, suggesting that loss-of-function germline mutations of PALB2 are important in both familial and sporadic breast cancer. Clinically, this information may be helpful in genetic counseling of breast cancer patients with PALB2 germline mutation.

1531 Poster Session (Board #189), Mon, 1:15 PM-4:45 PM

Clinical implementation of whole genome multi-omics analyses for patients with refractory cancers. *First Author: Milan Radovich, Indiana University School of Medicine, Indianapolis, IN*

Background: Relative lack of prior success of genomic technology has been a function of suboptimal target detection and poor timely implementation. We set out to improve patient access to targeted therapy through use of whole genome sequencing (WGS) to optimize targets and operational implementation to identify clinical trials and secure off-label drugs. **Methods:** We performed a retrospective analysis of our first 100 patients (Feb-Nov 2016) with metastatic disease whose tumors and matched blood were analyzed using whole genome (WGS) and transcriptome sequencing, as well as targeted proteomic analysis in a CLIA setting (NantOmics). Most common tumor types were Colorectal (20%), Breast (15%), and Ovarian (10%). Patients were seen in dedicated precision genomics clinics with results reviewed by a multi-disciplinary molecular tumor board. A dedicated service line with staff to match patients to clinical trials, medication acquisition, and genetic counseling for germline findings was provided. **Results:** 85% of patients had a finding either on WGS or proteomic analysis that pointed to an FDA approved drug or clinical trial. Common findings included: mutations in the PI3K pathway (15%), BRCA1&2/ATM (15%), and cell cycle genes (11%). Other markers of note include: HER2, TMB/MSI for immune checkpoint therapy, IDH1/2, and MET. WGS also enabled identification of rare actionable findings, particularly translocations, and viral integration for trials requiring HPV-positivity. Cancer predisposition germline findings were observed in 3 patients. Of the 85 patients with actionable findings, 22 went on to be treated with a genomically-directed agent, 13 did not follow recommendations or were sent to hospice, 4 were lost to follow-up, and 46 still remain on their therapy prescribed prior to sequencing. **Conclusions:** A higher proportion of patients in our program went on to be treated with a genomically-directed agent than previously reported in the literature secondary to comprehensive whole genome multi-omics profiling and a clinical service line dedicated to medication acquisition and matching to clinical trials.

1532 Poster Session (Board #190), Mon, 1:15 PM-4:45 PM

Multi-gene hereditary cancer testing among men with breast cancer. *First Author: Krystal Brown, Myriad Genetic Laboratories, Inc., Salt Lake City, UT*

Background: All men with a personal diagnosis of breast cancer (BC) are candidates for *BRCA1/2* genetic testing, as pathogenic variants (PVs) in these genes have a known association with BC risk in both men and women. As additional genes with known BC risk in women are now routinely included in multi-gene panel testing, we evaluated the outcomes of multi-gene panel testing in a large cohort of men with BC. **Methods:** This analysis includes the results of commercial genetic testing for 1,358 men with BC usinga multi-gene pan-cancer panel between September 2013 and January 2017. Clinical information was obtained from provider-completed test request forms. Age at diagnosis, personal, and family history were compared for men with PVs in *BRCA1/2* versus non-*BRCA1/2* genes. **Results:** Overall, 207 (15.2%) men with BC were found to carry a PV, where 147 (10.8%) men had a PV in *BRCA1/2* (*BRCA1*, 0.7%; *BRCA2*, 10.2%) and 60 (4.4%) men had a PV in a non-*BRCA1/2* gene (*CHEK2*, 2.0%; *ATM*, 1.0%; *PALB2*, 1.0%; *BARD1*, 0.2%; *NBN*, 0.2%; *MSH6*, 0.1%; *BRIP1*, 0.1%; *CDH1*, 0.1%; *CDKN2A*, 0.1%; *MLH1*, 0.1%, *TP53*, 0.1%). There were no substantial differences in the median age-at-diagnosis for men without a PV (65) compared to those with a *BRCA1/2* PV (66) or a non-*BRCA1/2* PV (63). Prostate cancer was the most common additional malignancy among all men with BC (9.0%), with a similar incidence among men with a *BRCA1/2* PV (9.2%) and a non-*BRCA1/2* PV (8.3%). In addition, 1.4% of men with a *BRCA1/2* PV and 3.3% of men with a non-*BRCA1/2* PV had a second BC. A family history of breast and/or ovarian cancer was present in 44.4% of the testing cohort, 66.7% of men with a *BRCA1/2* PV, and 48.3% of men with a non-*BRCA1/2* PV. This is consistent with the relative penetrance of *BRCA1/2* and other genes included here. There were no other substantial differences in family history among *BRCA1/2* PV carriers versus non-*BRCA1/2* PV carriers. **Conclusions:** Close to a third of all PVs identified here in men with BC were in a gene other than *BRCA1/2*. There were no obvious differences in the clinical presentation of men with a *BRCA1/2* PV compared to men with a PV in another gene or no PV at all. Collectively, this suggests that multi-gene panel testing is appropriate for all men with BC, regardless of other personal or family history.

1533 Poster Session (Board #191), Mon, 1:15 PM-4:45 PM

Underutilization of multigene panels among Ashkenazi Jewish patients. *First Author: Jessica Fields, New York Presbyterian Hospital, Weill Cornell Medical Center, New York, NY*

Background: Approximately one in forty Ashkenazi Jewish (AJ) individuals carry a *BRCA1/2* mutation and genetic screening in this population has largely focused on these two genes. With the recent rapid uptake of multigene panel testing for cancer genetic assessment, we sought to explore multigene panels in our cohort which is comprised of AJ and non-AJ patients. **Methods:** The results of all patients with known ancestry who underwent genetic testing and counseling at the hereditary breast and ovarian cancer center at a single institution between 7/1/2013-12/31/2016 were reviewed. **Results:** One thousand six hundred and fifty patients with known ancestry underwent genetic testing over the study period, including 681 AJ patients. The median age was 49 (range 20-86). AJ patients were more likely to undergo targeted testing than non-AJ patients (74% vs. 61 %, $P<0.001$). The use of multigene panels in AJ patients increased over time (2013 – 3.2%, 2014 – 18.7%, 2015 – 27.4%, 2016 – 48.4%, $P<0.001$). Mutations were more common in AJ patients (75, 11% vs. 66, 7%, $P=0.003$). Variants of uncertain significance (VUS) were less common in AJ patients (40, 6% vs. 124, 13%, $P<0.001$), even when excluding patients with single gene testing (32, 19% vs. 98, 27%, $P=0.05$). Among all patients, mutations in *BRCA1/2* were most common (75%). The majority (69%) of non-*BRCA1/2* mutations were identified on multigene panels. Rates of mutations in non-*BRCA*1/2 genes were the same among AJ and non-AJ patients (16, 21% vs. 20, 30%, $P=0.3$, Table 1). **Conclusions:** AJ patients have equivalent rates of non-*BRCA1/2* mutations and on multigene panels have lower rates of VUS compared to non-AJ patients. However, the majority of AJ patients underwent targeted gene testing. These findings suggest consideration of a change in paradigm for genetic assessment of AJ patients with a focus on *BRCA* and non-*BRCA*associated cancer genes through multigene panel testing.

Mutation frequency among Ashkenazi and non-Ashkenazi Jewish patients.

Gene	AJ Patients N (%)	NonAJ Patients N (%)
APC	3 (4)	1 (1%)
ATM	0 (0%)	4 (6%)
BRCA1	34 (46%)	20 (30%)
BRCA2	25 (34%)	27 (40%)
CHEK2	7 (9%)	12 (18%)
FANCC	3 (4%)	0 (0%)
MSH6	1 (1%)	0 (0%)
PALB2	0 (0%)	1 (1%)
PMS2	0 (0%)	1 (1%)
PTEN	0 (0%)	1 (1%)
RAD51D	1 (1%)	0 (0%)

1534 Poster Session (Board #192), Mon, 1:15 PM-4:45 PM

Knowledge outcomes in a randomized trial of telephone vs. in-person disclosure of genetic testing: The COGENT study. *First Author: Nina Beri, University of Pennsylvania, Philadelphia, PA*

Background: Telephone disclosure (TD) of genetic testing is non-inferior to in-person disclosure (IPD) for most outcomes but did not meet non-inferiority for knowledge change. We sought to understand which concepts patients don't understand and factors associated with lower knowledge. **Methods:** Patients were recruited to a multi-center, randomized trial (NCT01736345) comparing TD to IPD of genetic test results. 819 patients were randomized (IPD = 418; TD = 401); 165 declined randomization and requested IPD. Knowledge was assessed after pre-test counseling (V1) and test disclosure (V2). **Results:** There were no significant differences in genetic or multi-gene (MG) knowledge between disclosure groups after V1 and V2. On average, patients answered 73% (SD 1.19) of genetic knowledge and 57% (SD 1.78) of mg knowledge items correctly.After V1, most understood implications of a positive result (87%), that results are not deterministic (84%) and risks for their children (91%). Understanding of uninformative negative, true negative and variant of uncertain significance (VUS) results was lower (post-V1: 33%, 65%, 29%; post-V2 : 37%, 65%, 25%). In multivariable analyses, lower genetic knowledge after V1 was associated with study site, being older ($p < 0.01$), single ($p < 0.01$), non-white ($p < 0.01$), not Ashkenazi Jewish ($p = 0.01$), and not having a mutation in the family ($p = 0.03$), having more relatives with cancer ($p < 0.01$) and not graduating college ($p < 0.01$). Lower mg knowledge after V1 was associated with site and being non-white ($p = 0.01$). Lower genetic knowledge after V2 was not associated with disclosure method but associated with study site, being older ($p < 0.01$), not graduating college ($p < 0.01$) and being non-white ($p < 0.01$). Lower mg knowledge after V2 was only associated with not graduating college ($p = 0.02$). **Conclusions:** While there were no significant differences in genetic knowledge by disclosure method, understanding of several concepts (e.g. VUS and negative results) were lower regardless of arm. Several factors, including age, education and race/ethnicity were associated with lower knowledge. Interventions to improve genetic knowledge in real-world and diverse populations are needed. Clinical trial information: NCT07136345.

1535 Poster Session (Board #193), Mon, 1:15 PM-4:45 PM

Novel germline risk loci in familial melanoma (FM). *First Author: Esther Kazlow, New York University School of Medicine, New York, NY*

Background: While about 10% of cutaneous melanoma (CM) clusters in families, known high-risk loci explain not more than 40% of expected inherited risk. Besides the most frequently mutated genes in FM (e.g. *CDKN2A*), it is estimated that the remaining 60% of FM susceptibility is due to the interaction of environment with specific pools of rare known loci and yet unknown high-risk genes. In our study, we report the discoveries of novel germline genetic risk factors in FM in a recently developed FM cohort at New York University Langone Medical Center (NYULMC) consisting of CM and multiple primary melanomas (MPM) of Ashkenazi Jewish (AJ) and non-AJ European ancestries. **Methods:** As part of an ongoing ascertainment of FM at NYULMC, we assessed the status of *CDKN2A* mutations using Sanger sequencing, examining the coding regions of 47 AJ FM families and 81 non-AJ FM kindreds. In high-risk mutation-negative families, we applied whole-exome sequencing (WXS) and an innovative hot-spot mutational analysis of non-coding regions to identify novel high-risk loci associated with FM susceptibility. **Results:** We found that frequencies of *CDKN2A* deleterious mutations in our FM cohort (13%) are comparable with observations from previous studies. We have also identified a specific *CDKN2A* coding mutation in FM kindreds of AJ ancestry, which is particularly interesting as *CDKN2A* mutations in AJ cohorts have been sparsely reported in prior studies. The WXS/targeted non-coding sequencing of mutation-negative families identified putatively deleterious mutations in regulatory regions in the vicinity of several novel loci, including *SMAD4* and *PAX8*, co-segregating in FM kindreds. **Conclusions:** Our unique FM ascertainment, including > 50% AJ kindreds, provides an excellent platform for mapping high-risk genetic susceptibility in FM. Novel deleterious mutations identified in non-coding regulatory regions of *SMAD4* and *PAX8* genes, some with increased frequency in AJ families, suggest a need for a more thorough investigation of the non-coding genome using a founder FM population, as we propose here. As our ongoing ascertainment expands, we are pursuing validation of our observations through comprehensive sequencing efforts.

1536 Poster Session (Board #194), Mon, 1:15 PM-4:45 PM

Localization of non-receptor tyrosine kinase (nRTK) variants in solid tumor patients using next-generation sequencing (NGS). *First Author: Srishti Sareen, Department of Internal Medicine, The University of Tennessee Health Science Center, Memphis, TN*

Background: Non-synonymous SNPs (nsSNPs) in nRTKs may serve as oncologic targets and predictive biomarkers, with significant lesions described in various nRTK regions including the tyrosine kinase domain (TKD). NGS allows the entire coding sequence to be evaluated, facilitating the identification of novel lesions. **Methods:** We searched all nsSNPs in 14 nRTKs in the tumors of patients (pts) at our institution that received NGS with Caris from 2013-2015 with a diagnosis of advanced breast, colon or lung cancer. Substitutions were classified as either within or extra-TKD; in the case of *JAK1-3*, pseudokinase domain lesions were also identified. In order to predict the pathogenicity of nsSNPs, *in silico* analysis with PolyPhen-2 (Harvard) was completed. **Results:** 356 pts (79 breast, 110 colon and 165 lung (156 NSCLC, 11 small cell)) were identified with a median age of 61 years (range 26-86); 58% female; 62% white, 35% black. 245 variants were found, with 200 nsSNPs and 45 known pathologic mutations (Pmut); Pmut were *PIK3CA* (21 breast, 13 colon, 5 NSCLC) and *AKT1* (6 breast). 169/356 (47%) pts had ≥1 nRTK lesion (0-8). 52/200 (26%) nsSNPs were predicted-damaging (pnsSNPs) with *in silico* analysis among 49 pts (6 breast, 13 colon and 30 NSCLC). pnsSNPs were found in 14/14 nRTKs with median 3 (1-10). The most frequently mutated nRTKs in breast were *SRC* (2/2 variants were pnsSNPs) and *ABL2* (1/5); in colon *ABL1* (5/10), *JAK3* (3/27) and *CDK12* (2/8); and in NSCLC *JAK3* (6/20), *BTK* (5/8), *ABL1* (3/12), *JAK2* (3/11), *CDK12* (3/9) and *JAK1* (3/3). Of 180 nsSNPs with *in silico* results, 68% were extra-TKD (29/122 variants were pnsSNPs), 23% within the TKD (13/42) and 9% in pseudokinase domains of *JAK1-3* (10/16). Notably, 8/10 pseudokinase domain pnsSNPs were in NSCLC pts (3 *JAK1*, 2 *JAK2* and 3 *JAK3*). **Conclusions:** > 13% solid tumors held an nRTK nsSNP that was predicted-damaging by *in silico* analysis, with 69% of these mutations occurring outside of the TKD-proper. Further work is needed to determine how these pnsSNPs affect function and if they are clinically actionable.

1537 Poster Session (Board #195), Mon, 1:15 PM-4:45 PM

The frequency of a novel *KANK1* and *NTRK3* translocation and BRAF^{V600E} mutation in patients diagnosed with metanephric adenoma utilizing molecular mechanisms. *First Author: Aida Catic, ACL Laboratories, Department of Cytogenetics, Rosemont, IL*

Background: Renal metanephric adenoma (MA) is a very rare benign renal tumor, which is frequently misclassified when microscopic features alone are applied. Despite the classification of adenoma as a benign tumor, it is difficult to differentiate from other renal carcinomas such as malignant papillary renal cell carcinomas and in children it can be mistaken with Wilms tumor. The correct classification of a renal tumor is critical for diagnostic, prognostic, and therapeutic purposes. Despite the advancements in cancer genomics, there is limited data available regarding the genetic alterations critical to the metanephric adenoma development. Recent data suggest that 90% of MA have *BRAF*^{V600E}mutations; the genetics of the remaining 10 % are unclear. **Methods:** This study was conducted on 13 FFPE specimens from patients who were diagnosed with renal metanephric adenoma. H&E stained slides from all cases were reviewed by study pathologist, and representative tissue blocks were further selected for *BRAF*^{V600E} sequencing and fluorescent *in situ* hybridization was adapted to detect chromosomal rearrangement between *KANK1* on chromosome 9 (9p24.3) and *NTRK3* on chromosome 15 (15q25.3). **Results:** In this study, we identified a novel chromosomal translocation t(9;15)(p24;q24) between *KANK1* and *NTRK3*, and provided new insights into molecular mechanisms which might identify a subset of metanephric adenomas. Such findings imply that recurrent cytogenetic aberrations may be of prognostic significance as well. Interestingly, our data suggested mutual exclusivity of *BRAF*^{V600E}and t(9;15) aberrations. **Conclusions:** Molecular and cytogenetic analyses have allowed us to elucidate a genetic aberration, which may be specific to metanephric adenoma. Aberrant expression of the *KANK1-NTRK3* gene fusion may be one mechanism by which functionally relevant genes are altered in the development of metanephric adenoma, and thus mark a subgroup of metanephric adenomas with particular clinicopathological features. Also, our study adds *KANK1* and *NTRK3* to the list of candidate genes that may play a role in the 10% of renal metanephric adenomas that lack a *BRAF*^{V600E} mutation.

1538 Poster Session (Board #196), Mon, 1:15 PM-4:45 PM

A clinical and genomic profile of inflammatory myofibroblastic tumors. *First Author: Sugganth Daniel, Foudation Medicine, Inc., Morrisville, NC*

Background: Inflammatory Myofibroblastic Tumors (IMT) are tumors that morphologically traverse the neoplastic and inflammatory realms. With a predilection for children and young adults, many patients present with systemic symptoms and the tumors demonstrate local invasiveness and even metastasis. IMTs are composed of fascicles of myofibroblastic spindle cells with a marked lymphoplasmacytic infiltrate. **Methods:** Integrated genomic profiling of DNA and RNA from IMTs in 30 patients was performed using a hybrid capture, paired-end NGS sequencing method and customized pipeline analysis. **Results:** 23 patients were children or young adults (< 30y), overall the age ranged from 7 months to 72 years. The tumor was clinically aggressive in 10 patients; 3 metastatic, 5 multifocal and 2 locally invasive. Epithelioid morphology was documented in 2 cases, one demonstrated the ALK-RANBP2 fusion. ALK rearrangements were detected in 13 patients, with 7 different fusion partners. ALK IHC or FISH was performed in 23 patients and were all concordant with the genomic results. 22 gene fusions were detected in 21 patients, 4 tumors had ROS1-TFG fusions, 2 had NTRK3-ETV6 fusions. 3 had novel fusions in JAK1-PML, PDGFRB-NOTCH1 and MUTYH-TESK2 respectively. Intact tyrosine kinase domains (TKD) in JAK1 are transposed to the promoter coiled-coil motif in PML, in the rearrangement. While the TKDs are preserved in the PDGRB and TESK2 rearrangements, the functional roles of their partners are yet to be elucidated. The prevalence of rearrangements was higher in patients below 30 years of age (20/23) compared to that above 30y (3/7). All 10 aggressive tumors were detected to have rearrangements. **Conclusions:** IMTs are seen predominantly in younger age groups. Gene rearrangements are seen more frequently in patients with younger age and also in more aggressive tumors, in a statistically significant manner. Alterations in genes associated with hematopoietic neoplasms such as JAK1 among others, are interesting, given the hematologic component of the lesion, and the presence of novel tyrosine kinase rearrangements warrant further investigations to elucidate mechanistic models.

1539 Poster Session (Board #197), Mon, 1:15 PM-4:45 PM

Genetic, clinical and pathological characteristics of BRCA-associated breast cancer (BC) in Hispanic patients in the United States (US) and Latin America (LatAm). *First Author: Yanin Chavarri Guerra, Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico City, Mexico*

Background: Hispanic women with BC present at a younger age, have a higher frequency of BRCA mutations and show a worse incidence-to-mortality ratio than non-Hispanic women. Information regarding the characteristics of BRCA-associated BC in Hispanics is limited. Here, we assess differences in BRCA-associated BC between Hispanic patients in the US and in LatAm. **Methods:** Hispanic patients from the US and LatAm (Mexico, Colombia, Peru, and Puerto Rico) with a history of BRCA-associated BC enrolled in the Clinical Cancer Genomics Community Research Network registry were included. We compared the genetic, demographic, clinical and pathologic characteristics between Hispanics from the US and LatAm using Fisher's exact test and x^2statistics. **Results:** Between 1997 and 2016, 3670 Hispanic patients with a history of BC from LatAm (n = 1341) and the US (n = 2329) were identified, of which 490 (13.3%) had a deleterious BRCA mutation. The frequency of BRCA mutations was similar in Hispanics from LatAm (13.8%, n = 185) and the US (13.1%, n = 305). No significant differences were found in the frequency of BRCA1 vs BRCA2 mutations between patients from LatAm (BRCA1 68%, BRCA2 31.8%) and the US (BRCA1 61.3%, BRCA2 39%) (p = .12). The most frequent mutations found in BRCA1 were: ex 9-12del (LatAm n = 24, US n = 15), 185delAG (LatAm n = 13, US n = 18) and 943ins10 (LatAm n = 3, US n = 8), and in BRCA2 3492insT (LatAm n = 3, US n = 28). Mean age at BC diagnosis was 39.1 (SD 9.5) in LatAm and 41.7 (SD 10.6) in the US (p = 0.01). US patients were significantly more likely to present with Stage 0-II BC than those from LatAm (77.1% vs. 47.6%, p < .001). We found no differences in the proportion of hormone receptor positive tumors between patients from LatAm (45%) and the US (47%) (p = .78). **Conclusions:** The frequency of BRCA-associated BC was similar between Hispanics in LatAm and the US. Women from LatAm with BRCA mutations present at a younger age, as seen for sporadic BC; the causes for this finding warrant further research. Women with BRCA-associated BC in LatAm are more likely to have advanced BC at presentation, which may be a reflection of disparities and barriers in access to care.

1540 Poster Session (Board #198), Mon, 1:15 PM-4:45 PM

The relationship between statins and colorectal cancer stage in the Women's Health Initiative. *First Author: Brian Rutledge, Wayne State University School of Medicine, Detroit, MI*

Background: Statins are the most widely prescribed cholesterol-lowering drugs in the United States. The anti-carcinogenic effect of statins may reduce the metastatic potential of cancer cells leading to 'stage migration' with users more likely diagnosed with early rather than late stage cancer. We evaluated the relationship between prior statin use and colorectal cancer (CRC) stage at diagnosis in the Women's Health Initiative (WHI). **Methods:** The study population included 132,322 post-menopausal women aged 50-79 years, among which there were 2,628 pathologically confirmed cases of insitu (3.3%), local (43.6%), regional (40.4%) and distant (12.7) stage CRC, after an average of 13.9 (SD = 4.7) years of follow-up. To reduce the possibility of detection bias among women more likely to be prescribed statins, we excluded women who did not report a mammogram within 5 years of study entry and who had no health insurance or medical care provider (n = 28,237). Stage was coded using criteria implemented in the Surveillance, Epidemiology and End Results (SEER) Program into early (in situ and local) vs. late (regional and distant) stage disease. Information on statin use prior to diagnosis was collected by self and interviewer-administered questionnaires at baseline and at one, three, six and nine years post-baseline. Self- and interviewer-administered questionnaires were used to collect risk factor information. Hazards ratios (HR) and 95% confidence intervals (CIs) evaluating the relationship between statin use at baseline only, and in a time-dependent manner, and diagnosis of late-stage CRC were computed from multivariable-adjusted Cox proportional hazards analyses. Statistical tests were two-sided. **Results:** Statins were used by 10,868 women (8%) at baseline. There was no significant relationship between statin use at baseline and late stage CRC cancer (HR = 1.03, 95% CI (0.82-1.30) and no significant association by type of statin or duration of use. In the multivariable-adjusted time-dependent model, use of statins was associated with a reduction in diagnosis of late-stage colorectal cancer (HR 0.79, 95% CI 0.67-0.94, p = 0.007). **Conclusions:** Prior statin use may have an influence on colorectal cancer stage at diagnosis.

1541 Poster Session (Board #199), Mon, 1:15 PM-4:45 PM

The scientific impact and value of large, NCI-sponsored randomized phase III cancer prevention trials. *First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The cooperative cancer research groups of the National Cancer Institute's National Clinical Trials Network have a history of successful conduct of large randomized phase III trials of prevention for cancer. An important question for funding agencies is whether the conduct of large prevention trials provides strong scientific return on investment. **Methods:** We used study data from a single NCI-sponsored cooperative group (SWOG) over a 20-year period (1990-2009, inclusive). During this time, SWOG conducted two large prevention trials (the Prostate Cancer Prevention Trial and the Selenium and Vitamin E Cancer Prevention Trial) and numerous treatment trials. Scientific impact for prevention and treatment trials was examined using citation analysis. Average annual citation counts were compared using t-tests. Scientific impact was also assessed as a function of trial costs. **Results:** Twenty-six treatment trials with 16,391 patients and two prevention trials with 54,415 patients were examined. The mean annual citation rate for primary articles was higher for prevention trials compared to treatment trials (173.6 vs. 41.7, p = .003). For both primary and secondary article publications, mean annual citations for articles associated with prevention trials were also higher (557.2 vs. 67.6, p < .0001). Large prevention trials were estimated to provide 70% greater scientific impact on a cost-adjusted basis. **Conclusions:** Based on these criteria, the scientific impact of large phase III cancer prevention trials was very high in absolute terms and after accounting for trial costs. For appropriate scientific questions, large prevention trials provide a strong scientific return on investment for federal funding agencies.

1542 Poster Session (Board #200), Mon, 1:15 PM-4:45 PM

Soft palatal melanosis as a predictor for neoplasia in the upper aerodigestive tract. *First Author: Kenro Hirata, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan*

Background: Squamous cell dysplasia and carcinoma in the upper aerodigestive tract (UAT) was frequently accompanied by melanosis in the UAT. Soft palatal melanosis can be detected by visual inspection during routine physical examination or even personally in a mirror. **Methods:** We reviewed digitalized records of high-quality endoscopic images of the soft palate of 1786 Japanese alcoholic men who underwent endoscopic screening combined with esophageal iodine staining and evaluated to what extent the presence of soft palatal melanosis combined with other risk factors can predict the risk of UAT neoplasia. **Results:** Soft palatal melanosis was observed in 381 (21·3%) of the subjects (mild, 15·0%; distinct, 6·3%). An older age, an inactive heterozygous aldehyde dehydrogenase-2 genotype, smoking, and a high mean corpuscular volume (MCV) were positively associated with the presence of soft palatal melanosis. The age-adjusted odds ratio (OR [95% CI]) for neoplasia in the UAT was 1·92 [1·40–2·64] in the group with melanosis and 2·51 (1·55–4·06) in the group with distinct melanosis, compared with the melanosis-free group. A multiple logistic analysis including the alcohol and aldehyde dehydrogenases genotypes and non-genetic risk factors showed that the presence of soft palatal melanosis was independently associated with a high risk of neoplasia in the UAT. We calculated the individual number of risk factors out of four easily identifiable and significant factors: age ≥55 years, current/former alcohol flushing, MCV ≥106 fl, and distinct soft palatal melanosis. Compared with the risk-factor-free condition, the OR (95% CI) values of UAT neoplasia for one, two, three and four risk factors were 1·49 (0·97–2·30), 3·14 (2·02–4·88), 4·80 (2·71–8·51) and 7·80 (2·17–28·1), respectively. **Conclusions:** Soft palatal melanosis combined with other simple risk assessments provides a simple new strategy for identifying heavy drinkers with a high risk for UAT neoplasia.

1543 Poster Session (Board #201), Mon, 1:15 PM-4:45 PM

Breast cancer risk assessment and chemoprevention use among VA primary care. *First Author: Joseph Merriman, Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN*

Background: Despite recommended guidelines and available medicationsto reduce breast cancer risk by up to 50-65%, <5% of the 10 million eligible women are offered chemoprevention in the U.S. The comfort level, practice patterns, and barriers to breast cancer risk assessment and chemoprevention use within the VA have not been reported. **Methods:** We assessed VA primary care providers using a REDcap survey. We obtained provider demographics, use and comfort level with breast cancer risk models and chemoprevention and knowledge about chemoprevention. Data was analyzed with Fishers exact or chi-square tests. **Results:** Of the 200 survey respondents, 167 were included for analysis. Overall, 30% used the Gail model monthly or more often, and 1.5 % prescribed chemoprevention in the last 2 years. Fewer than 30% correctly answered chemoprevention knowledge questions. Designated women's health providers were more comfortable with risk assessment and chemoprevention (p<.046, p<.004) and used risk models more often (p<.045). 63% expressed interest in education about breast cancer prevention. **Conclusions:** Breast cancer risk assessment and chemoprevention use by VA primary care is limited by lack of comfort and familiarity. Women's health providers are more comfortable and knowledgeable about breast cancer risk models and chemoprevention, offering an opportunity for partnership with high-risk oncologists to improve breast cancer risk assessment and chemoprevention use among female Veterans.

Survey responses by demographics.

		VA WOMEN'S HEALTH PROVIDER	
		No n=43	Yes n=87
Comfort using risk models?	Very Uncomfortable	23%(10)	13% (11)
	Uncomfortable	21% (9)	22% (19)
	Neutral	42% (18)	28% (24)
	Comfortable	12% (5)	27% (23)
	Very comfortable	2% (1)	12% (10)
		*p<0.046	
Comfort prescribing medication for prevention?	Very Uncomfortable	58% (25)	31% (27)
	Uncomfortable	30% (13)	32% (28)
	Neutral	9% (4)	28% (24)
	Comfortable	0	8% (7)
	Very comfortable	2% (1)	1% (1)
		*p<0.004	
In last 2 years, used a risk model?	No	74% (32)	56% (49)
	Yes	26% (11)	44% (38)
		**p<0.045	
In last 2 years, prescribed medication for prevention?	No	100% (43)	95% (83)
	Yes	0	5% (4)
		*p<0.196	

*Fisher's exact **Chi square

1544 Poster Session (Board #202), Mon, 1:15 PM-4:45 PM

Does the extent of therapy differ between breast cancers detected by screening mammogram and non-screening methods? *First Author: Wendie-Lou D. Den Brok, BC Cancer Agency, Vancouver, BC, Canada*

Background: There is ongoing debate about the role of screening mammography and its impact on overall survival in breast cancer. We hypothesized that women with screen-detected breast cancers (SDBC) receive less surgery, regional radiotherapy (RRT), and chemotherapy (CH) than women with non-screen-detected breast cancers (NSDBC). Less therapy equates to less personal and societal burden, including less time away from work, fewer side effects, lower health care and disability costs, and reduced psychosocial distress. These may be adequate justification for screening programs even in the absence of an overall survival benefit. **Methods:** Women aged 40-79 years with stage 0-III breast cancers diagnosed between 2007-2012 and referred to the British Columbia Cancer Agency were identified using the Breast Cancer Outcomes Unit database. Clinical and tumor characteristics and type/extent of treatment were extracted. Linkage with the Screening Mammography Program of British Columbia segregated cases into SDBCs and NSDBCs. Interval breast cancers arising in regularly screened women (minimum 2-year interval) were excluded. **Results:** We identified 12,393 women; 7807 with SDBC and 4586 with NSDBC. Compared with NSDBCs, SDBCs were lower stage, less often treated with mastectomy and CH, and occurred in slightly older women (Table 1). SDBC received more radiation than NSDBC. **Conclusions:** Women with NSDBC are more likely to present with higher stage breast cancer. Rates of mastectomy and CH were 20% higher in NSDBC whereas SDBC had a modest 5% higher rate of RRT. These findings suggest that screening mammography decreases the extent of local and systemic treatment for breast cancer.

Tumor and treatment characteristics.

	SDBC	NSDBC	p-value
N (%)	7807 (63)	4586 (37)	
Median age	60	57	<0.0001
Stage 0	1534 (19.7)	349 (7.6)	<0.0001
I	4150 (53.2)	1322 (28.8)	
II	1660 (21.3)	1947 (42.5)	
III	451 (5.8)	950 (20.7)	
Chemotherapy	27.4	48.5	<0.0001
Mastectomy	29.9	49.7	<0.0001
Loco-regional RT	72.3	66.7	<0.0001

1545 Poster Session (Board #203), Mon, 1:15 PM-4:45 PM

Immune profiling of oral pre-malignant lesions (OPLs): An Erlotinib Prevention of Oral Cancer (EPOC) study biobank analysis. *First Author: William Nassib William, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We previously demonstrated that high-risk loss of heterozygosity (LOH) profiles (i.e., 3p14/9p21 LOH) and EGFR gene copy number gain (CNG) in OPLs were associated with inferior oral cancer-free survival (OCFS) in patients enrolled in the randomized EPOC trial. Herein, we performed comprehensive immune profiling of OPLs and correlated the findings with molecular features and outcomes, using the prospectively collected and clinically annotated EPOC biobank. **Methods:** We evaluated OPL specimens by multiplex immunofluorescence using the Opal 7-color fIHC Kit and the Vectra multispectral microscope / inForm Cell Analysis software. Markers included AE1/AE3 pancytokeratins, PD-L1 (clone E1L3N), CD3, CD8, and CD68. Wilcoxon rank-sum and Fisher's exact tests were used to assess the associations between binary markers and continuous and categorical variables, respectively. Cox model was used to investigate associations of markers with OCFS. **Results:** The cohort included 188 OPL patients with hyperkeratosis/hyperplasia (18%), mild/moderate (44%), or severe dysplasia (5%); 65% had high-risk LOH profiles. The 5-year OCFS was 72.3% (median follow-up of 50 months). PD-L1 expression in $>$ 1% of epithelial cells occurred in 28% of OPLs. Intraepithelial CD3+, CD3+/CD8+, CD68+, and CD68+/PD-L1+ cells were detected in 100%, 88%, 88%, and 54% of the samples, respectively. OPLs with high-risk LOH profiles had increased epithelial PD-L1 expression (P = 0.007), intraepithelial CD68+/PD-L1+ cells (P = 0.002), and a trend towards more CD3+/CD8+ cells in the stroma (P = 0.06) but not in the epithelium (P = 0.97), compared with low-risk LOH OPLs. Increased epithelial PD-L1 expression was associated with inferior OCFS on univariate (P = 0.023), and multivariate analysis including LOH status and EGFR CNG as co-variates (P = 0.018). **Conclusions:** High-risk OPLs defined by LOH profiles had increased PD-L1 expression in epithelial cells and intraepithelial macrophages, as well as stromal CD3+/CD8+ immune infiltration. Higher PD-L1 expression was associated with increased oral cancer risk. The findings may support evaluation of (PD-1-targeted) immunoprevention strategies in high-risk OPLs.

1546 Poster Session (Board #204), Mon, 1:15 PM-4:45 PM

Association of baseline plasma levels of 25OH vitamin D and breast cancer risk in a chemoprevention trial. *First Author: Bernardo Bonanni, European Institute of Oncology, Milan, Italy*

Background: Observational studies have shown a correlation of higher serum 25-hydroxyvitamin D (25OHD) concentrations and reduced cancer risk, including breast cancer (BC). We assessed the association of 25OHD and Vitamin D Receptor (VDR) polymorphisms (SNPs) with breast cancer events within a chemoprevention trial in premenopausal women at risk for BC. **Methods:** Premenopausal women with history of intraepithelial neoplasia (IEN) or at risk women according to the Gail model were included in a 4 arm phase II prevention trial (low dose tamoxifen vs fenrerinide vs their combination vs placebo). Level of 25OHD were measured at baseline. VDR SNPs (*Fok*I, *Bsm*I, *Taq*I, *Apa*I, and *Cdx2)* were determined using the Applied Biosystems' Taqman Allelic Discrimination Assay according to manufacturer's instructions. Survival analysis for breast cancer events was performed using competing risk models, adjusted for BMI, age, season and risk strata. **Results:** Plasma samples were available for 228 subjects. At baseline the median plasma 25OHD concentrations were slightly higher in 53 unaffected women, 19.6 ng/ml (IQR 12.7-27.3 ng/mL) than in 175 women with IEN, 18.8 ng/ml (11.7-25.8). After a median follow up of 15 years, 79 women developed a breast cancer event, 12 had different neoplastic events. The median level of 25OHD was 19.7 ng/ml (IQR 12.8-26.1) in subjects free from oncological events and 17.8 ng/ml (9.7-23.9) in subjects with breast events. Women in the lowest 25OHD quartile ($\leq$12 ng/ml) had an increased risk of breast cancer events: HR = 1.79 (95%CI, 1.07-2.99, p = 0.03). Considering all cancer events, the associations with 25OHD were confirmed (P = 0.005). Among the VDR SNPs the *Apa*I variant in homozygote or heterozygote versus wild type showed an HR of 1.83 (95%CI, 1.04-3.21 p = 0.03). **Conclusions:** Our results support a role of plasma vitamin D levels in breast cancer risk. Subjects in the lowest quartile had a two-fold increased risk of a cancer event. Our findings support trials of 25OHD supplementation to prevent breast cancer in 25OHD insufficient subjects.

1547 Poster Session (Board #205), Mon, 1:15 PM-4:45 PM

Impact of patient-provider race/ethnicity and gender concordance on cancer screening: Findings from medical expenditure panel survey. *First Author: Jyoti Malhotra, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Racial/ethnic minority groups experience lower rates of cancer screening compared to non-Hispanic (NH) whites. Previous studies evaluating the role of patient-provider race/ethnicity and gender concordance in cancer screening have been inconclusive. **Methods:** We conducted a cross-sectional study of 18,690 patient-provider pairs using the 2003-2010 Medical Expenditure Panel Survey (MEPS) data. We assessed association between patient-provider race/ethnicity and gender concordance and, screening adherence for breast, cervical, and colorectal cancer using American Cancer Society guidelines. Separate multivariable logistic regression adjusting for demographics, self-reported health and MEPS survey year were conducted to examine relationships of interest. **Results:** Seventy percent of patients were NH-white, 15% were NH-black and 15% were Hispanic. Patients adherent to cancer screening were more likely to be non-Hispanic, better educated, married, wealthier, and privately insured. Among NH-black and NH-whites, patient-provider racial/ethnic concordance was not associated with screening adherence. Among Hispanics, patient-provider racial/ethnic discordant pairs had higher colorectal cancer screening rates as compared to concordant pairs (OR 1.48; 95% CI 1.28-1.71). This association was significant even on adjusting for gender concordance and survey language (English vs. Spanish). Conversely, patient-provider gender discordance was associated with lower rates of breast (OR 0.81; 95% CI 0.74-0.89), cervical (OR 0.79; 95% CI 0.72-0.87) and colorectal cancer (OR 0.86; 95% CI 0.80-0.93) screening adherence in all patients. This association was also significant on restricting analysis to racial/ethnic concordant pairs. **Conclusions:** Patient-provider gender concordance positively impacts adherence to cancer screening and this finding may guide future interventions. Patient-provider racial/ethnic concordance is not associated with screening adherence among whites and blacks but Hispanic patients seen by Hispanic providers have lower colorectal cancer screening rates. This counter-intuitive finding requires further study.

1548 Poster Session (Board #206), Mon, 1:15 PM-4:45 PM

Use of a marketing plan for recruitment to a lung cancer screening study. *First Author: John R. Goffin, Juravinski Cancer Centre, Burlington, ON, Canada*

Background: Recruitment to clinic trials is typically poor. Among barriers to recruitment may be the limited knowledge of trialists with respect to marketing techniques. Improvements in marketing could decrease recruitment time and shorten the time to access new interventions. We hypothesized that a marketing plan would improve recruitment to a lung cancer screening study. **Methods:** The Pan-Canadian Early Detection of Lung Cancer Trial recruited subjects from 8 centres to a screening study of low-dose CT scan and autofluorescence bronchoscopy. Recruitment processes were undertaken independently at each centre. One centre (M) used marketing expertise and a marketing plan, including surveying study candidates for motivators, resulting in specific newsprint advertisements. Screened trial candidates provided demographic and tobacco use data and indicated how they had heard about the study (bus, friend/family, MD, mail, newsprint, radio, TV, other). No site paid for radio or TV time. We used regression analyses to assess whether newsprint advertisements were more effective for recruitment at site M compared with all other sites. **Results:** From 2008 to 2010, 7059 candidates contacted all centres for eligibility screening, including 779 at centre M. Overall, 50.2% were female; median age was 59 yrs. Compared with other centres, candidates at centre M had less education ($p < 0.001$), a higher median 3-year lung cancer risk (2.3 vs 2.0%, $p < 0.001$), but were more likely to have learned of the study by newsprint (58.8 vs 53.3%, chi-squared $p = 0.004$), and were more likely to be recruited (44.0 vs 34.9%, $p < 0.001$). It was more likely that newsprint was the driver for screening contact among candidates with higher education level (OR 1.05/level), higher age (OR 1.03 / yr) and contact at site M (OR 1.31) (all < 0.001). Recruitment after eligibility screening was higher when newsprint was the driver for contact on univariable but not multivariable analysis. **Conclusions:** The effectiveness of newsprint advertising in motivating study contact may be improved by the formal use of marketing expertise. Newsprint advertising may improve the likelihood of recruitment after study screening, possibly through improved initial self-screening by the candidate. Clinical trial information: NCT00751660.

1549 Poster Session (Board #207), Mon, 1:15 PM-4:45 PM

Ten year experience of an integrated cancer prevention center screening for multiple cancer types. *First Author: Ido Wolf, Tel Aviv Sorasky Medical Center, Tel Aviv, Israel*

Background: Cancer is the leading cause of mortality worldwide. Prevention and early detection are pivotal tools for reducing cancer burden. **Methods:** We describe the 10 year experience (2006-2016) of an integrated cancer prevention center that provides screening for prevention and early detection of 11 most common cancer types. Healthy individuals (20-80 yr) were included. Extensive clinical and epidemiological data was obtained. DNA was extracted from all participants and genotyped for APC I1307K and E1317Q. Patients were examined by specialists in internal medicine, surgery, plastic surgery, OBGYN, urology, oncology, oral surgery, gastroenterology, and others. Women underwent vaginal US and pap smear and (40yr) mammography and US/MRI with a clinical indication. PSA and free PSA for Men ($>$ 40yr). LDCT for heavy smokers. Colonoscopy was recommended to all subjects ($>$ 40yr). **Results:** A total of 6258 (49%) men and 6461 (51%) women mean age 47.0 ± 11.5 year were screened. New malignant lesions were detected in 389 (1.75%) of screeners. The most common cancers were of skin (74, 0.6%), prostate (62, 0.5%), thyroid (51, 0.4%), breast (36, 0.3%), colorectal (22, 0.2%), ovarian (19, 0.1%), uterus (14, 0.1%), testis (12, 0.09%) urinary (9, 0.07%) and lung (10, 0.08%). In 28 patients (0.22%) more than one cancer was detected. Twenty eight of the cancer patients (7.2%) died after 32.4 ± 28.1 months at a mean age of 69.4 ± 14.2 years. Significantly, better than the expected cancer mortality. The APC I1307K and E1317Q variants were detected in 572 (4.8%) and 182 (1.5%) subjects respectively. First degree family member with cancer (OR = 2.02), I1307K carrier ship (OR = 1.53), female gender (OR = 1.23) and advanced age (OR = 1.06) were all associated with statistically significant ($P < 0.05$) increased cancer risk. Advanced age and first degree family history were also associated with detection of more than one cancer types. **Conclusions:** One stop shop screening, in the setting of a multidisciplinary outpatient clinic, is feasible and can prevent and detect cancer at an early stage. It significantly improve morbidity and mortality. Impressively the APC I1307K carries an overall increase cancer risk.

1550 Poster Session (Board #208), Mon, 1:15 PM-4:45 PM

Breast cancer screening practices with high-risk women: A cross-sectional survey. *First Author: Anne Hudson Blaes, University of Minnesota, Minneapolis, MN*

Background: Little literature exists on primary care providers' knowledge and preferences towards breast cancer screening for high-risk women. While guidelines recommend MRI and mammography, it is unclear how frequently these recommendations are used. **Methods:** This web-based survey of providers licensed to practice in Minnesota was conducted. This analysis focuses on breast cancer screening practices for high-risk women. Data were summarized using descriptive statistics; professional characteristic comparisons were conducted using Chi-squared tests. **Results:** 805 of 10,392 (8%) invitees completed the survey. 72.2% were female. 43.9% were physicians (20.8% internists, 71.7% family medicine, 6.3% gynecology), 11.4% physician assistants (PAs), 44.8% advanced practice registered nurses (APRNs). 84.8% were in community practice, 38% $>$ 20 years of experience and 27.1% $<$ 10 years. When asked how effective screening was for reducing cancer mortality in high risk women, mammography was thought to be very effective (48.8%) or effective (46.8%) in women ages 40-49 years, for women ages 50+ years, 60.8% and 35.7%, respectively. 62.4% thought breast MRI was very effective in reducing cancer mortality in high risk women. There was no difference in breast MRI recommendation based on professional background, experience or practice setting. Female practitioners, less experience, and those working in gynecology or women's health were more likely to recommend breast MRI. A case vignette for high risk screening cancer survivors is provided (Table). **Conclusions:** Most primary care providers believe mammography is helpful in women at high risk for developing breast cancer. Less than half of practitioners, however, are following guideline specific recommendations of both mammography and MRI for breast cancer screening in high-risk patients.

Providers' recommendations for breast cancer screening of 40 y/o treated with mantle radiation for Hodgkin lymphoma at age 20 years*.

	Recommendation								
	Mammography and MRI		Mammography Only		MRI only		Other/None		
Background	N	%	N	%	N	%	N	%	P-value
Physician	50	25.9	94	48.7	40	20.7	9	4.7	0.04
PAs	11	22.0	29	58.0	8	16.0	2	4.0	
APRNs	65	33.0	85	43.2	26	13.2	21	10.7	

*National guidelines recommend breast MRI and mammogram

1551 Poster Session (Board #209), Mon, 1:15 PM-4:45 PM

Prospective randomized biomarker study of metformin and lifestyle intervention for prevention in obese postmenopausal women at increased risk for endometrial cancer. *First Author: Melinda S. Yates, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Obesity significantly increases risk of endometrial cancer (EC) through systemic metabolic effects and local tissue action, driven by estrogen and dysregulated insulin signaling. EC is most commonly diagnosed in postmenopausal women. Metformin, an antidiabetes drug, and lifestyle intervention were evaluated for effects on endometrial proliferation and serum biomarkers, in parallel with weight loss. **Methods:** Obese postmenopausal women were randomized into 4 groups for a 16 week intervention using a 2 (metformin 1700 mg/day vs placebo) x 2 (lifestyle intervention vs no lifestyle intervention) factorial design based on the Diabetes Prevention Program. Pre- and post-intervention endometrial biopsies were assessed for proliferation (% Ki67+). Body weight and serum markers were measured pre- and post-intervention (estrone, FSH, DHEA-S, SHBG, IGF-1, adiponectin, omentin, insulin, glucose, A1C, ALT, triglycerides, and others). **Results:** Of 576 women approached for the study, 29 women were randomized and 26 completed the study. Similar adherence was seen for placebo and metformin, with 88% and 94% of doses taken, respectively. Adverse events were grade 1 or 2, most commonly flatulence, headache, and diarrhea. Metformin+lifestyle group lost the most weight (-7.4%), followed by lifestyle (-5.2%), metformin only (-3.1%), and placebo (+0.1%). Endometrial proliferation was not changed. Overall proliferation was low (7.1% at baseline) with substantial variability even in this postmenopausal cohort. Biopsies produced limited endometrium, precluding evaluation of other tissue markers. Metformin significantly increased serum DHEA ($p = 0.002$). SHBG increased ($p = 0.031$) and insulin decreased with lifestyle intervention ($p = 0.035$) but were not statistically significant after multiple comparisons correction. **Conclusions:** Metformin and lifestyle intervention produced positive changes in serum markers and weight loss. While it is known that obese postmenopausal women are at increased risk for EC, improved biomarkers are needed to stratify risk and test prevention strategies, particularly at the endometrial tissue level. Clinical trial information: NCT01697566.

1552 Poster Session (Board #210), Mon, 1:15 PM-4:45 PM

What puts physicians and patients discussing cancer screening on the same page? *First Author: Danielle Seiden, Mount Sinai Beth Israel, New York, NY*

Background: Shared decision making requires effective provider-patient communication. We studied concordance in recalled discussions and factors that affected it. **Methods:** In a cluster-randomized trial of educational supports for providers (MDs), we are enrolling an age-(30-89 years) and sex-stratified sample of 216 patients (PTs) who underwent a physical examination at 2 urban hospitals, 18 for each of 12 primary care MDs. Screening guideline formatting (colorcoding) and academic detailing were randomly assigned in a 2x2 design. Immediate post encounter surveys recorded PT and MD recall of screening discussions. **Results:** The first 174 participants were diverse (63% white) and highly educated (77% college degree). PTs and MDs differed in recall of screening discussions, and the differences varied by screening test. When MDs reported a colorectal cancer (CRC) screening discussion, 21% of PTs did not; 20% of MDs disagreed when PTs reported the discussion. The discrepancies were greater for prostate specific antigen (PSA) screening, 29% and 29%, respectively, but much less for mammograms (MAM), 8% and 5%, respectively. Recall of the MD recommendation also differed: 15% of PTs disagreed when their MD reported it, and 33% of MDs when their PT reported it. For PSA, disagreement was 26% and 33%, respectively, and for MAM, disagreement was 17% and 10%, respectively. Overall, agreement between all PTs and MDs on whether screening was recommended was fair for CRC, PSA and MAM: kappa = 0.33, 0.34 and 0.29, respectively. For PTs $>$ 70 agreement was nonexistent on recalled CRC and PSA recommendations (kappa = -0.02 and -0.03, respectively) but preserved for MAM (kappa = 0.39). Sex did not affect CRC agreement. Recall concordance improved when SDM was recalled. For CRC, kappa rose from -0.12 to 0.52 if the MD recalled any MDM element. **Conclusions:** In a highly educated, diverse patient population, patients and physicians often disagreed on recalled cancer screening discussions. Discordance was greatest with PSA and least with MAM. Discordance was greater in older patients. If MDs recalled any shared decision making, agreement increased significantly. Communication varies by cancer screen, PT age and elements of shared decision making. Clinical trial information: NCT02430948.

1553 Poster Session (Board #211), Mon, 1:15 PM-4:45 PM

Awareness of cervical cancer and screening among rural Nepalese women. *First Author: Anju Shrestha, Nepal Cancer Hospital and Research, Kathmandu, Nepal*

Background: Cervical cancer is leading female cancer in Nepal. Despite the existence of effective screening using Pap smear, the uptake of screening is poor. Objectives of this study were to determine the baseline information about the knowledge of cervical cancer and explore attitude and practice of Pap smear screening among the women of rural community of Nepal. **Methods:** A cross sectional population based descriptive study of female attending free cervical cancer screening camp in different rural community of Nepal organized by Nepal cancer Support group and Nepal cancer Hospital, funded by Direct Relief was conducted from 1/06/2016 to 31/12/2016- using self- administered questionnaire to elicit information on demographic characteristics, knowledge, screening behaviors and determinants of cervical cancer. **Results:** A total of 2529 women participated in nine screening camp, out of which 55.95% (1416) were illiterate whereas only 4.95% (129) were graduate. Mean age of participates were 40.5± 11.97 (17-83)yrs. 31.63% (800) of women married before age of 16 and 32.08% (811) women had their first childbirth before age of 18 years. Only 6.88% (174) women were working outside and rest were working in household work and farming. 76.24% (1928) women knew nothing about cervical cancer. Although 38.71% (979) women heard about Pap smear, only 10.36% (262) knew about eligibility of screening, 1.58% (40) knew about screening interval and 16.57% (419) know that Pap smear is used for detections of cancerous and precancerous lesions of cervix. However, knowledge of risk factors for cervical cancer was found in 5.9% (150). Of the female respondents, 78.09% (1975) did not feel susceptible to cervical cancer and 82.25% (2080) had never been screened before. The most common reason for not doing Pap test is they never heard about it (59.99%: 1516). The other reason includes do not have any symptoms (17.79%:450); embarrassment (2.49%:62); do not know where to do (1.27%:32); fear of finding out cancer (0.51%:13) and never advised by doctor (0.4%:10). **Conclusions:** The study revealed very low cervical cancer knowledge and poor screening behavior among the women. This may be due to lack of awareness, education and low priority of women's health issue.

1554 Poster Session (Board #212), Mon, 1:15 PM-4:45 PM

Risk factors of colorectal adenoma recurrence among individuals under 50 years of age compared to those 50 years of age or older. *First Author: Christine Louise Sardo Molmenti, Northwell Health/Hofstra Northwell School of Medicine, Great Neck, NY*

Background: Colorectal cancer incidence and mortality are increasing among individuals $<$ 50 years of age. Data are limited regarding the epidemiology of colorectal adenomas in this younger age group. This study investigated and compared risk factors associated with recurrence of adenomas in individuals under and over 50 years of age. **Methods:** Pooled analyses from the Wheat Bran Fiber and Ursodeoxycholic Acid phase III, randomized, controlled clinical trials included 1,623 participants, aged 40-80 years. Each completed baseline questionnaires related to family history and lifestyle habits, had one or more colorectal adenomas removed at baseline, and had a follow-up colonoscopy during the trial (mean follow up 36 months). Univariate and multivariate logistic regression modeling estimated the association between age and colorectal adenoma recurrence, and evaluate multiple risk factors, while controlling for confounding factors. **Results:** A statistically significant increased trend was found for colorectal adenoma recurrence with increasing age (P_{trend}= $<$ 0.001). Multivariate logistic regression revealed that risk factors significantly associated with adenoma recurrence in the ≥50 age group (n = 1,523) included history of previous polyps, characteristics of adenomas removed at baseline (multiple adenomas and villous feature), current smoking, and an increased waist circumference. Although risk profile in the $<$ 50 age group (n = 95) shared similarities with that in the ≥50 age group (e.g., current smoking), there were a few notable differences: history of previous polyps was a more prominent predictor for recurrence for the $<$ 50 ($OR_{<50}$ = 4.76 and $OR_{\geq 50}$ = 1.33, $P_{interaction}$ = 0.042), whereas baseline characteristics of adenomas were more important for the ≥50 (multiple adenomas: $OR_{<50}$ = 0.40 and $OR_{\geq 50}$ = 2.28, $P_{interaction}$ = 0.043). **Conclusions:** Predisposition to colorectal adenoma is a more important risk factor for recurrence in the $<$ 50 as compared to the ≥50. Future studies need to identify susceptibility factors contributing to the increasing incidence of colorectal cancer in this younger age group.

1555 Poster Session (Board #213), Mon, 1:15 PM-4:45 PM

Health4Families: An intervention to improve weight and health behaviors in families with hereditary breast/ovarian cancer or Lynch syndrome. *First Author: Susan K. Peterson, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Physical activity, diet, and healthy weight may reduce cancer risk in hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (LS) families. Evidence-based programs to help affected families make these behavioral changes are lacking. We evaluated data from a 16-week family-centered lifestyle intervention trial for individuals with HBOC or LS germline gene mutations and their relatives. **Methods:** Index cases with HBOC- or LS-associated mutations were recruited from an institutional registry and advocacy organizations, and identified relatives to participate with them in the study. Those eligible had BMI$>$25 and/or did not meet recommendations for exercise or fruit/vegetable consumption. Participants were randomized to multiple conditions including text messaging, online weight/diet monitoring, an online social network, and E-mail or telephone coaching. All monitored activity using Fitbits. Behavioral outcomes were assessed online at baseline and 8 weeks. **Results:** 65 HBOC index cases with 63 family members, and 35 LS index cases with 36 family members participated in the study. At 8 weeks, participants lost 3.2 pounds on average (p$<$.0001) and increased weekly physical activity from 126 to 172 minutes (p=.0012). LS participants decreased self-reported sedentary time (p=.0126). Program effects did not differ between index cases and family members. Participants reported high program satisfaction; 78% would recommend it to a family member. **Conclusions:** Hereditary cancer families can benefit from behavioral interventions to improve weight and physical activity. Data show that distance-based methods are effective, and are ideally suited for families with a hereditary predisposition to cancer but who are often geographically dispersed. Clinical trial information: NCT02194387.

Baseline body composition and physical activity in index cases and family members.

	HBOC index cases	HBOC family members	LS index cases	LS family members
BMI (M±SD)	29.6 ± 7.2	29.3 ± 6.9	29.3 ± 6.6	29.7 ± 6.1
Weekly min MVPA*	127 ± 140	129 ± 195	107 ± 119	82 ± 94
Weekly hours sedentary time	49.5 ± 28.3	48.5 ± 29.4	45.6 ± 26.4	48.4 ± 30.0
≥ 150 min MVPA/week (%)	42	33	31	22

*MVPA = moderate-vigorous physical activity

1556 Poster Session (Board #214), Mon, 1:15 PM-4:45 PM

Effect of metformin chemoprevention on metabolomics profiles in Li-Fraumeni Syndrome (LFS). *First Author: Farzana L. Walcott, George Washington University, Washington, DC*

Background: LFS is a highly-penetrant, autosomal dominant, cancer predisposition disorder characterized by early onset cancer; germline mutations in *TP53*are present in 70% of LFS. We previously observed metformin inhibition on mitochondrial function in LFS patients. Metformin may reduce TCA cycle and glycolytic intermediates during cellular transformation, indicating inhibition of complex I of the mitochondria. To further explore this, we performed untargeted metabolomics profiling on stored serum of study participants. To our knowledge, there are no previous studies of metabolomics profiling in LFS patients treated with metformin. **Methods:** Adult LFS patients (≥18 years old) were enrolled for 20 weeks. Metformin was initiated at 500 mg per day and increased in 500 mg dose increments every two weeks to a maintenance dose of 2000 mg of metformin. Patients were taken off metformin for the last six weeks of the study (week 20). Global biochemical profiles were determined in human serum samples collected in 21 patients, each providing one sample at baseline, week 14 (on 2000 mg metformin) and week 20 (off metformin). Metabolomics analyses were performed by Metabolon, Inc. **Results:** Treatment with metformin induced a strong metabolic signature of increased fatty acid beta-oxidation in LFS patients. Acylcarnitines, long chain fatty acids, and 3-hydroxy fatty acids were significantly elevated following metformin treatment. TCA cycle intermediates, aconitate, malate, and fumarate were also increased as were levels of ketone body 3-hydroxybutyrate (BHBA)indicating robust β-oxidation, presumably to support increased energy production via the TCA cycle. Clearance of metformin results in normalization of levels to comparable baseline values, indicating a causal role of metformin in these changes. **Conclusions:** Global metabolomics profiling suggests an increase in TCA cycle intermediates and a strong signature of fatty acid oxidation with metformin treatment in LFS, suggesting metformin effect on the mitochondria and TCA cycle is more dynamic than previously shown. LFS patients may have distinct metabolic profiles which may be altered by treatment with metformin. Funding: ASCO Young Investigator's Award 2016. Clinical trial information: NCT01981525.

1557 Poster Session (Board #215), Mon, 1:15 PM-4:45 PM

High accumulation of metformin in colonic tissue of subjects with diabetes or metabolic syndrome. *First Author: Andrea De Censi, Division of Medical Oncology, E.O. Galliera Hospital, Genova, Italy*

Background: Epidemiological studies consistently observed an association between metformin use in diabetic patients and decreased colon cancer incidence and mortality at clinical doses (1500-2250 mg day), corresponding to plasma levels of 0.003-0.045 mM. Preclinical models report much higher doses of metformin, ranging between 1 and 40 mM for *in vitro* and 0.006-0.145 mM for *in vivo* studies. A recent trial using a low dose of metformin (250 mg/day, Higurashi T et al. Lancet 2016;17:475) showed a 40% reduction of colorectal adenoma recurrence. We performed a pilot study to measure metformin in plasma and colonic tissue of subjects with diabetes or metabolic syndrome and to explore their correlation with different tissue biomarkers, including Ki-67, pS6k, a mTOR effector protein, and EGFR expression. **Methods:** We used LC-MS/MS to quantify metformin in plasma and colonic tissues from 13 volunteers with diabetes or metabolic syndrome undergoing screening colonoscopy. All patients had received metformin at 1000-1850 mg/day for a median of 6.5 yrs (range 2-15), except for one who served as untreated control. Tissue quantifications were performed on specimens derived from right and left colon biopsies with or without washing to exclude a potential contamination due to lumen accumulation by the drug. Biomarker assessment was performed by standard IHC assay. **Results:** The mean plasma metformin was 0.025 mM/L (range $5x10^{-5}$-0.017), whereas the colonic tissue was ~100 fold higher in right [0.39 mM/Kg (range 0.034-1.75)] and left colon [0.46 mM/Kg (range $5x10^{-3}$-1.86)]. There was no significant difference between washed and unwashed biopsies. No significant correlations were detected between metformin levels in plasma/tissue and tissue biomarkers. **Conclusions:** Metformin can attain ~100 fold higher colonic tissue levels than in plasma. These levels are in the range of a direct antitumor effect observed in *in vivo* preclinical models. A two-by-two clinical trial of metformin and aspirin in colon cancer patients is underway by our group to further elucidate independent and synergistic antitumor effects.

1558 Poster Session (Board #216), Mon, 1:15 PM-4:45 PM

Risk of breast or ovarian cancer in family members who do not carry the *BRCA1* or *BRCA2* family mutation: Findings from the EMBRACE study. *First Author: Fabio Girardi, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom*

Background: *BRCA1/BRCA2* true-negatives are proven non-carriers of the *BRCA* mutation segregating within their family. Currently, there is no conclusive evidence on the risk of developing breast or ovarian cancer in these individuals, potentially leading to non-uniform clinical practices. The purpose of this study was to estimate breast and ovarian cancer risks for true-negatives from the EMBRACE prospective cohort study. **Methods:** Risks were calculated separately for incident invasive breast cancer and epithelial ovarian cancer (EOC). We used cohort analysis to estimate incidences, cumulative risks and standardised incidence ratios (SIRs). **Results:** A total of 1895 unaffected women were eligible for inclusion in the breast cancer analysis and 1736 for the ovarian cancer analysis. There were 23 incident invasive breast cancers and 2 EOCs diagnosed during follow-up. The cumulative risk of invasive breast cancer was 9.4% (95% CI 5.9%-15%) by the age of 85-years, whilst the corresponding risk of EOC was 0.6% (95% CI 0.2%-2.6%). The SIR for breast cancer was 0.93 (95% CI 0.62-1.40) in the overall cohort, 0.85 (95% CI 0.48-1.50) in non-carriers from *BRCA1* families and 1.03 (95% CI 0.57-1.87) in non-carriers from *BRCA2* families. The SIR for EOC was 0.79 (95% CI 0.20-3.17) in the overall cohort and 1.74 (95% CI 0.44-6.98) in non-carriers from *BRCA2* families. **Conclusions:** This is the largest cohort to date of prospectively ascertained true-negatives from *BRCA1/BRCA2* families. Our results did not provide evidence for elevated risks of invasive breast cancer or EOC in proven non-carriers. Risk-reducing bilateral mastectomy and risk-reducing salpingo-oophorectomy may not be appropriate for these individuals. Female relatives of a known *BRCA1/BRCA2* mutation carrier should be advised towards genetic testing to avoid unnecessary surgical procedures. However, we were not able to investigate variation in risks by cancer family history. Therefore, we cannot rule out that risks may be slightly higher for close relatives of affected mutation carriers. In such cases, model-based estimates incorporating family history, such as those given by BOADICEA, can be used in the counselling process.

1559 Poster Session (Board #217), Mon, 1:15 PM-4:45 PM

Breast cancer in male veterans: The Veterans Affairs (VA) informatics and computing infrastructure (VINCI) big data analysis. *First Author: Anita Aggarwal, VAMC-DC, Potomac, MD*

Background: Male breast cancer (MBC) management from diagnosis to treatment is generalized from female breast cancer (FBC) because of its rarity and paucity in literature. VINCI is a unique database for cross sectional and longitudinal analysis. The objective of this retrospective analysis was to compare characteristics and outcome of MBC with FBC in veterans. **Methods:** Detailed demographics, diagnosis, treatment and outcome of all patients diagnosed with breast cancer between 1998 and 2016 at 152 VA medical centers were obtained and analyzed with Chi-square and t-test univariate statistics. **Results:** In total 9765 patients' records were reviewed, 1613 MBC were compared with 8152 FBC. The mean age at diagnosis is 68.5 and 57.3 years for MBC and FBC, respectively (Table1). After a median follow up of 3.5 years, 48% MBC and 22% FBC died. Breast cancer mortality is 18% and 9% in MBC and FBC, respectively. A cox regression survival analysis indicates that males were 33% (Hazard Ratio 1.33, P=<0.0001) more likely to die from breast cancer than females. **Conclusions:** This is the largest comparison series of MBC with FBC to date in the Veteran population to author's knowledge. Males have higher breast cancer specific mortality than females most likely because of older age and higher stage at the time of diagnosis. Differences in the biology and pathology may be contributing factors which needs further prospective studies.

Demographics and outcome comparison analysis of male and female veterans with breast cancer.

	Total Sample N=9,765		
	Male (n=1,613) # (%)	Female (n=8,152) # (%)	P-Value
Mean Age (SD)	68.5 (11)	57.3 (11.8)	<0.0001
Mean BMI	38.2	32.8	0.24
Race (N, %)			<0.001
White	1,183 (73)	5,767 (71)	
African-American	386 (24)	2,009 (25)	
Other/Unknown	44 (3)	376 (5)	
Stage (N, %)			<0.001
0	106 (7)	1,448 (18)	
1	373 (23)	2,836 (35)	
2	596 (37)	2,306 (28)	
3	268 (17)	734 (9)	
4	141 (9)	331 (4)	
Unknown	129 (8)	497 (6)	
Mean time to Death (years SD)	4 (3.2)	4.6 (3.6)	<0.001
Mortality	774 (48)	1,809 (22)	<0.0001
Breast Cancer Specific Mortality	286 (18)	719 (9)	<0.0001

1560 Poster Session (Board #218), Mon, 1:15 PM-4:45 PM

The clinical impact of the Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score on breast cancer patients survival. *First Author: Nami Yamashita, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*

Background: Recent reports show that the preoperative immunonutritional status correlate with the survival rate in cancer patients. The Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score are used as screening tools for immunonutritional status and reported to be a predictor of postoperative recurrence in patients with various gastrointestinal cancers. However, the clinical importance of the PNI and CONUT in breast cancer has not been elucidated. The aim of this study is to investigate the clinical impact of preoperative PNI and CONUT on long-term survival of breast cancer patients. **Methods:** We retrospectively analyzed 653 consecutive stage I-III breast cancer patients who were treated from January 2002 to December 2013. The PNI score was calculated as 10 x serum albumin (g/dl) + 0.005 x total lymphocyte count (per mm^3). The CONUT score is calculated from three parameters, serum albumin, cholesterol, and total lymphocytes count. The patients were divided into two groups according to the PNI and CONUT score. The uni- and multivariate Cox regression analyses were performed to evaluate the prognositic value of the PNI and CONUT in breast cancer. **Results:** The malnutritional status was observed in 170 (26%) and 131 (20%) patients as low-PNI and high-CONUT, respectively. The relapse-free survival (RFS) and overall survival (OS) rates were significantly lower in the low-PNI group (RFS: $p < 0.0001$, OS: $p < 0.0001$) and high-CONUT group (RFS: $p = 0.0009$, OS: $p = 0.0018$). In the multivariate analysis, low-PNI was independent prognostic factors for both RFS and OS (RFS: HR2.33, $p = 0.032$, OS: HR5.01, $p = 0.0009$). In the subset analysis, the low-PNI group showed poor prognosis especially in the postmenopausal, hormone receptor negative patients. The low-PNI also had poorer prognosis in post-recurrence survival. **Conclusions:** The preoperative PNI is a strong independent predictor of long-term survival among breast cancer patients.

1561 Poster Session (Board #219), Mon, 1:15 PM-4:45 PM

Hormone replacement therapy (HRT) among *BRCA* mutation carriers. *First Author: Nicole Centers, Florida Hospital Celebration Health, Celebration, FL*

Background: BRCA mutation carriers are often offered risk-reducing surgery (oophorectomy, hysterectomy) and medication regimens (hormone modulators, chemotherapy) in a preventative format. These therapies cause premature menopause and associated symptoms including reduced libido and sexuality. Hormone replacement therapy (HRT) is beneficial in alleviating climacteric symptoms of menopause. However, due to high risk for breast cancer in BRCA mutation carriers, many within the healthcare community oppose the use of HRT, despite recent studies that fail to demonstrate an adverse effect on oncologic outcomes. The purpose of this study was to identify current HRT practices among BRCA1,2 mutation carriers. **Methods:** The study population included 763 BRCA1,2 mutation carriers (52% previvors, 48% survivors) who are members of Facing Our Risk of Cancer Empowered, a support, education, and advocacy group for individuals with gene mutations. Data was collected via an online survey that included questions pertaining to patient characteristics, preventative procedures, menopausal status and symptoms, HRT use, and provider recommendations. **Results:** According to the survey findings, 73% of BRCA mutation carriers were postmenopausal (59% previvors, 88% survivors) and, among these, 81% had become menopausal prematurely due to risk-reducing surgery or medications. Major postmenopausal concerns of BRCA mutation carriers involved low libido/sexuality (78%) and an increased risk for weight gain (83%), cardiovascular disease (77%), and osteoporosis (65%). Despite the high incidence of premature menopause and associated symptomatology of the population, HRT usage was low (13% previvors, 28% survivors). According to the survey respondents, only 26% of healthcare providers for the previvors and 8% for the survivors favored HRT use. **Conclusions:** High rates of premature menopause with related symptoms occur among BRCA1,2 mutation carriers in association with cancer preventative therapies. Despite the young age of this postmenopausal population, only a small percentage are on HRT. These findings suggest the need for improved education to patients and providers regarding HRT and cancer risk, as well as the exploration of HRT options.

1562 Poster Session (Board #220), Mon, 1:15 PM-4:45 PM

The association between proton pump inhibitors (PPI) use for gastro-esophageal reflux disease (GERD) and lung cancer (LC): A nested case-control study. *First Author: Hadas Dresler, Meir Medical Center, Kfar-Saba, Israel*

Background: Data suggests that GERD with recurrent reflux and micro-aspiration of stomach contents, may be associated with lung injury, inflammation, activation of proliferative signals, and eventually DNA damage and malignant transformation. Recently, a large population based cohort study found that GERD may increase the risk of lung cancer in Asians. In the present nested case control study, we aimed to evaluate the association between PPI use as a surrogate for GERD and lung cancer in a large western population. **Methods:** We conducted a matched case-control study within a population-representative database from the United Kingdom. Study cases were defined as individuals with any diagnostic code of lung cancer. For every case, four eligible controls were matched on age, gender, practice site, time and duration of follow-up. Exposure of interest was PPI use prior to cancer diagnosis. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for lung cancer were estimated using conditional logistic regression. Adjustment was performed for smoking. **Results:** The study population included 19143 lung cancer cases and 74473 matched controls. PPI use was associated with a significantly increased lung cancer risk (adjusted OR 1.70, 95%CI 1.64-1.77, $p < 0.001$). In a sensitivity analyses we observed similar associations when PPI use was initiated more than one year prior to cancer diagnosis (adjusted OR 1.18, 95%CI 1.13-1.23, $p < 0.001$) and more than two years prior to cancer diagnosis (adjusted OR 1.15, 95%CI 1.10-1.20, $p < 0.001$) **Conclusions:** ChronicPPI use, as a surrogate for symptomatic GERD, may be associated with a higher lung cancer risk.

1563 Poster Session (Board #221), Mon, 1:15 PM-4:45 PM

Socio-demographic variations in lung cancer screening before and after USPSTF recommendation: Results from national health interview surveys (NHIS). *First Author: Qian Wang, Department of Internal Meidicine, Icahn School of Medicine at Mount Sinai St. Luke's, New York, NY*

Background: In 2013, USPSTF recommended low-dose CT screening (LCS) for lung cancer in high-risk adults. The change in real-world practice is largely unknown, as well as the association with socio-demographic factors. **Methods:** Data were extracted from the population-based 2010 and 2015 NHIS. LCS was defined as a chest CT to check for lung cancer within the past year. We included adults aged 55 to 80 years who 1) have 30+ pack-year smoking history; 2) are currently smokers or have quitted within the past 15 years. We excluded adults who 1) have lung cancer; 2) had not seen a physician in the past year. We used weighted analyses to estimate national lung cancer screening rates. **Results:** A total of 874 and 1041 high-risk smokers responded to the LCS questions for lung cancer in 2010 and 2015, respectively. The screening rate more than doubled from 4.1% to 9.1% ($P < 0.01$) in all respondents. The increase was greater in women (2.9% to 9.5%, $p < 0.01$) than men (5.2% to 8.8%, $p = 0.03$) and in age 65-80 (4.7% to 12.3%, $p < 0.01$) than age 55-64 (3.8% to 6.3%, $p = 0.16$). White saw the largest increase and highest rate in 2015 (4.0% to 9.3%, $p = < 0.01$). Those with some college or above education had the highest rate in 2010, but the lowest in 2015. Household income above 75,000 dollars was associated with the lowest rate in both 2010 and 2015. **Conclusions:** Since the recommendation of USPSTF, LCS rate for lung cancer has doubled but remains less than 10%. Higher education and household income are associated with lower screening rate, in contrast to studies of other cancers.

LCT screening rates for lung cancer in 2010 and 2015.

	2010 (%)	2015 (%)	p-value
All	4.1	9.1	<0.01
Gender			
Men	5.2	8.8	0.05
Women	2.9	9.5	<0.01
Age			
55-64	3.8	6.3	0.19
65-80	4.7	12.3	<0.01
Race			
Hispanic	1.4	6.2	0.20
Non-Hispanic White	4.0	9.3	<0.01
Non-Hispanic Black	6.3	9.3	0.44
Education			
Less than high school	3.2	10.0	<0.01
High school graduate	3.0	12.1	<0.01
Some college or above	5.8	6.8	0.69
Annual Household Income			
< $35,000	4.7	8.4	0.06
$35,000 - $74,999	4.9	12.0	0.03
> $74,999	2.4	7.6	0.04

1564 Poster Session (Board #222), Mon, 1:15 PM-4:45 PM

Breast cancer screening in transgender patients: Findings from the 2014 BRFSS survey. *First Author: Anand Narayan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Transgender patients undergoing transitions often receive cross sex hormonal therapies, placing them at uncertain risk for developing breast cancer. There is limited population-based information about the extent to which transgender patients undergo mammography screening. Our purpose was to determine the extent to which transgender patients undergo mammography screening using nationally representative survey data. **Methods:** Transgender participants in the 2014 Behavioral Risk Factor Surveillance System survey were included. Proportions undergoing mammography screening in the last year or two years were calculated stratified by age category and transition status (male to female(MtF), female to male(FtM), non-conforming(people who do not follow societal notions how they should look or act based on the sex they were assigned at birth)). For each transition status, predictors of mammography screening (demographics, indices of access to health care) were calculated using logistic regression. **Results:** 656 transgender patients were included (343 were MtF, 203 were FtM and 110 classified themselves as gender non-conforming). For MtF respondents, 61.5% of women underwent mammography screening within the last year (71.9% within last two years). For FtM respondents, 66.1% underwent mammography screening within the last year (74.2% within the last two years). For gender non-confirming transgender patients, 57.9% underwent mammography screening within the last year (74.4% within the last two years). For all transgender patients, income category (OR 1.16, 0.82 - 1.64), higher education category (OR 1.09, 0.31 - 3.86) and health insurance (OR 0.38, 0.10 - 1.41) were not associated with increased adherence to mammography screening. Adjusted for age, education, race and income, transgender patients were comparably likely to undergo mammography screening compared with non-transgender patients (OR 0.97, 0.58 – 1.62). **Conclusions:** High proportions of transgender survey respondents undergo mammography screening (57.9 – 66.1% within the last year, 71.9 – 74.4% within the last two years), proportions comparable to non-transgender survey respondents.

1565 Poster Session (Board #223), Mon, 1:15 PM-4:45 PM

Effects of physical condition and body composition on cancer risk in a nationwide cohort of 31,158 men from Finland. *First Author: Jorma Tauno Juhani Sormunen, University of Tampere, Tampere, Finland*

Background: Regular physical activity seems to protect men from colorectal cancer and possibly also from prostate cancer. In the case of other cancers the evidence is adding up, and physical activity seems to have a small protective effect to its incidence. The aim of this study was to analyse the effects of physical condition (PC) in early adulthood on cancer incidence later in life. **Methods:** We collected data on general health, anthropometry and PC for 31,158 Finnish men born in 1958 from the time of their military service between the ages of 17 and 30 years. Using linkage with the Finnish Cancer Registry, all men were followed-up for cancer incidence up to 2014. **Results:** Overweight and obesity (body mass index (BMI) $\geq$ 25 kg/m^2) were associated with an increased overall cancer risk [hazard ratio (HR): 1.08, 95% confidence interval (CI): 0.89-1.30] when compared to those with BMI $<$ 25 kg/m^2. Those with normal weight but bad PC had an increased risk of all cancers combined as compared to those with normal weight and good PC (HR 1.18, 95% CI: 1.01-1.38), which further increased in those who were also overweight (HR 1.30, 95% CI: 1.01-1.69). We noticed an increased overall cancer risk in men in who entered service with minor health problems (HR 1.46, 95% CI 1.19-1.80), when compared to those that were completely healthy. This was especially observed for advanced prostate cancer (HR: 3.35, 95% CI: 1.14-9.90). Increased HRs, yet statistically insignificant, were also seen for colorectal and other obesity-related cancers. **Conclusions:** Good PC at young age seems to protect men from cancer later in life. Early adulthood obesity, when combined with bad PC, seems to further increase cancer risk.

1566 Poster Session (Board #224), Mon, 1:15 PM-4:45 PM

Anti-cancer effect among patients with familial Mediterranean fever: Outcome of 258,803 person-years analysis. *First Author: Ronen Mordechay Brenner, Wolfson Medical Center, Tel Aviv, Israel*

Background: Familial Mediterranean fever (FMF) is an autoinflammatory disease that causes recurrent serosal inflammation. The association between FMF and malignancy has not been previously described. We estimated cancer risk in a large single-institution cohort of FMF patients. **Methods:** The study cohort consisted of 8,534 FMF patients registered in the Israel National FMF Center at Tel Hashomer, Israel. We linked the study cohort to the database of the Israel National Cancer Registry using the national identity number. Cancer incidence in FMF patients was determined and stratified by age and gender. Standardized incidence ratios (SIR) for cancers were calculated. **Results:** Among 8,534 FMF patients (4,400 men, 4,134 women), 350 developed cancer during the years 1970-2011. Overall cancer risk among patients with FMF was significantly lower than that expected in the following gender and population groups, based on cancer incidence rates in those groups in the Israeli population: males of Jewish ethnicity SIR 0.66, CI 95% [0.55-0.77], $p< 0.001$; females of Jewish ethnicity SIR 0.75 CI 95% [0.64-0.86], $p< 0.001$; males of Arabic ethnicity SIR 0.34, CI 95% [0.07-0.99], $p= 0.024$. **Conclusions:** FMF patients have a significantly lower incidence of cancer than the general population. This pattern was demonstrated in two different ethnic populations, Jewish and Arabic. We speculate that the lower cancer incidence could be attributed to the direct physiological effect of FMF or to the anti-FMF treatment.

1567 Poster Session (Board #225), Mon, 1:15 PM-4:45 PM

Incidence and survival trends of cancers diagnosed in young adults (20-39 years): A population-based study. *First Author: Husson Olga, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Cancer in young adults (YAs; 20–39 years) is rare but its incidence is increasing globally. In The Netherlands, care for YA cancer patients is mostly dispersed, in contrast to centralized care for all pediatric cancer patients. Aim of this population-based study was to examine trends in YA cancer incidence and survival. **Methods:** Data from all YAs diagnosed between 1989-2015 (n = 89,675) were obtained from The Netherlands Cancer Registry. Age-standardized incidence rates with estimated annual percentage of change and five-year relative survival rates were calculated. **Results:** Cancer incidence in YAs increased significantly from 48 to 67 per 100,000 person years in males (1.7%) and from 78 to 97 per 100,000 person years in females (1.1%). In both males and females, significant rising incidence trends were found for melanoma (2.3%), skin (2.3%) and thyroid cancer (3.2%), CML (7.2%), Hodgkin (1.3%) and Non-Hodgkin lymphoma (0.9%). In females, the incidence of breast cancer increased (1.2%), while it decreased for lung (-1.3%) and ovarian cancer (-4.3%). In males, testicular cancer incidence increased significantly (4.1%). The most common cancers in male YAs were testicular cancer (33%), melanoma (15%), gastrointestinal cancer (8%), Non-Hodgkin and Hodgkin lymphoma (both 7%), whereas in females breast cancer (34%), melanoma (19%), gynecological (14%), thyroid and gastro-intestinal cancer (both 5%) were most frequently diagnosed. Over time, the five-year relative survival increased significantly from 72% to 85%. Survival improved for almost all tumor types, except for pediatric tumors: medulloblastoma (~60%), Ewing sarcoma (~43%) and rhabdomyosarcoma (~41%). A $<$ 80% five-year survival rate was also found for tumors of the lung (36%), gastro-intestinal tract (61%), ALL (60%), AML (65%) and soft tissue sarcomas (77%). **Conclusions:** Over the last 26 years, a marked increase in the incidence of a diverse spectrum of hematological and solid malignancies, pediatric and adult-type cancers was found for YAs. Survival improved over time, however remains poor for certain tumor types. Our data underpin the importance of knowledge of tumors at YA age to guide centralization of care and clinical research.

1568 Poster Session (Board #226), Mon, 1:15 PM-4:45 PM

The age specific genomic landscape of cancer. *First Author: Caitlin F. Connelly, Foudation Medicine, Inc., Cambridge, MA*

Background: The frequency of genomic alterations in cancer is known to differ based on a patient's age. Many studies have characterized the genomic characteristics of pediatric cancers; however, less is known about how the genomic landscape of mutations changes with age in adult patients. Accurately characterizing these differences will help guide personalized treatment strategies and illuminate differences in the genetic etiology of cancer at different ages of onset. **Methods:** Comprehensive genomic profiling was performed on > 100,000 patients in the course of routine care for patients with predominantly relapsed, refractory or metastatic cancer. For 117 types of cancer with ≥ 100 cases, logistic regression was used to identify genomic features with statistically significant dependence on patient age. **Results:** Many known associations with age were identified, including increased prevalence of BRCA1/2 mutations in younger breast and ovarian cancer patients and increased prevalence of mismatch repair mutations in younger colorectal and endometrial adenocarcinoma patients. In lung adenocarcinoma, we identified 19 genes for which alteration prevalence was significantly associated with patient age. The genes *ALK, ROS1,* and *RET* were more commonly altered in younger patients, *KRAS* and *MET* were altered more frequently in older patients, and *TP53* was most frequently altered at intermediate ages (40-60). Interestingly, a set of genes that have previously been associated with clonal hematopoiesis (CH) were found to be more frequently detected in older patients across a wide variety of cancer types. Based on the statistical power provided by this large cohort, several novel age based differences in gene alteration rates across multiple tumor types were detected and will be presented. **Conclusions:** Clear differences in genomics based on patient age were observed. This methodology can be used to identify novel associations between germline alterations and cancer types and somatic alterations that occur predominantly in young or elderly patients. These results also highlight the importance of accurately identifying and properly reporting somatic CH mutations during tumor genomic profiling.

1569 Poster Session (Board #227), Mon, 1:15 PM-4:45 PM

Association of dietary fiber intake and gut microbiota in healthy adults. *First Author: Daniel Lin, NYU Langone Medical Center, New York, NY*

Background: Increasing evidence has shown that gut microbiota alterations may play a role in colorectal cancer risk. Diet, particularly fiber intake, may modify gut microbiota composition, which may consequently impact cancer risk development. We investigated the relationship between dietary fiber intake and gut microbiota in healthy humans. **Methods:** Using 16S rRNA gene sequencing, we assessed gut microbiota in fecal samples from 151 healthy adults in two independent study populations: Study A, n = 75 (healthy controls from a colorectal cancer case-control study), and Study B, n = 76 (polyp-free subjects from a cross-sectional colonoscopy study). We calculated energy-adjusted total dietary fiber intake of participants based on food frequency questionnaires. For each study population, we evaluated the relationship between quartiles of higher fiber intake as a continuous ordinal variable, and global gut microbiota community composition (via PERMANOVA of weighted UniFrac distance) and specific taxon abundance (via DESeq2). **Results:** We found that fiber intake was significantly associated with overall microbial community composition in Study B ($p = 0.003$) but not Study A ($p = 0.68$), after adjustment for age, sex, race, body mass index, and cigarette smoking. In a taxonomy-based meta-analysis of these two study populations, higher fiber intake was associated with lower abundance of genus *Actinomyces* (fold change [FC] = 0.769, p = 0.003), and higher abundance of genera *Faecalibacterium* (FC = 1.153, p = 0.03), *Lachnospira* (FC = 1.167, p = 0.04), and *SMB53* (FC = 1.201, p = 0.05). A species-level meta-analysis showed an association between higher fiber intake and higher abundance of *Faecalibacterium prausnitzii* (FC = 1.165, p = 0.03) and lower abundance of *Ruminococcus bromii* (FC = 0.828, p = 0.08). **Conclusions:** Our results suggest that higher intake of dietary fiber may alter gut microbiota in healthy adults. Given the potentially modifiable nature of the gut microbiota through diet, these findings warrant further study of diet-microbiota based colorectal cancer prevention strategies.

1570 Poster Session (Board #228), Mon, 1:15 PM-4:45 PM

The epidemiology of metaplastic breast cancer: A review of 2,500 cases from the national cancer database. *First Author: Brittany Morgan Campbell, Duke University School of Medicine, Durham, NC*

Background: Metaplastic breast cancer (MBC) is a rare, aggressive, sarcomatoid breast cancer that was first described in 1973 but only became recognized as a histologically distinct entity in 2000. Given the paucity of data on the epidemiology of MBC, we performed a population-based analysis to delineate sociodemographic and clinicopathological characteristics associated with increased likelihood of MBC diagnosis. **Methods:** Adult female breast cancer patients with stage I-III MBC and non-MBC histology diagnosed between 2010 and 2013 were identified in the National Cancer Database (NCDB). Multivariate logistic regression was used to identify factors associated with diagnosis of MBC, and Cox proportional hazards modeling was used to estimate the effect of MBC on overall survival. **Results:** 2,451 MBC and 568,057 non-MBC patients were identified. After adjusting for receptor status (ER, PR, HER2), age, stage, grade, and treatment variables, MBC patients had worse survival than non-MBC patients (HR 1.45, $p < 0.001$). Compared to non-MBC patients, a higher proportion of MBC patients were non-Hispanic black (16.7% vs 10.5%), had an annual income < $35k (29.0% vs 25.5%), had lower high school completion rates (36.7% vs 33.9%), were treated at academic centers (35.5% vs 30.8%), and had government-sponsored insurance (48.8% vs 43.7%, all $p < 0.01$). MBC diagnosis was more likely in patients with triple-negative breast cancer (OR 20.71), higher clinical T stage (cT4 vs cT1: OR 6.18), and lower clinical N stage (cN1 vs cN0: OR 0.38, all $p < 0.001$). MBC patients were also more likely to be diagnosed based on pathology from their first operation rather than preoperatively (OR 1.41, $p < 0.001$). **Conclusions:** Black women and women of low socioeconomic status were at increased risk for diagnosis with MBC. Though MBC was more likely to be treated at academic centers, MBC was less likely to be diagnosed prior to surgical intervention. Many of the sociodemographic factors associated with MBC have also been associated with triple-negative breast cancer. Additional research is needed to determine the contribution of sociodemographic factors to the epidemiology of MBC independent of receptor status.

1571 Poster Session (Board #229), Mon, 1:15 PM-4:45 PM

PD-L1 expression in patients with metastatic gastric cancer in South Korea. *First Author: Hyo Song Kim, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea*

Background: Data are limited and conflicting regarding programmed death ligand 1 (PD-L1) expression as prognostic of clinical outcomes in patients (pts) with metastatic gastric cancer (mGC) treated with standard of care (SOC). Factors affecting the association between PD-L1 expression and outcomes include type of assay and antibody, scoring system for PD-L1 expression, and method of tissue collection. We analyzed the association between tumor PD-L1 expression and clinical parameters in Korean pts with inoperable mGC. **Methods:** A retrospective study was performed in 201 pts with inoperable mGC from Yonsei Cancer Center in Seoul, South Korea. Biopsy samples were collected at diagnosis. Tumor PD-L1 expression was measured by IHC using the 22C3 PD-L1 antibody pharmDx kit (Dako North America, Carpinteria, CA, USA). PD-L1 positivity was defined as a combined positive score (CPS) of ≥1%, where CPS is PD-L1$^+$ cells (tumor cells, macrophages, lymphocytes) over the total number of tumor cells, expressed as a percentage. Survival was analyzed using Kaplan-Meier methods, log-rank test, and Cox proportional hazards models, adjusting for age, sex, and ECOG performance status. **Results:** A total of 189/201 (94%) pts received chemotherapy as SOC and were included in this analysis. Median age was 56 years (range, 21-82), 37% of pts were women, and 28% had a BMI ≥24. All pts had stage IV metastatic disease and 27%, 49%, and 24% had well to moderately differentiated, poorly differentiated, and signet ring cell tumors, respectively. Prevalence of PD-L1 positivity was 72.5%. PD-L1 positivity was not associated with age, BMI, or histologic grade. Median overall survival (OS) for the PD-L1$^+$ and PD-L1$^-$ groups was 10.9 and 10.2 months, respectively (P= 0.92). The hazard ratio for the PD-L1$^+$ vs the PD-L1$^-$group was 1.02 (95% CI, 0.74-1.39) before adjusting for age, sex, and ECOG performance status and 1.08 (95% CI, 0.77-1.51) after adjusting. **Conclusions:** Based on this preliminary assay and cutoff, results suggest that PD-L1 expression is not a prognostic factor for mGC. Additional biomarker analyses (eg, immune gene expression profile and microsatellite instability) are planned.

1572 Poster Session (Board #230), Mon, 1:15 PM-4:45 PM

BROCA gene panel testing in African descendants from northeastern Brazil: Genetic susceptibility profile of an admixed population. *First Author: Gabriela Espirito Santo Felix, Centro de Pesquisas Gonçalo Moniz, Fundação Oswaldo Cruz Bahia, Salvador, Brazil*

Background: The rising global burden of breast cancer (BC) in developing countries demands innovative interventions to accelerate progress in cancer control and prevention. Given the high rates of aggressive young onset breast cancer in Brazil, we sought to examine genetic susceptibility to the disease in the State of Bahia in the Northeast of Brazil, which has the largest population of African descendants. **Methods:** We screened cases, high-risk breast cancer patients with and without family history of breast cancer, and controls (cancer-free women) for twenty-eight breast cancer susceptibility genes using a validated targeted capture and multiplex sequencing approach – the BROCA panel. Each participant gave informed consent under IRB approved protocols and provided clinical-pathological and epidemiological data. **Results:** A total of 292 consecutive and unrelated individuals (173 cases and 119 controls) were included. Nearly 2/3rds of the cases (116/173) and about 90% of the controls (108/119) self-reported as African-descendant. Mutations considered pathogenic were identified in 37 (21.4%) cases and in one control (0.84%, RAD51C c.266insA), OR = 27.75 and p = 0.008. The mutated genes in cases were *BRCA1* (in 12 patients), *BRCA2* (10), *ATM* (3), *PALB2* (3), *BRIP1* (3), *BRCA2*/*BARD1* (1), *FAM175A* (1), *FANCM* (1), *NBN* (1), *SLX4* (1) and *TP53* (1). Three recurrent mutations accounted for 12.4% (9/37) of the total: 3 *BRCA1* c.3331_3334delCAAG (known European mutation), 3 *BRCA1* c.211A > G (known Galician mutation), and 3 *PALB2*c.1671_1674delTATT (novel mutation). **Conclusions:** Mutations in *BRCA1* and *BRCA2* (64.85%) or another breast cancer gene (35.15%) occur in one in five high-risk breast cancer patients in the largest study of Northeastern Brazil to date, and a significant proportion were recurrent mutations of European origin, which can be explained by the admixture pattern of the Brazilian population. This result underscores the importance of using multigene panel in cancer genetic epidemiologic research of understudied populations where unexpected findings, such as the recurrent and novel variant in *PALB2* c.1671_1674delTATT, can be detected.

1573 Poster Session (Board #231), Mon, 1:15 PM-4:45 PM

Smoldering Waldenström's macroglobulinemia (SWM): Analysis from the National Cancer Database (NCDB). *First Author: Priyanka Avinash Pophali, Hematology and Medical Oncology, Mayo Clinic, Rochester, MN*

Background: There are no epidemiologic studies of SWM due to lack ofICD codes specific for smoldering status. **Methods:** The NCDB represents ~70% of cancer cases in the US. It records the time to initial treatment or reasons for not receiving treatment. Using the 2004-2012 database, we estimated the overall proportion of new adult WM cases that are smoldering and analyzed outcomes according to socio-geo-demographic subgroups. Patients who were recommended treatment (irrespective of administration status) or died within 120 days of diagnosis were considered to have active WM while those who did not require treatment and had follow-up ≥120 days after diagnosis were considered to have SWM. **Results:** 2322 (28%) of 8302 patients diagnosed with WM were SWM. Median age at diagnosis was 71 (range 28-90) years. Median age did not change significantly during 2004-2012 (P = 0.83) but the proportion of smoldering disease decreased with time (P = 0.02). The proportions of SWM according to socio-geo-demographic subgroups are shown in the Table. Conditional survival (given survival to 4 months) at 5-years was 66% vs. 70% and at 10-years was 38% vs. 46% for active WM vs. SWM, respectively. The OS for SWM was significantly better among females and those who were younger, privately insured, with less co-morbidities and residing closer to a health facility. However, the OS did not differ by racial groups or era of diagnosis 2004-2008 vs 2009-2012. On multivariate analysis, sex, age group and co-morbidity index were significant factors affecting OS while race, insurance, distance from health facility and era of diagnosis were not. **Conclusions:** Approximately 28% of WM cases in the US are smoldering at diagnosis. The prevalence of SWM varied among socio-geo-demographic subgroups. Sex, age and co-morbidities significantly affect survival of SWM.

	Proportion of SWM	P-value
Sex	Males : 27.72% Females : 28.31%	0.13
Race	White, non-hispanic : 28.97% White, Hispanic: 24.79% Black : 21.01% Asian: 20.41% Other: 26.08%	0.0007
Age	18-49: 18.32% 50-64 : 25.91% 65-79 : 30.8% ≥80 : 27.26%	< 0.0001
Charlson/Deyo Score	0 : 29.43% 1 : 21.39% ≥2 : 22.10%	< 0.0001
Travel distance (miles)	< 12.5 : 28.84% 12.5-49.9 : 26.21% ≥ 50 : 28.18%	0.0005

1575 Poster Session (Board #233), Mon, 1:15 PM-4:45 PM

Major stressful life events and risk of developing lung cancer. *First Author: Syed Hasan Raza Jafri, The University of Texas, Houston, TX*

Background: Lung cancer is the leading cause of cancer-related mortality linked with smoking, though only 6-18% of heavy smokers die of lung cancer. We hypothesized that major stressful life events are a risk factor for developing lung cancer. **Methods:** In our matched case-control study, cases (CA) were lung cancer patients diagnosed within past 12 months. Controls (CO) were patients without a prior history of malignancy. CA and CO were matched for age, gender and smoking status. Smokers had at least 10 packs/years history of smoking. Data was collected using standardized research questionnaire on 11 major stressful life events using Holmes and Rahe stress scale. The primary endpoint was odds of having a major stressful life event. A sample of 360 patients (120 CA and 240 CO), was needed to achieve 80% power to detect an odds ratio (OR) of 2.00 using Chi-Square test with a P = 0.05 significance. The study was IRB approved at each institution. **Results:** Between May 2015 and December 2016, 324 patients were enrolled (23 were excluded due to prior cancer history or incomplete information). 301 (CA = 102; CO = 199) were included in the final analysis. The two groups were well matched in median age (CA = 64.4 years; CO = 63.9years), gender (CA-Male = 48%; CO-Male = 49.2%) and smoking status (ever smoker, CA = 86%; CO = 85%). There was no difference in lifetime stressful life event between CA and CO (95% vs 93.9% P = 0.68%). However, CA were significantly more likely to have had a major stressful life event within the past 5 years than controls (CA = 77.4% vs CO = 65.8%, P = 0.03, (OR = 1.78). Serious life-threatening illness of an immediate family member (P = 0.04) and retirement (P = 0.07) within the past 5 years were noticeably more common among CA. Holmes-Rahe stress score in the last 5 years was higher in men (86.3 vs 63.3, P = 0.07) and those > 65 years old (82.4 vs 57.2,P = 0.04) as compared with CO and in those with squamous histology than with adenocarcinoma (115.6 vs 63.4, P = 0.005). **Conclusions:** Patients with lung cancer (CA) were significantly more likely to have had a major stressful life event within the past 5 years than the matched controls (CO), especially in older men with squamous histology. Major stressful life events should be considered a risk factor for developing lung cancer.

1576 Poster Session (Board #234), Mon, 1:15 PM-4:45 PM

Safety of multiplex gene testing for inherited cancer risk in a fully accrued prospective trial. *First Author: Allison W. Kurian, Stanford School of Medicine, Stanford, CA*

Background: Sequencing more genes increases the chance of finding a pathogenic mutation and/or a variant of uncertain significance (VUS). Little is known about potential harms of multiplex testing for cancer risk, such as unwarranted surgery or adverse psychological effects. **Methods:** We conducted a prospective trial of sequencing 25 genes*: APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*. Patients were eligible if they met standard testing guidelines or predictive models estimated ≥2.5% mutation probability. Participants were surveyed 3 months post-test: the Multidimensional Impact of Cancer Risk Assessment (MICRA) scale measured distress, uncertainty and positive experiences. We report on the fully accrued trial (N = 2000). **Results:** 1998/2000 (99.9%) participants currently have reported results: 12.1% tested positive for a pathogenic mutation (Pos), 34.5% had VUS only and 53.5% tested negative (Neg). Median age was 51, 81% were female, 40% Hispanic, and 72% had a cancer history. Self-reported preventive surgery rates were low (mastectomy 9.3%, hysterectomy 1.5%, oophorectomy 1.6%), with no difference between VUS and Neg patients (p = 0.346). Most patients never or rarely had thoughts of cancer affecting daily activities (Pos 59.5%, VUS 66.9%, Neg 71.0%), never regretted testing (Pos 84.1%, VUS 90.0%, Neg 93.6%), and wanted to know all results, even those that doctors do not fully understand (Pos 81.7%, VUS 78.8%, Neg 77.1%). Pos patients had higher MICRA distress and uncertainty scores than VUS and Neg patients, whose distress and uncertainty scores did not differ significantly (p = 0.165, p = 0.129). Relatives of Pos patients completed genetic testing (30.4%) more often than VUS (5.8%) or Neg patients (5.1%, p < 0.001). **Conclusions:** After multiplex testing of 2000 diverse patients, few reported preventive surgery at 3 months; VUS patients had no more distress, regret or uncertainty than Neg patients. Pos patients most often advised relatives to test, suggesting that participants understood the implications of test results. Longer-term follow-up of test-related outcomes is underway. Clinical trial information: NCT02324062.

1577 Poster Session (Board #235), Mon, 1:15 PM-4:45 PM

Determining the clinical value of germline genetic testing coupled with tumor mutation profiling. *First Author: Edward Esplin, Invitae, San Francisco, CA*

Background: Somatic mutation analysis by next-generation sequencing (NGS) is an expanding clinical assessment offered to cancer patients. Studies report that 4–12% of patients have a positive tumor mutation profiling (TMP) result in a known cancer predisposition gene also identified in their germline, which has potential implications for the patient's acute treatment, ongoing surveillance, and the screening of family members. We report a series of patients with TMP coupled with germline genetic testing and include yield of pathogenic germline mutations, discordance between germline and TMP findings, and potential clinical impact. **Methods:** Our study used de-identified data from 182 consecutive patients who underwent TMP followed by germline testing with an NGS-based hereditary cancer gene panel. **Results:** 50/182 cases (27%) had one or more likely pathogenic or pathogenic (LP/P) germline variants, which is higher than previous reports. Among these 50, 28 (56%) met guidelines for germline testing by personal or family history criteria, 10 (20%) met recently established NCCN criteria for germline testing of patients with BRCA1/2 tumor variants, and 12 (24%) had TMP results that suggested a germline mutation but did not meet any guidelines for germline testing. We identified 52 LP/P germline variants in BRCA2 (17), BRCA1 (7), PALB2 (6), MUTYH (5), CHEK2 (2), and 15 other genes, all with established guidelines that would impact the clinical management of patients and their family members. In 9/50 cases, germline testing revealed variants that were absent in TMP results and provided new information with clinical implications for patients and their families, including variants in BRCA1 and CHEK2. **Conclusions:** In TMP patients, 50 of 182 had a medically actionable germline mutation with established management guidelines. Among these 50, 12 (24%) met neither current personal or family criteria nor the latest NCCN guidelines for germline testing in patients with TMP. Also striking were nine patients whose germline LP/P mutations were absent in TMP results. These data suggest that indications for germline testing of cancer patients must be expanded to avoid missing important germline findings in patients undergoing TMP.

1578 Poster Session (Board #236), Mon, 1:15 PM-4:45 PM

Does race play a role in genetic screening for hereditary cancer syndromes? *First Author: Sudeshna Chatterjee, New York Presbyterian Hospital, Weill Cornell Medical College, New York, NY*

Background: Molecular analysis of cancer predisposition genes may influence cancer screening, prevention strategies and options for targeted therapy. We sought to identify ethnic differences in patterns of genetic testing. **Methods:** Results of all patients with known ancestry who underwent genetic testing at the hereditary breast and ovarian cancer center at a single institution between 7/1/2013-12/31/2016 were reviewed. Race was stratified as Black, White, Asian, and Hispanic. Ashkenazi Jews were excluded from the White subgroup because of their higher rates of testing for deleterious founder mutations. White patients were utilized as the reference population for all statistical analysis. **Results:** 894 patients were included: 139 Black, 613 White, 33 Hispanic and 108 Asian. Black patients were more likely to undergo genetic testing for a personal history of cancer rather than family history risk assessment compared to White patients ($p = 0.002$). There was no difference in genetic testing rates based on personal or family history of cancer between Asians or Hispanics and Whites ($p = 0.398$;$p = 0.366$). Black patients were more likely than White patients to undergo testing with targeted-gene rather than multigene panels ($p = 0.026$). The use of targeted and multigene panels were not different among Asians or Hispanics ($p = 1.0$). Blacks, Asians and Hispanics had a lower rate of known deleterious mutations but a higher rate of variants of unknown significance (VUS) than Whites (15.1% $p = 0.048$; 22.2% $p = .001$; 33.3%$p = .002$ respectively). *BRCA1/2* mutations accounted for 100% of identified mutations across all the non-White populations. Among Blacks, *BRCA1/2* accounted for 38.1% of VUS compared to 27.9% in Whites ($p = .2114$). VUS in the *ATM* gene accounted for 28.6% in Blacks compared to 8.2% in Whites ($p = 0.028$). **Conclusions:** Black patients were less likely to undergo testing based on family history, suggesting a missed opportunity for cancer prevention. They were more likely to undergo targeted testing and100% of identified mutations were in *BRCA1/2* genes. Non-white patients had higher rates of VUS, emphasizing the need for improved VUS reclassification in non-White populations.

1579 Poster Session (Board #237), Mon, 1:15 PM-4:45 PM

Development and validation of a residual risk score to predict breast cancer risk in unaffected women negative for mutations on a multi-gene hereditary cancer panel. *First Author: Elisha Hughes, Myriad Genetics, Inc., Salt Lake City, UT*

Background: Women who are unaffected with cancer but have a significant family history of breast cancer (BC) are frequently referred for hereditary cancer testing with multi-gene panels; however, $< 10\%$ test positive for clinically actionable mutations. Large-scale genotyping studies have identified common variants (primarily single-nucleotide polymorphisms) that individually confer modest BC risk, but together may explain the genetic susceptibility for BC in many women without monogenic mutations. Here, we describe the development and validation of a polygenic residual risk score in a large, consecutive cohort of women who tested negative for mutations in known BC susceptibility genes. **Methods:** This IRB-approved study includes women of European ancestry tested with a multi-gene hereditary cancer panel who were negative for mutations in 11 genes associated with BC (*BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, PALB2, CHEK2, ATM, NBN, BARD1*). Clinical information was collected from provider-completed test request forms. The dataset was divided into a training (July – November 2016) and validation cohort (November 2016 – April 2017). Multivariable logistic regression models were used to evaluate 94 common variants and develop candidate residual risk scores as predictors of personal BC history (invasive ductal carcinoma, IDC) in the training cohort. Independent variables included age, personal/family cancer history, and ancestry. An optimal subset of the 94 common variants and a residual risk score will be selected through cross-validation followed by independent validation. **Results:** The training cohort includes 11,838 women (median age 47 years), 18% of whom reported a personal history of IDC and 36% of whom reported BC in a first-degree relative. Results from validation of the residual risk score in an independent cohort of approximately 12,000 women will be completed at the time of presentation. **Conclusions:** The validation and clinical implementation of a residual risk score for women at risk for hereditary BC may offer significant potential for the management of high-risk, unaffected women who test negative for monogenic BC mutations.

1580 Poster Session (Board #238), Mon, 1:15 PM-4:45 PM

Patterns of genetic screening for hereditary cancer syndromes: Effect of Supreme Court's ruling invalidating single gene patent rights. *First Author: Zhen Ni Zhou, New York Presbyterian Hospital, Weill Cornell Medical College, New York, NY*

Background: In 6/2013 the Supreme Court ruled that isolated DNA sequences found in nature could not be patented, resulting in rapid uptake of multigene panels. We sought to explore trends in genetic testing since this ruling. **Methods:** Results of all patients undergoing genetic testing and counseling at a single institution between 7/1/13 and 12/31/16 were reviewed. Associations between categorical variables were evaluated by chi-square tests or Fisher's exact tests as appropriate for category size. **Results:** 1663 patients underwent genetic testing over the study period. The median age was 49 years (range 18-86). Use of multigene panels versus targeted gene testing increased significantly in the years following the Supreme Court ruling (Table 1, $P<0.001$). While the percentage of patients found to have pathogenic mutations remained stable over the study period (9%), detection of variants of uncertain significance (VUS) increased significantly (Table 1, $P<0.001$). In 2013 *BRCA1/2* mutations accounted for 91% of identified mutations; however this number decreased over time (2014-83%, 2015-70%, 2016-58%, P=0.01). Use of multigene panels detected 71% of mutations in non-*BRCA1/2* genes such as *CHEK*(19), *APC* (44), *MSH6*(1), *P53*(1), and *PTEN*(1). Patients with a personal history of breast and/or ovarian cancer were more likely to have targeted testing than patients with other cancer types (590, 66% vs. 9, 33%, P=0.001). **Conclusions:** The uptake of multigene panels has increased since the 2013 Supreme Court ruling. While this technology allowed for the identification of many cancer-related genes that would be missed on targeted *BRCA1/2* testing, it also resulted in a significantly increased detection of VUS, a finding with unknown clinical implications.

Percentage of patients undergoing single gene testing versus multigene panel testing and identified mutations versus variants of uncertain significance (VUS) following the Supreme Court invalidation of exclusive gene patents.

Year	Targeted gene testing (%)	Multigene panel testing (%)	Mutations detected (%)	VUS detected (5)
2013	92.5	7.5	9.9	2.3
2014	76.6	23.4	8.7	9.7
2015	61.7	38.3	6.6	13.1
2016	44.6	55.4	10.9	10.9

1581 Poster Session (Board #239), Mon, 1:15 PM-4:45 PM

Germline mutations in cancer predisposition genes among patients with thyroid cancer. *First Author: Junne Kamihara, Dana-Farber Cancer Institute, Boston, MA*

Background: Thyroid cancers are known component tumors of both well-described and emerging hereditary cancer syndromes. To assess the contribution of germline variants in thyroid cancer predisposition, we examined the prevalence of germline mutations among individuals with a history of thyroid cancer, compared to those with thyroid and breast cancer or breast cancer alone. **Methods:** Clinical histories and molecular results were reviewed for individuals with a history of thyroid and/or breast cancer, ascertained from a cohort of > 140,000 patients who underwent hereditary cancer multigene panel testing at a single commercial laboratory. Clinical history information was obtained from test requisition forms completed by ordering clinicians and from pedigrees/clinic notes, if provided. **Results:** Among 2,678 thyroid cancer patients, the majority were Caucasian (66.9%), female (92.3%), and/or had an additional cancer primary (71.9%), with nearly half reporting an additional breast cancer primary (49.1%). Among those with available pathology information, 4.1% had medullary thyroid cancer. The median (IQR) age at diagnosis was 38 (26,48) years, and while 94.1% had a family history of cancer, 78.8% had at least one affected 1st degree relative. Overall, 11.1% were identified as mutation carriers, defined as ≥1 pathogenic or likely pathogenic variant. Among those with thyroid cancer alone, 9.7% had a mutation, similar to those with breast cancer alone (9.7%) and those with breast and thyroid cancer only (10.5%). Genes most frequently mutated in the thyroid only group included *CHEK2* (3.1%), *MUTYH* (monoallelic) (2.4%), *APC* (2.0%), *ATM* (1.6%), and *PALB2* (1.2%). *CHEK2* was the most frequently mutated gene observed in all groups, with a higher frequency seen among those with thyroid and breast cancer (5.5%) compared to breast cancer (2.5%) or thyroid cancer (3.1%) alone ($p < 0.001$). **Conclusions:** A high rate of germline mutations is observed among individuals with thyroid cancer presenting for clinical genetic testing, even in the absence of other primary cancer diagnoses. Thyroid cancer may be an under-recognized component tumor of hereditary cancer predisposition syndromes suggesting the need for further investigation.

1582 Poster Session (Board #240), Mon, 1:15 PM-4:45 PM

Melanoma genetic testing to promote reductions in tanning: Results from the Utah BRIGHT project. *First Author: Lisa Aspinwall, University of Utah, Salt Lake City, UT*

Background: Predictive genetic testing for familial cancer may alert people to highly elevated risk prior to disease onset. Genetic test reporting has been shown to improve uptake of prophylactic screening and procedures, but whether test reporting also promotes increased performance of primary preventive behavior is unknown. **Methods:** Unaffected adult participants (N= 124) from high-risk melanoma families, ages 16-69 (mean = 35.24, 52% men) were enrolled. Participants from families that carried a *CDKN2A/p16* mutation received a personal genetic test result *and* counseling about management recommendations whereas control participants from families without a *CDKN2A/16* mutation received equivalent counseling and management recommendations based on family history alone. Photoprotection outcomes were compared between *CDKN2A/p16* participants (31 carriers, 44 noncarriers) and the no-test control group (n= 49), allowing the effects of receiving a genetic test result to be distinguished from the effects of counseling alone. Assessments were seasonally timed to capture tanning during the summer months. Melanin Index (MI) scores, measures of skin tanning obtained through reflectance spectroscopy, were assessed at the dorsal wrist and face. Tanning of the dorsal wrist and face were calculated by subtracting baseline MI scores at an unexposed site on the same individual. **Results:** Multilevel model analyses examined changes in tanning over time while controlling for clinician-rated skin type, age, gender, date of assessment, and group differences in phenotypic factors and family medical history. Participants who received positive test results were significantly less tan at the wrist one year after their previous summer baseline (b= -.11, p< .001). No-test controls and noncarriers had no change in tanning. The magnitude of decrease in tanning measurements observed among *CDKN2A/p16* carriers approximated one skin type. Facial tanning did not differ from baseline for any group. **Conclusions:** A positive melanoma genetic test result promotes reduced UVR exposure. Future research should examine why positive genetic test reports were more motivating to patients than equivalent counseling based on family history.

1583 Poster Session (Board #241), Mon, 1:15 PM-4:45 PM

BRCA1 and BRCA2 mutations in ovarian cancer patients from China: Association of ethnic-specific mutations in BRCA1 with an increased risk of ovarian cancer. *First Author: Tingyan Shi, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: *BRCA1/2* are cancer predisposition genes involved in hereditary breast and ovarian cancer (HBOC). Mutation carriers display an increased sensitivity to inhibitors of poly (ADP-ribose) polymerase (PARP). Despite a number of small-size hospital-based studies being previously reported, there is not yet, precise data of *BRCA1/2*mutations among Chinese epithelial ovarian cancer (EOC) pts. **Methods:** We performed a multicenter cohort study including 916 unselected consecutive EOC pts from eastern China, to screen for *BRCA1/2*mutations using the next-generation sequencing approach. **Results:** 153 EOC pts were found to carry pathogenic germline mutations in *BRCA1/2*, accounting for an overall mutation incidence of 16.7% with the predominance in *BRCA1* (13.1%) compared with *BRCA2* (3.9%). We identified 53 novel pathogenic mutations, among which the c.283_286delCTTG and the c.4573C>T of *BRCA1* were both found in two unrelated patients. More importantly, the most common mutation, c.5470_5477del8 was most likely to be Chinese population-related without an apparent founder origin. This hot-spot mutation was presumably associated with an increased risk of EOC. Taken together, germline *BRCA1/2*mutations were common in Chinese EOC pts with distinct mutational spectrum compared to Western populations. **Conclusions:** Our study contributes to the current understanding of *BRCA1/2* mutation prevalence worldwide. We recommend *BRCA1/2*genetic testing to all Chinese women diagnosed with EOC in order to identify HBOC families, to provide genetic counselling and clinical management for at-risk relatives. Mutation carriers may also benefit from PARP-targeted therapies.

	Total (%)	Mutation (%)	P	Pathogenic mutation (%)	P
Cases	916 (100)	194 (21.8)		153 (16.7)	
Histology			0.005		0.004
Serous	726 (79.3)	163 (22.5)		131 (18.0)	
Clear cell	51 (5.6)	2 (3.9)		1 (2.0)	
Endometrioid	49 (5.3)	12 (24.5)		9 (18.4)	
Mucinous	38 (4.1)	2 (5.3)		0	
Transitional cell	6 (0.7)	2 (33.3)		1 (16.7)	
Mixed	4 (0.4)	0		0	
Adenocarcinoma	41 (4.5)	13 (31.7)		11 (26.8)	
Undifferentiated	1 (0.1)	0		0	
HBOC-related tumor			<0.001		<0.001
Yes	84 (9.2)	43 (51.2)		39 (46.4)	
No	832 (90.8)	151 (18.1)		114 (13.7)	

1584 Poster Session (Board #242), Mon, 1:15 PM-4:45 PM

Unexpected germline mutations in a pan-cancer analysis including sarcoma, renal, and other cancers. *First Author: Shan Yang, Invitae, San Francisco, CA*

Background: Multi-gene testing for cancer predisposition is increasingly utilized in clinical care. Although the diagnostic yield and management implications of such testing in breast, ovarian and colorectal cancer are relatively well understood, data for other cancer types are still emerging. In this study we retrospectively examined 39,147 patients referred for hereditary cancer syndrome testing for pathogenic germline variants in 80 cancer risk genes, focusing on those patients with renal, sarcoma, paraganglioma, melanoma, and pancreatic cancers. **Methods:** Test results and personal/family history were extracted from a sequential series of de-identified clinical test reports. Data for genes not clinically ordered were analyzed under an IRB approved research protocol. Common low penetrance risk alleles were excluded. **Results:** Overall, 14.3% (5,589) of patients carried germline pathogenic mutations in 80 cancer risk genes. Of the 949 patients with renal cancer 20% (190) were positive, and 44% of these findings were "unexpected", meaning they appeared in genes that are not commonly requisitioned in renal cancer patients. Of the 423 sarcoma patients, 16% (68) had positive findings, 45% of which were "unexpected". For both cancer types, greater than 90% of these "unexpected" findings were in genes with published management recommendations. Similar results were observed in melanoma, paraganglioma and pancreatic cancer patients. A second or third pathogenic variant, many of which were also "unexpected", were found in 3.6% of positive cases. **Conclusions:** In this series of patients we estimate almost 12% of pathogenic variants across cancer indications are "unexpected". These data suggest many actionable pathogenic variants are being missed due to adherence to overly restrictive, narrowly constructed tumor-specific panels. Clinicians should expand the scope of their test panels in order to capture variants with the potential to impact patients and their family members by informing implementation of established management guidelines.

1585 Poster Session (Board #243), Mon, 1:15 PM-4:45 PM

Are we still adjusting to multigene panel testing? An NCI-designated cancer center's 2-year experience. *First Author: Chethan Ramamurthy, Fox Chase Cancer Center, Philadelphia, PA*

Background: Genetic testing for hereditary cancer predisposition has rapidly changed over the past few years with the introduction of multigene panel testing. Multigene testing has evolved from disease-agnostic comprehensive (C) panels alone to include disease-specific but expanded (DSE) panels as well as guideline-based (GB) panels. We analyzed trends in utilization of genetic testing over a two-year period in one NCI-designated Cancer Center, hypothesizing that over time genetic testing usage would trend toward more disease-specific panels. **Methods:** We conducted a retrospective analysis of our program's database for all germline genetic tests ordered from 9/1/2013 to 8/31/2015 (n = 619; 246 in year 1, and 373 in year 2). Tests were categorized into three groups based on specificity: GB (range: 2-12 genes tested), DSE (12-35 genes tested), and C (28-80 genes tested). The Chi-square test was used to analyze test types ordered in year 1 (9/1/2013-8/31/2014) and year 2 (9/1/2014 – 8/31/2015) and the proportions of resulting mutation types. **Results:** A total of 604 germline genetic tests met the inclusion criteria: 39 GB (20 year 1, 19 year 2), 171 DSE (43 year 1, 128 year 2), and 394 C (180 year 1, 214 year 2). Compared to year 1, a larger proportion of DSE tests (35% v. 18%, $p < 0.001$), and a smaller proportion of C tests (59% v. 74%, $p < 0.001$) and GB tests (5% vs. 8%, $p = 0.146$) were ordered. DSE panels revealed a pathogenic variant (PV) at a rate of 16% and a variant of unknown significance (VUS) at a rate of 24%. C tests revealed a PV and VUS at rates of 14% and 29%, respectively. GB tests revealed a PV and VUS at rates of 21% and 18%, respectively. No statistically significant differences in detection rates of mutation types (PV or VUS) were found between GB, DSE, or C tests. **Conclusions:** The rates of PV detection were not significantly different between test types, but the profile of tests ordered changed over time to favor DSE panels. Exploration of factors contributing to changing trends in genetic testing are warranted as counselors and clinicians adapt to the quickly expanding number of genes associated with hereditary cancer risks, many of them moderate-risk, and the evolving landscape of multigene panel testing.

1586 Poster Session (Board #244), Mon, 1:15 PM-4:45 PM

Decision support for family history intake to determine eligibility for *BRCA* testing among multiethnic women. *First Author: Julia E. McGuinness, Columbia University College of Physicians and Surgeons Department of Medicine, New York, NY*

Background: The U.S. Preventive Services Task Force (USPSTF) recommends that women who meet family history criteria for hereditary breast and ovarian cancer (HBOC) be referred for genetic counseling. However, HBOC genetic testing is under-utilized, particularly among racial/ethnic minorities. We evaluated different methods of family history intake, including a validated family history screener, documentation in the electronic health record (EHR), and a web-based decision aid (DA). **Methods:** Among women undergoing screening mammography, we administered a validated family history screener to determine eligibility for *BRCA* genetic testing based upon USPSTF guidelines. We developed a patient-centered DA (*RealRisks*) which includes modules on breast cancer risk, collection of detailed family history, and information on HBOC genetic testing. Women who met high-risk criteria for breast cancer were enrolled in an intervention trial to determine whether exposure to *RealRisks* increases referrals for high-risk consultations. *BRCA* genetic counseling/testing uptake was assessed by self-report and EHR review. **Results:** From November 2014 to June 2016, 3077 women completed the family history screener. Median age was 59 years (range, 29-99), including 76% Hispanic, 4% Ashkenazi Jewish, and 60% with a high school education or less. 12% met family history criteria for *BRCA* genetic testing based upon the family history screener, of which only 5.9% had previously undergone genetic counseling or testing. Sixty high-risk women were enrolled to access *RealRisks*. When family histories based upon the screener, DA, and EHR were compared, 12 (20%) had discrepancies in number of affected relatives, type of cancer, and age at diagnosis which changed eligibility for *BRCA* testing. Follow-up is ongoing to determine whether the DA facilitates appropriate referrals for genetic counseling. **Conclusions:** In a population of predominantly Hispanic and less educated women, a large proportion met USPSTF family history criteria for *BRCA* testing, but uptake of genetic counseling was low. Developing decision support for accurate family history intake is critical to identifying appropriate candidates for genetic referrals.

1587 Poster Session (Board #245), Mon, 1:15 PM-4:45 PM

Remote genomic consultation to support uptake of a multi-gene genomic tumor panel (MGTP) by community oncologists (COs): Results of a pilot study. *First Author: Michael J. Hall, Fox Chase Cancer Center, Philadelphia, PA*

Background: MGTP use in routine cancer (CA) care is likely to increase w/lower costs for NGS-based testing and growing numbers of actionable targets coupled with targeted therapeutics. Early MGPT uptake has been slow among community oncologists (COs) due to their lower confidence to order, interpret, and act upon results of MGTP. This study evaluated the provision of telephone genomic consultation (GC) via an academic clinician link to an institutional genomic tumor board to support MGTP testing of CA patients (PTs) by COs. **Methods:** 4 practices of COs participated: 9 COs recruited 25 PTs w/metastatic CA. All PTs/COs completed baseline and follow-up (FU) assessments. Tumor blocks were evaluated at Fox Chase Cancer Center (FCCC) and tested w/a 50-gene MGTP. 12% blocks were inadequate. MGTP results were presented when appropriate at FCCC's Genomic Tumor Board. All MGTP yielded > 1 variant (Var) [range 1-6]: 13/22 (59%) pts tested had a clinically relevant V; 6 other Vars were potentially actionable w/ approved therapy, while 3 Vars have novel therapies in Phase I/II studies. MGTP were called out to COs (by MJH) < 2 wks of resulting. A tailored summary was provided to COs. **Results:** At baseline, COs (n = 9) had limited experience w/MGTP (78%, < 5 ordered). Barriers for COs were: poor understanding of MGTPs (67%), cost (89%), uncertain benefit (44%), and poor access to targeted therapies (67%). At FU, 4/8 (50%) COs found GC "very useful", and 63% reported MGPT paired w/GC would "probably/definitely" increase their use of MGTPs. Most (88%) felt MGPTs should be offered to PTs w/incurable CA. Among PTs at baseline (n = 25), awareness of MGTP was moderate (50%), but 79% reported it would help doctors take better care of their PTs. Valuation of MGTP was mixed—30% would pay $0 out of pocket, yet 30% also said they would travel "any distance" for an MGT-targeted experimental therapy. At FU (n = 14), 86% PTs felt MGPT was valuable, yet only 46% would "definitely" retest, and only 31% would pay > $100 to retest, even for 500+ genes. **Conclusions:** GC can be effective to support COs to use MGTPs. PTs w/CA have high expectations of MGTPs to improve their care, and yet attribute modest value to retest or to have a larger MGTP.

1588 Poster Session (Board #246), Mon, 1:15 PM-4:45 PM

VHVT: An ultra-sensitive somatic mutation detection and performance assessment program. *First Author: Jilong Liu, BGI-Shenzhen, Shenzhen, China*

Background: NGS as a high throughput technique is particular valuable for cancer given its ability to detect multiple driver mutations. While reads contain SNVs and short InDels can be mapped to the right position using gatk-like programs, a program designed for germline mutation detection, reads contain long InDels such as EGFR EX19 deletions often wrongly mapped especially when deletions near the ends of the reads. Thus, gatk would not recognize these reads, consequently underestimate the mutation allelic frequency, and even missed out InDels when supporting reads were rare. **Methods:** Here we present a variation hotspot validation toolkit (VHVT), a validation based method to precisely detect the ultra-low frequency somatic mutations. As far as we know, it is the first specialized somatic mutation detection software. First, reference sequences aimed at the hotspot mutations were assembled, then reads were be mapped to the new assembled reference to precisely distinguish the supporting reads. Moreover, log odds (LOD) and Poisson mathematical model were integrated to control sequencing error, as a result, VHVT can achieve a limitation of detection at 0.01% with sensitivity and specificity above 95% and 99% respectively. In addition, we developed a method to quantitatively assess the performance of variation detection program using standard reference data. By mapping to the reconstructed reference, all supporting reads will be detected in sequencing data, and comparing theses with the number of supporting reads delivered by a program we can define recognition ratio of supporting reads. **Results:** Our reference standard data showed that VHVT can recognize average 30% more support reads than gatk for EGFR EX19 deletions. In a total 498 NSCLC clinical samples test, VHVT detected actionable mutations in 289 samples. 243 positive mutations were verified (168 by SANGER sequencing, 75 by ddPCR) with concordance rate at 100%. **Conclusions:** Taken all together, our results demonstrated the robust performance of VHVT for somatic mutation detection and program assessment and thus facilitate the development of personalized cancer therapy.

1589 Poster Session (Board #247), Mon, 1:15 PM-4:45 PM

Assessment of BRCA testing uptake in ovarian cancer patients during the implementation of an oncologist-led genetic counseling model at an urban and suburban teaching hospital. *First Author: Jennifer Jorgensen, Montefiore Medical Center, Bronx, NY*

Background: *BRCA* testing has become an integral component of ovarian cancer management; however, low testing uptake remains an obstacle. This study evaluated the impact of an oncologist-led counseling and testing model on *BRCA* testing uptake. **Methods:** The ENGAGE study (NCT02406235) is a prospective study of an oncologist-led *BRCA* counseling and testing model in patients with epithelial ovarian, primary peritoneal and fallopian tube cancer (EOC). The United States lead accruing gynecologic oncology sites were Montefiore, an urban academic medical center; and Winthrop, a suburban teaching hospital. Oncologists were trained in *BRCA* counseling prior to site activation, and directly submitted patients' samples for *BRCA* testing. Prior to the ENGAGE study, EOC patients were referred to genetics professionals for counseling and testing. We determined the number of *BRCA* tests performed, and simple descriptive statistics were used to summarize the data. **Results:** A combined total of 141 EOC patients underwent BRCA testing during the 20 consecutive months analyzed. In the 10 months pre-ENGAGE, 8 Montefiore patients had *BRCA* testing, all submitted through the genetics division. Nineteen Winthrop patients had *BRCA* testing, 16 from their oncologist's office and 3 from an external genetics office. During the 10-month ENGAGE trial, 64 Montefiore patients and 50 Winthrop patients had *BRCA* testing. This represents a four-fold increase in *BRCA* testing uptake, with 114 patients tested during ENGAGE versus 27 patients tested pre-ENGAGE. Of these 114, 99 had *BRCA* counseling and testing through their oncologist's office. **Conclusions:** Implementation of an oncologist-led genetic counseling and testing model was associated with increased *BRCA* testing among ovarian cancer patients in both the urban and suburban hospitals. Increased *BRCA* testing could be related to increased patient convenience and standardized training of the clinical team. These findings may guide other institutions as they implement streamlined genetic counseling and testing protocols.

1590 Poster Session (Board #248), Mon, 1:15 PM-4:45 PM

Dissemination of universal genetic testing to three unique oncology care settings. *First Author: Erica Bednar, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Efforts are occurring across the United States to improve the rates of identification and standard of care genetic counseling (GC) and genetic testing (GT) of pts with breast and ovarian cancer. Following a successful quality improvement (QI) initiative to increase referrals and utilization of GC/GT among pts with breast and ovarian cancer to >80% at our host site (HS), we sought to disseminate the QI project to three unique oncology care settings (OCS). **Methods:** The OCS described in the Table are certified members of the HS network, were strategically identified, and agreed to participate in the QI project. Genetic counselors at the HS and OCS built teams to plan and initiate the project. A 130-item environmental scan was created by the HS team to assess OCS structure, resources, and GC/GT processes. OCS teams completed the environmental scan and a semi-structured interview with the HS; and from this, barriers to GC/GT were identified, then categorized using Ishikawa diagrams. Clinical interventions were designed to address these barriers. Resulting QI protocols follow the PDSA-cycle QI model. A database was built for retrospective and prospective data collection of eligible pts and rates of GC/GT referral and completion from 2015-2018. **Results:** Although unique barriers were identified at each OCS, all identified: pt referral/scheduling issues, technology and electronic medical record system inefficiencies, and inconsistent physician referral/GT practices. OCS interventions include: implementation of physician-coordinated GT, GC within chemo infusion suites, physician education sessions, GC scheduling improvements, creation of pt education documents, and development of referral tracking processes. **Conclusions:** Genetic counselors collaborated, planned, and initiated dissemination of a QI project to improve GC/GT utilization at three unique OCS. QI interventions were developed to address the unique environment and barriers at each OCS.

OCS demographics.

	OCS		
State	**Indiana**	**Georgia**	**Ohio**
Certified Member Hospitals	5	4	7
Hospital Beds	1594	1028	2504
Certified Oncology Physicians	38	36	68
Cancer GC Clinic Locations as of 8/2016	4	2	5
Cancer Genetic Counselors as of 8/2016	2.8	3	5

TPS1591 Poster Session (Board #249a), Mon, 1:15 PM-4:45 PM

ASAMET: A randomized, 2x2 biomarker prevention trial of low-dose aspirin and metformin in colorectal cancer. *First Author: Marilena Petrera, Division of Medical Oncology, E.O. Galliera Hospital, Genoa, Italy*

Background: Epidemiological studies and cardiovascular prevention trials have shown that low-dose aspirin (ASA) can inhibit colorectal cancer (CRC) incidence and mortality, including inhibition of distant metastases. Metformin (MET) has also been associated with decreased CRC incidence and mortality in meta-analyses of epidemiological studies in diabetics and has been shown to decrease by 40% colorectal adenoma recurrence in a randomized trial. Recent studies have shown that ASA is an inhibitor of mTOR/S6K1 and an activator of AMPK, targeting regulators of intracellular energy homeostasis and metabolism, and that the combination of ASA and MET, another AMPK activator and S6K1 inhibitor, has a striking additive effect on AMPK activation and mTOR inhibition, with increased autophagy and decreased cell growth in CRC cell lines. While both drugs are being tested as single agents, their combination has not been tested in clinical trials. **Methods:** This is a randomized, placebo-controlled, double-blind, 2x2 biomarker trial of ASA and MET to test the activity of either agent alone and the potential synergism of their combination on a set of surrogate biomarkers of colorectal carcinogenesis. After surgery, 160 patients with stage I-III CRC will randomly be assigned in a 4-arm trial to either ASA, 100mg qd, MET 850mg bid, their combination, or placebo for 1 year. The primary endpoint is the change, defined as the difference between pre- and post-treatment expression, of NFκBin the unaffected mucosa of proximal and distal colon obtained by multiple biopsies in paired colonoscopies one year apart. Additional biomarkers will include: 1) the genomic profile of candidate genes, pathways, and overall genomic patterns in tissue biopsies by genome-wide gene expression arrays; 2) the IHC expression of tissue pS6K, p53, beta-catenin, PI3K; 3) the associations of mutations and SNPs with treatment response by NGS of primary tumors; 4) the measurement of circulating IL-6, CRP and VEGF, and 5) plasma and colonic MET concentrations and their correlation with biomarker profiles. A favorable biomarker modulation may provide important clues for a subsequent phase III adjuvant trial. Clinical trial information: EudraCT Number: 2015-004824-77.

TPS1592 Poster Session (Board #249b), Mon, 1:15 PM-4:45 PM

Effect of bariatric surgery on breast tissue and biomarkers in obese women at increased risk for breast cancer. *First Author: Tarah Jean Ballinger, Indiana University, Indianapolis, IN*

Background: Obesity represents a challenging epidemic associated with increased risk of several malignancies, including breast cancer in postmenopausal women. Proposed mechanisms for the association between obesity and breast cancer risk include increased insulin resistance, elevated levels of circulating estrogens, and chronic inflammation. Intentional weight loss from bariatric surgery has been associated with decreased risk of breast cancer. While rapid improvements in serologic markers of metabolism and inflammation are seen following bariatric surgery, short- and long- term changes in breast tissue remain less clear. This study investigates the effect of bariatric surgery on breast density and biomarkers of increased risk in breast tissue. **Methods:** This pilot, single institution, observational study (NCT02681120) is recruiting pre- and post-menopausal women with BMI ≥30 from a University bariatric surgery clinic using the Hughes risk application as a screening tool. Eligible patients must have a lifetime risk for breast cancer of ≥20%. Participants are evaluated by imaging, breast biopsy, and blood samples at baseline, 14 days post-operatively to determine the effects of rapid metabolic changes, and 1 year post-operatively to determine the effects of significant weight loss. The impact of bariatric surgery on known imaging parameters of breast cancer risk is assessed by background parenchymal enhancement on MRI and breast density on mammogram. Breast tissue is evaluated for changes in immune infiltrates, aromatase expression, and the presence of crown-like structures, a marker of inflammation seen in the breast tissue of obese women. Tissue samples at each time point are also compared to samples from lean women in the Susan G. Komen Tissue Bank at the IU Simon Cancer Center. Blood is collected for correlative studies evaluating markers of inflammation, insulin resistance, metabolism, and hormone synthesis. Enrollment is currently ongoing with a planned accrual of 40 patients, and data collection is estimated to complete by the end of 2018. Clinical trial information: NCT02681120.

2000 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Randomized, double-blind, phase III trial of a personalized peptide vaccination for human leukocyte antigen-A24-positive glioblastoma multiforme patients refractory to temozolomide-based therapy. *First Author: Mizuhiko Terasaki, Department of Neurosurgery, Kurume University, Kurume, Japan*

Background: To establish whether personalized peptide vaccination (PPV) is clinically beneficial for human leukocyte antigen (HLA)-A24-positive glioblastoma multiforme (GBM) patients refractory to temozolomide (TMZ)-based therapy. **Methods:** From January 2012 to March 2016, 88 HLA-A24-positive GBM patients refractory to TMZ-based therapy from 20 Japanese hospitals were randomly assigned to receive PPV treatment (n = 58) or best supportive care (BSC) (n = 30) at a 2 to 1 ratio. Four peptides chosen from 12 peptide candidates based on pre-vaccination IgG levels specific to each peptide or 4 corresponding placebos were injected subcutaneously once weekly for 12 times at the first course followed by biweekly vaccinations until disease progression. The primary endpoint was overall survival (OS). **Results:** The primary endpoint was not met in this clinical trial. Unfavorable prognostic factors were performance status (PS) 3, higher plasma levels of pre-vaccination granulocyte macrophage-colony stimulating factor (GM-CFS), and PPV containing SART2-derived peptides. Therefore, 78 patients with PS of 0 to 2 (50 with PPV and 28 with BSC) were provided for the subgroup analysis. Among them, the median OS of 39 PPV patients (10.4 months, 95% CI, 7.8-12.0 months) who had either lower levels of GM-CSF ($<$ 0.9 pg/mL) or 4 peptide vaccinations that did not include SART2-derived peptides was significantly (p = 0.03) longer than that of the corresponding 19 BSC patients (6.8, 4.6-12.7). In contrast, the median OS of 10 PPV patients (4.1, 1.1-8.3) who had both higher levels of GM-CSF ($>$ 0.9 pg/mL) and 4 peptide vaccinations containing SART2-derived peptides was significantly (p = 0.01) shorter than that of the corresponding 9 BSC patients (not reached, 1.6-not reached). A single grade 3 adverse event was the only PPV-related adverse event of grade $>$ 3 in this study. **Conclusions:** PPV monotherapy could be a new treatment modality for HLA-A24-positive GBM patients refractory to TMZ-based therapy, since this approach showed clinical benefit and safety under precision medicine-based pre-vaccination selection of appropriate patients. Clinical trial information: UMIN000006970.

2001 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Histopathologic review of suspected disease progression in patients with recurrent glioblastoma (GBM) receiving nivolumab ± ipilimumab: CheckMate 143. *First Author: Solmaz Sahebjam, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: Patients treated with immunotherapies can have a transient increase in lesion size due to immune cell infiltration that is suggestive of disease progression, but undergo subsequent regression with continued treatment. For patients with GBM, distinguishing progression from immune-related treatment effects using neuroimaging is challenging. Histopathologic examination of tumors could show the activity of immunotherapies in GBM and potentially minimize premature discontinuation of therapy and increase clinical benefit. Neuropathologic data from patients with recurrent GBM treated in CheckMate 143 who underwent biopsy/resection after suspected progression are presented. **Methods:** Patients received nivolumab 3 mg/kg (nivo 3) Q2W or nivo 3 + ipilimumab 1 mg/kg (ipi 1) Q3W $\times$ 4 doses then nivo 3 Q2W. Tissue collected from patients with suspected radiologic progression was submitted for blinded central review by 2 neuropathologists. Potentially significant treatment effect was defined as $\geq$30% necrosis/reactive changes and $\leq$50% viable solid tumor by area in posttreatment samples, or significant morphological changes from a prior biopsy if available. Results were compared with those from automated morphometry, pretreatment biopsy, and control pairs from unrelated patients with GBM treated with standard of care. **Results:** Of patients treated with nivo 3 (n = 20) or nivo 3 + ipi 1 (n = 1), 13 had potential treatment-related effects and 8 had no evidence of treatment effects (consistent with disease progression). Results were sent in real time to the treating physician to help inform treatment decisions; 4/13 patients with potential treatment effects continued therapy. Treatment effects were unrelated to age, *MGMT* methylation status, or PD-L1 expression (clone 28-8; archival tissue). Results were similar for automated morphometry analyses and showed differences between patients receiving nivo ± ipi and unrelated controls. **Conclusions:** These results suggest that histopathologic analyses may help better inform decisions on continuing nivo ± ipi in challenging cases, and show that immunotherapies may have intracerebral biological activity. Clinical trial information: NCT02017717.

2002 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase 1b open-label randomized study of the oncolytic adenovirus DNX-2401 administered with or without interferon gamma for recurrent glioblastoma. *First Author: Frederick F. Lang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: DNX-2401 is a replication-competent, tumor-selective, oncolytic adenovirus with enhanced infectivity that causes durable tumor control by killing tumor cells and eliciting antitumor immunity. To increase immune activation, a phase 1b randomized study of intratumoral DNX-2401 alone versus DNX-2401 with interferon gamma (IFN) was conducted. **Methods:** A total of 27 patients with biopsy-confirmed glioblastoma at first or second recurrence received a single intratumoral injection of 3e10 vp DNX-2401. Patients were randomized in a 2:1 ratio to receive 50 mcg/m^2 of subcutaneous IFN (Actimmune) Q3W initiated 14 days after DNX-2401 or to be followed without further treatment for safety and survival. **Results:** Twenty-seven (27) patients were enrolled following first (59%) or second (41%) recurrence having previously failed surgery, radiation, and temozolomide (100%). The median longest tumor diameter was 40 mm (range 20-77 mm). Patients were randomized to DNX-2401 followed by IFN (n = 18) or to DNX-2401 alone (n = 9). Due to the poor tolerability of IFN, the median duration of treatment was only 6 weeks (range 0-30 weeks), and two patients did not initiate treatment as scheduled due to early clinical deterioration. The most frequent grade 3-4 AEs across treatment groups were fatigue, headache, and seizures consistent with pre-existing symptoms, underlying disease and/or surgery. Based upon a preliminary intent-to-treat analysis, IFN did not appear to provide additional benefit. However, OS-12 and OS-18 for all patients enrolled was 33% and 22%, respectively regardless of treatment assignment. Three patients remain alive at 19, 21, and 22 months (DNX-2401, n = 1; DNX-2401 + IFN, n = 2). Interestingly, 50% of patients with a baseline tumor diameter of $\leq$ 42 mm survived beyond 12 months, potentially identifying a sub-population of patients that may live longer following intratumoral DNX-2401. **Conclusions:** DNX-2401 was well tolerated as monotherapy. Although the addition of IFN did not improve survival, clinical activity following a single injection of DNX-2401 is encouraging and supports an ongoing Phase II study of DNX-2401 for recurrent glioblastoma. Clinical trial information: NCT02197169.

2003 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Efficacy analysis of ABT-414 with or without temozolomide (TMZ) in patients (pts) with EGFR-amplified, recurrent glioblastoma (rGBM) from a multicenter, international phase I clinical trial. *First Author: Andrew B. Lassman, Columbia University Medical Center, New York, NY*

Background: GBM is the most common malignant primary brain tumor in adults. Pts with rGBM have a poor prognosis. EGFR is amplified (amp) in ~50% of GBMs and is a compelling therapeutic target. ABT-414 is an antibody-drug conjugate composed of an EGFR-directed antibody conjugated to a microtubule toxin, MMAF. ABT-414 binds a unique epitope exposed during EGFR activation, either through ligand stimulation or mutation such as EGFR variant III (EGFRvIII), releasing MMAF into the cancer cell. Here, we report a pooled safety and efficacy analysis of ABT-414 +/- TMZ in EGFR amp, rGBM. **Methods:** M12-356 is a Phase 1, open-label, multi-arm study. Results from the 2 arms accruing rGBM pts were pooled for analysis. Eligible adults had rGBM, centrally confirmed EGFR amp, and KPS $\geq$ 70. Pts received 0.5-1.25 mg/kg ABT-414 on days 1 and 15 +/- 150-200 mg/m^2 TMZ on days 1-5 of 28-day cycles until progression (per RANO). **Results:** As of 11 January 2017, 126 pts were treated. The most common adverse events (AEs, $\geq$ 25% pts) were ocular (90%) and included blurred vision (64%) and photophobia (31%), which were mainly reversible. Common non-ocular AEs were fatigue (36%) and headache (30%). Grade 3/4 AEs ($\geq$ 5% pts) included ocular toxicities (29%) and decreased platelets/thrombocytopenia (10%). Serious AEs included seizure and keratitis (2% each). Of 125 pts evaluable by RANO, 52% had improvement or stabilization as best response (2 CR, 9 PR, 54 SD), and the remaining 60 (48%) had PD. Of 115 pts with measurable disease at baseline, the objective response rate (ORR) was 10% (2 CR + 9 PR). For 5 pts, re-resection for radiographic PD revealed mostly necrotic tissue and pts were classified as SD, suggesting the ORR may be an underestimate. Of all 126 pts, the 6-month PFS rate (PFS6) was 26%; median OS was 8.5 months. **Conclusions:** In this Phase 1 trial of EGFR amp, rGBM, we observed encouraging disease control (52%, CR + PR + SD) and PFS6 (26%) rates. Toxicity was mainly ocular, and reversible. A global, randomized trial of ABT-414 vs. ABT-414 + TMZ vs. TMZ/lomustine in EGFR amp, rGBM has completed accrual with results expected later this year (NCT02343406). Clinical trial information: NCT01800695.

2004 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Vemurafenib in patients with *BRAF*^{V600} mutant glioma: A cohort of the histology-independent VE-basket study. *First Author: David Michael Hyman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recurrent malignant gliomas (MG) are a universally fatal disease in desperate need of better therapies. Pleiomorphic xanthoastrocytomas (PXA) and juvenile pilocytic astrocytomas (JPA) typically have better outcomes, although when recurrent, also represent an aggressive disease with no proven effective chemotherapy. *BRAF*^{V600} alterations have been identified in a substantial proportion of gliomas, including glioblastoma (GBM), astrocytoma, PXA, and JPA. The phase 2, open-label, histology-independent VE-BASKET study of vemurafenib, a selective BRAF^{V600} kinase inhibitor, in patients with *BRAF* mutation-positive non-melanoma tumors, included those with gliomas in the 'all-others' cohort. We now report final data for patients with recurrent gliomas. **Methods:** Patients received vemurafenib (960 mg bid) until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed response rate; secondary endpoints included clinical benefit rate (confirmed complete or partial response or stable disease lasting ≥6 months), progression-free survival (PFS), overall survival (OS), and toxicity. ClinicalTrials.gov NCT01524978. **Results:** 24 patients (median age 32 years; 18 female, 6 male) with glioma were treated, including mg (n = 11; 6 GBM and 5 anaplastic astrocytoma [AA]), PXA (n = 7), anaplastic ganglioglioma (AG, n = 3), JPA (n = 2), and unknown (n = 1). In patients with mg (n = 11), best response included PR (n = 1; AA), SD (n = 5), PD (n = 3), and unknown (n = 2). Two patients with mg had durable SD lasting 12.9 months (GBM) and 14.9 months (AA). In patients with PXA (n = 7), best response included CR (n = 1), PR (n = 2), SD (n = 3), and PD (n = 1). Additionally, 1 patient with JPA and 1 with AG achieved a PR. The most frequent AEs included arthralgia (67%), melanocytic nevus (38%), palmar-plantar erythrodysesthesia (38%), photosensitivity reaction (38%) and alopecia (33%). **Conclusions:** Vemurafenib demonstrated activity in patients with *BRAF*^{V600} mutant glioma. The safety profile was similar to that seen in previous melanoma studies. Survival data will be presented. Clinical trial information: NCT01524978.

2005 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Phase I study of AZD1775 with radiation therapy (RT) and temozolomide (TMZ) in patients with newly diagnosed glioblastoma (GBM) and evaluation of intratumoral drug distribution (IDD) in patients with recurrent GBM. *First Author: Brian Michael Alexander, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA*

Background: The standard of care treatment for newly diagnosed GBM is maximal safe surgical resection followed by two DNA damaging agents, RT and TMZ. Cellular response to DNA damage involves checkpoints that halt the cell cycle to allow DNA repair. AZD1775 is an oral small molecular inhibitor of a nuclear tyrosine kinase Wee1, a key regulator of the G2/M checkpoint. Abrogation of the G2/M checkpoint prevents repair and pushes cells into mitosis with unrepaired DNA damage. AZD1775 was shown to enhance TMZ and RT effects in preclinical models. **Methods:** The Adult Brain Tumor Consortium 1202 trial (NCT01849146) is a phase I, open label, multicenter dose-finding study of AZD1775 in combination with standard RT and TMZ followed by an IDD study for patients undergoing surgery for recurrent GBM. The dose finding portion is comprised of two arms, one with AZD1775 given Monday through Friday during concurrent RT/TMZ and a second arm given with adjuvant TMZ qd x 5d/28d cycle. Each arm had standard 3+3 design. A combination cohort with both concurrent and adjuvant AZD1775 at MTD and analysis of PK/PD and IDD at MTD in patients undergoing surgery for recurrent GBM followed. **Results:** 51 patients enrolled in the dose finding arms. For the concurrent arm, the MTD was 200 mg. At 275 mg one patient had grade 3 fatigue and another had grade 4 thrombocytopenia and neutropenia. Two of 6 total patients enrolled at 200 mg experienced DLTs (grade 4 neutropenia and grade 3 ALT elevation). The MTD for the adjuvant arm was 425 mg as 1 of 6 patients had DLT (grade 4 decrease in ANC). At 500 mg, 2 of 3 patients experienced intolerable diarrhea despite prophylaxis. Enrollment in the combination cohort is completed and evaluation of safety is underway. The drug concentration in contrast enhancing and non-enhancing brain tumor was 4-8 x and 0.5-2.6 x greater than plasma, respectively for patients on IDD portion. **Conclusions:** The MTD for AZD1775 in combination with RT/TMZ is 200 mg qd M-F with concurrent RT/TMZ and 425 mg qd x 5d/28d cycle in combination with adjuvant TMZ. IDD and PK/PD analysis is ongoing to inform the decision to proceed to phase II testing. Clinical trial information: NCT01849146.

2006 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Phase I study (BLOOM) of AZD3759, a BBB penetrable EGFR inhibitor, in patients with TKI-naïve, EGFRm NSCLC with CNS metastases. *First Author: Myung-Ju Ahn, Division of Hematology and Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: The dose escalation phase is complete forAZD3759, the first EGFR inhibitor primarily designed to cross the blood brain barrier (BBB) to treat patients with EGFRm NSCLC with CNS metastases. AZD3759 is being further evaluated in patients with brain (BM) and leptomeningeal metastases (LM) in TKI-naïve and TKI pre-treated cohorts (data presented separately) (NCT02228369). **Methods:** The primary objective is safety and tolerability, and secondary objectives include anti-tumor efficacy. Dose levels of 200 and 300 mg BID AZD3759 were assessed based on safety and efficacy data in dose escalation cohorts. **Results:** As of24 September, 2016,38 patients with EGFRm NSCLC were recruited into the expansion cohorts of this study: 16 patients with TKI naïve BM and 4 patients with TKI naïve LM. 15 and 5 patients were treated with 200 and 300 mg BID of AZD3759, respectively. No DLTs were observed at either dose, while 200 mg BID AZD3759 was better tolerated than 300 mg BID during > 2 month treatment. The longest duration on treatment was > 9 months. Drug-related adverse events (AEs) seen are typically observed for EGFR TKIs. In BM cohort, 56% and 13% of patients had dose interruptions and reductions respectively due to drug-related AEs. The C_{trough} free plasma and CSF exposure at both doses were above pEGFR IC_{90}. By investigators' assessment, the intracranial objective response rate (ORR) was 63% (12 out of 19 evaluable patients) and achieved confirmed/unconfirmed partial/complete response [PR/CR]), extracranial ORR was 50% (10 out of 20 evaluable patients), and the overall ORR was 60% (12 out of 20 evaluable patients). 4 patients have not reached the 6-week RECIST assessment at the data cut-off. 18 of 20 patients are still ongoing (median 4-month follow up). 2 patients have withdrawn, one due to disease progression (de novo T790M mutation in both plasma and CSF), and another due to a non-drug related SAE. **Conclusions:** AZD3759 was well tolerated at the selected doses, achieved sufficient CNS exposure for target inhibition and demonstrated promising anti-tumor efficacy in both intracranial and extracranial tumors in TKI-naïve patients with CNS metastases. Updated clinical data will be shared at the meeting. Clinical trial information: NCT02228369.

2007 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Identification of single nucleotide polymorphism of PI3k-AKT-TOR pathway as a risk factor of central nervous system metastasis in metastatic breast cancer. *First Author: Jacques Bonneterre, Centre Oscar Lambret, Lille, France*

Background: Although new therapeutic options are available, an early diagnosis of central nervous system (CNS) metastasis may be needed to improve the prognosis. The PI3k-Akt-mTor pathway has been shown to be relevant in the development of CNS metastasis. Our aim was to identify risk-associated single nucleotide polymorphisms (SNP) of the PI3K Akt-mTOR pathway in the development of CNS metastasis in patients with metastatic breast cancer. **Methods:** We performed a secondary analysis in a subpopulation of patients from the GENEOM study (NCT00959556). In this previous study, blood samples were collected from 914 breast cancer patients treated by chemotherapy in the neoadjuvant, adjuvant or metastatic setting for genomic analysis. We identified CNS metastatic patients (both leptomeningeal and parenchymal) and non-CNS metastatic patients (no neurological symptoms or normal brain MRI before death or during 5-years metastatic period). Based on the literature, 88 SNPs of the PI3K-Akt-mTOR pathway were analyzed, including AKT1 (17 SNPs), AKT2 (4), FGFR1 (2), mTOR (7), PDK1 (4), PI3KR1 (11), PI3KCA (20), PTEN (17), RPS6KB1 (6). **Results:** Of the 342 patients with metastases in the GENEOM cohort, 100 patients with CNS metastasis (parenchymal lesions only, n = 51; leptomeningeal lesions only, n = 18; both, n = 31) and 107 patients without CNS metastasis were included. Negative hormonal status (p = 0.002) and presence of vascular emboli on breast cancer samples (p = 0.006) were associated with CNS metastasis. In univariate analysis, genotypes CC of AKT1 rs3803304, AA of AKT2 rs3730050, CC of AKT2 rs8100018, TT of PDK1 rs1168690, GG of PDK1 rs11904366 and GG of PI3KR1 rs251408 were associated with CNS metastasis at the $p < 0.05$ threshold. Only genotype TT of PI3KR1-rs706716 was statistically associated with CNS metastasis after Bonferroni correction ($p = 0.0003$, < 0.00085). **Conclusions:** PI3KR1-rs706716 is associated with CNS metastasis in metastatic breast cancer patients, in addition to negative hormonal status and presence of vascular emboli and could be combined in a composite score to predict the risk of and to detect early CNS metastasis in this population.

2008 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Cambridge Brain Mets Trial 1 (CamBMT1): A proof of principle study of afatinib penetration into cerebral metastases (mets) for patients (pts) undergoing neurosurgical resection, combined with low-dose, targeted radiotherapy (RT)—Phase 1b results. *First Author: Richard D. Baird, Cambridge Cancer Trials Centre, Cambridge, United Kingdom*

Background: Failure of drugs to cross the blood brain barrier (BBB) can be a major reason for treatment failure in pts with brain tumours. Preliminary data suggest that low-dose RT may disrupt the BBB, and could facilitate increased drug delivery into brain tumours. CamBMT1 is a phase 1b/2 preoperative window-of-opportunity trial designed to test if the delivery of afatinib into brain mets might be enhanced by targeted, low dose-RT. **Methods:** Pts with operable brain mets from breast or lung origin were treated with afatinib for 11 days prior to surgery on day 12. Pts also received a single fraction of targeted RT on day 10 (pts in either 2Gy or 4Gy arm). In phase 1b, afatinib dose (20, 30, or 40mg QD) was escalated in each arm using an accelerated titration design. Primary endpoint: steady-state afatinib concentration in resected brain mets, compared with plasma. Secondary endpoints: safety and tolerability. **Results:** 10 pts were treated (4 breast, 6 lung), with no dose-limiting toxicities seen, thus completing recruitment to phase 1b. Treatment was generally well tolerated. Median afatinib concentrations on day 12 were: plasma 22.7ng/mL (range 9.94-179); and tumour 405ng/g (range 120-1129). **Conclusions:** It was feasible to conduct a window-of-opportunity study of afatinib plus RT in pts with operable brain mets. The recommended phase 2 dose of afatinib was 40mg QD for both 2Gy and 4Gy arms. Afatinib concentrations in resected tumour were on average >15-fold higher than those in plasma. Phase 2 of CamBMT1 is now underway in multiple UK sites, and randomises patients into 3 treatment arms (n=20 per arm): 1. afatinib 40mg QD; 2. afatinib 40mg QD + 2Gy# RT; 3. afatinib 40mg QD + 4Gy# RT. Clinical trial information: NCT02768337.

Dose escalation, treatments received and pharmacokinetic results.

Patient ID	1001	1004	1006	1007	1008	1003	1005	1009	1010	1011
RT dose (Gy)	2	2	2	2	2	4	4	4	4	4
Afatinib dose (mg)	20	30	40	40	40	20	30	40	40	40
Afatinib concentrations										
Day 10 - plasma (ng/mL)	9.09	26.8	39.2	19.1	84	13.3	47	17.7	204	42
Day 12 - plasma (ng/mL)	9.94	23.2	32.2	22.2	179	17.7	33.4	12	84.7	14.5
Day 12 - tumour (ng/g)	230	476	894	120	1129	341	140	673	163	469

2009 **Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

Final results of the EORTC Brain Tumor Group randomized phase II TAVAREC trial on temozolomide with or without bevacizumab in 1st recurrence grade II/III glioma without 1p/19q co-deletion. *First Author: Martin J. Van Den Bent, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Although bevacizumab (BEV) is frequently used in recurrent grade II and III glioma without 1p/19q co-deletion, this use is without evidence from randomized trials. **Methods:** The TAVAREC trial (NCT01164189) is a randomized phase II study in locally diagnosed non-1p/19q co-deleted grade II or III glioma, with a first and contrast-enhancing recurrence after initial radiotherapy. Prior chemotherapy was allowed provided patients were at least 6 months off treatment. Patients were treated with either 200mg/m^2 temozolomide (TMZ) day 1-5 every 4 weeks for a maximum of twelve cycles, or with the same TMZ regimen in combination with BEV 10 mg/kg every 2 weeks until progression. Response, Quality of Life (QOL, using the EORTC QOL C30/BCM20 questionnaire) and neurocognitive function (NCF) using a standardized test battery with Hopkins Verbal Learning, Trail Making test A/B and Controlled Oral Word Association were evaluated every 3 months. Primary endpoint is the Overall Survival (OS) rate at 12 months (OS12). Tumor samples were centrally analyzed for *MGMT* status (Illumina methylation arrays) and *IDH1/2* mutations (*IDHmt*). **Results:** Between 8/2/2011 and 31/7/2015, 155 patients were randomized; median age was 44 years, 88 (70%) of 125 tested tumors showed an *IDHmt*, 27% of patients had received prior chemotherapy. OS12 was 61% in the TMZ arm and 55% in the TMZ+BEV arm, with overlapping OS and progression free survival (PFS) Kaplan Meier curves and similar response rates (TMZ: 42%; TMZ + BEV: 49%). Post-progression, 33% of the TMZ and 17% of the TMZ + BEV patients received BEV. OS was longer in *IDHmt* tumors compared to *IDH wild type* tumors (15 mo vs 10.7 mo, p = 0.001) but PFS was clinically similar (6.7 mo vs 5.1 mo, p = 0.056). *IDH* mutational status was not predictive for benefit to BEV. Compliance to NCF testing and QOL was above 60% in the 1st year. At the group level, NCF was similar in the TMZ and in the TMZ+BEV patients. QOL and *MGMT*results will be presented at the meeting. **Conclusions:** The addition of BEV to TMZ does not improve OS, PFS, or cognitive function in recurrent grade II and III 1p/19q intact gliomas; regardless of IDH mutational status. Clinical trial information: NCT01164189.

2010 **Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

A phase I study of convection enhanced delivery (CED) of ^{124}I-8H9 radiolabeled monoclonal antibody in children with diffuse intrinsic pontine glioma (DIPG). *First Author: Mark M. Souweidane, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Diffuse intrinsic pontine glioma (DIPG) represents one of the most deadly central nervous system tumors of childhood with a median survival of less than 12 months. Convection-enhanced delivery (CED) has been recently hypothesized as a means for augmenting distribution of therapeutic agents within the brain stem. We conducted this study to evaluate CED in children with DIPG. **Methods:** We performed a standard 3+3 phase I, open-label, dose escalation study in patients with non-progressive DIPG 4 to 14 weeks post-completion or radiation therapy. Seven dose levels of a single injection of ^{124}I-8H9 (range 0.25 to 4.0 mCi, 250 to 4000 mcl) were studied. **Results:** 25 children were treated. The average age at enrollment 8 years old (range 3-17). There was no dose limiting toxicity (DLT) and adverse events were limited to grade 1 or 2 (CTCAE v4.0). Estimations of distribution volumes were dose dependent and ranged from 1.5 to 20.1 cm^3. The mean volume of distribution/volume of infusion (Vd/Vi) was 3.4 (SD 1.2). The mean lesion absorbed dose was 1527 rad/mCi. The mean tumor coverage on dose level 7 was 107%. **Conclusions:** CED in the brain stem of children with DIPG who were previously irradiated is a safe therapeutic strategy. Up to 4 mCi of ^{124}I-8H9 was well tolerated. An infusion volume of 4000 mcl appears to be a reasonable single dose for good tumor coverage. PET-based dosimetry validates the conceptual basis for direct drug delivery. Based on our finding CED merits further exploration in early phase clinical trials for children with DIPG. Clinical trial information: NCT01502917.

2011 **Clinical Science Symposium, Sat, 3:00 PM-4:30 PM**

A phase II of everolimus and octreotide for patients with refractory and documented progressive meningioma (CEVOREM). *First Author: Thomas Graillon, Neurosurgery Department, Hopital La Timone, AP-HM, Marseille, France*

Background: After iterative surgeries and radiotherapy (RT)/radiosurgery (RS) failure, aggressive meningiomas remain an unmet medical need. We have shown in vitro that everolimus (EVE) combined to octreotide (OCT) is active in meningiomas. **Methods:** Prospective multicentric single arm phase II study (NCT02333565) including pts with recurrent meningioma with documented progression (> 10% increase of tumor surface over 6 months) after surgery and RT/RS. EVE was orally administrated at 10mg/day and OCT by IM injection 30 mg/28 days. MRI was performed every 3 months with planned central review of imaging including volumetric progression at inclusion and during treatment. The primary endpoint was PFS6. The criteria for success was defined as a PFS6 > 40%. **Results:** 20 pts were included, aged 30-75 years (median 55) with 37 progressive intra cranial meningiomas (WHO: 2 grade I, 27 grade II, 8 grade III) including 4 NF2 pts. Median KPS was 70%. All pts previously underwent at least one surgery and more than 1 in 18/20 patients. 19/20 pts were treated with radiotherapy or radiosurgery and 5 pts with prior chemotherapy. 1 pt was not evaluable at 3 months. With a median f/u of 12.3 months (2-24 months), PFS6 was 58.2% (95% CI 33.5-76.5%) and PFS12 was 38% (95% CI 16-60%). Volumetric analysis at 3 months demonstrated a decrease in tumor volume superior to 10% in 8 tumors (4 pts). Pre therapeutic growth rate was decreased of more than 50% in 29/35 tumors (18/20 pts) during the first 3 months. Inclusion (I)-to-3 months tumor growth rate (mean at 1.9%/month) was significantly lower than pre inclusion (Pre-I)-to-I growth rate (mean at 18.5%/month) (p = 0.0003). 3 highly aggressive tumors (3 pts) were separately assessed: Pre-I-to-I growth rate superior to 1000%/month was decreased to 3%, 15% and 44%/month in the first 3 months. Toxicity included 7 grade III AE (stomatitis, 3; pneumopathy, 1). AE of special interest included stomatitis (10, 50%), rash (8, 40%), abdominal pain and diarrhea (11, 55%) and nausea and vomiting (4, 20%). **Conclusions:** Everolimus and octreotide combination appears active in refractory aggressive and progressive meningiomas with acceptable and manageable toxicity and should request further evaluation. Clinical trial information: NCT02333565.

2012 Poster Discussion Session; Displayed in Poster Session (Board #254), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Phase II trial of bevacizumab and temozolomide for upfront treatment of elderly patients with newly diagnosed glioblastoma. *First Author: Phioanh Leia Nghiemphu, University of California, Los Angeles, Los Angeles, CA*

Background: Randomized clinical trials in newly diagnosed, elderly GBM patients have shown that treatment with temozolomide chemotherapy is at least equivalent to treatment with radiotherapy. Glioblastoma in elderly patients may also have high angiogenic activities. Bevacizumab is an antiangiogenic agent, a humanized monoclonal antibody directed against the vascular endothelial growth factor. We conduct a clinical trial of temozolomide and bevacizumab to evaluate the safety and efficacy of this combination in the treatment of elderly patients with newly diagnosed GBM, good performance status, and willing to forgo upfront treatment with radiation therapy. **Methods:** This is a phase II trial of newly diagnosed GBM patients age ≥70 with no prior treatments other than surgery and Karnofsky Performance Status (KPS) ≥60. Patients receive treatments 4-6 weeks after surgery with bevacizumab (10mg/kg every 2 weeks) and temozolomide (150-200 mg/m^2 for 5 days out of 28 days, up to 12 cycles) until tumor progression. Primary outcome measures are overall survival and safety evaluations. **Results:** From June 2010 to January 2016, 50 GBM patients enrolled in this study. To date, all patients have tumor progression and 3 are still alive. The median age is 75 (range 70 - 87), and median KPS is 80 (range 60-100). 15 patients have a gross total resection. 26 out of 49 patients with tissues available for evaluation have methylation of the MGMT promoter, and no patient has IDH-1 mutation. Median overall survival is 12.3 months (14.8 months for those with methylation of MGMT, 10.0 months for unmethylated MGMT). Serious adverse events related to treatments include wound healing problems (2), CNS hemorrhage (3), pulmonary embolism (4), and bowel perforation (1). Serious hematological adverse events include thrombocytopenia (3) and neutropenia (5). **Conclusions:** For patients with newly diagnosed GBM age ≥70, KPS ≥60, treatment with temozolomide and bevacizumab may show promising survival benefits and have tolerable side effects. More detailed safety and efficacy analysis will be presented. Clinical trial information: NCT01149850.

2013 Poster Discussion Session; Displayed in Poster Session (Board #255), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Clinical and molecular features associated with long-term survival of elderly patients with glioblastoma. *First Author: Michael Weller, Laboratory of Molecular Neuro-Oncology, Department of Neurology, and Neuroscience Center Zurich, University Hospital and University of Zurich, Zurich, Switzerland*

Background: Glioblastomas in elderly patients are associated with particularly poor outcome, with only few patients demonstrating long-term survival (LTS). **Methods:** To better characterize clinical and molecular correlates of LTS in elderly glioblastoma patients, we searched the German Glioma Network (GGN) database for patients aged 71 years or more with histological confirmation of glioblastoma and survival of at least two years after diagnosis. **Results:** Of 2071 glioblastoma patients enrolled in the GGN from 2004-2012, 425 patients were aged 71 years or more; of these, 27 patients (6.4%) survived for 2 years or more (median survival: 37.1 months, 95% confidence interval: 30.0-44.2 months). A comparison of these 27 patients with the 398 patients who survived shorter than 2 years (median survival: 6.2, 95% confidence interval: 5.2-7.2 months) revealed more intensive upfront treatment and a trend towards higher initial Karnofsky performance score as distinguishing clinical factors. Molecular analyses additionally showed more frequent O^6-methylguanine-DNA methyltransferase (*MGMT)* promoter methylation in the LTS patients. Isocitrate dehydrogenase (IDH) mutation was restricted to single patients and the frequency of telomerase reverse transcriptase (*TERT*) promoter mutation did not differ between groups. Genome-wide DNA copy number and methylation profiling using 450k microarray analysis performed for 16 LTS patients and 40 control patients revealed limited differential DNA methylation and no specific copy number profiles linked to LTS. **Conclusions:** Collectively, our findings confirm that LTS is rare in elderly patients with glioblastoma and that clinical and tumor-associated molecular factors linked to LTS resemble those in standard age patients, except for less common IDH mutation.

2014 Poster Discussion Session; Displayed in Poster Session (Board #256), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Bevacizumab plus hypofractionated radiotherapy versus radiotherapy alone in elderly patients with glioblastoma: Efficacy and imaging analyses of the ARTE trial. *First Author: Hans-Georg Wirsching, Department of Neurology, University Hospital, Zürich, Switzerland*

Background: The addition of bevacizumab (BEV) to first-line temozolomide chemoradiotherapy prolonged progression-free survival (PFS), but not overall survival (OS) in newly diagnosed glioblastoma in two phase III trials. Elderly and frail patients are underrepresented in most clinical trials, but early uncontrolled reports of BEV treatment of glioblastoma suggested preferential benefit in this patient population. **Methods:** ARTE was a 2:1 randomized, multi-center, open-label trial of hypofractionated radiotherapy (RT) in combination with intravenous BEV every 2 weeks (Arm A, N = 50) versus RT alone (Arm B, N = 25) in patients with newly diagnosed glioblastoma aged 65 years or older. Quality of life (QoL) was monitored by the EORTC QLQ-C30/BN20 modules. Response was assessed using Response Assessment in Neuro-Oncology (RANO) criteria. Exploratory imaging studies included apparent diffusion coefficient (ADC) mapping and 18F-fluoro-ethyl-tyrosine (FET) positron emission tomography (PET). **Results:** Established prognostic factors including age, Karnofsky performance score (KPS), O6-methylguanine DNA methyltransferase (MGMT) gene promoter methylation and steroid intake at study entry were balanced between arms. Median PFS was longer in Arm A vs. Arm B (7.6 vs. 4.8 months, p = 0.003), but OS was similar (12.1 vs 12.2 months, p = 0.8). Prior to progression, no differences in QoL were noted, but clinical deterioration was deferred in Arm A vs. Arm B. In a Cox model that controlled for established prognostic factors, an association with prolonged PFS was detected for Arm A versus Arm B (hazard ratio [HR] 0.36, p = 0.001) and for KPS 90-100% versus 60-80% (HR 0.50, p = 0.02). Applying a similar Cox model to OS detected an association with age 65-69 vs 70+ (HR 0.52, p = 0.02) and KPS 90-100% versus 60-80% (HR 0.53, p = 0.03). Exploration of imaging predictors of OS for Arm A identified response by RANO (HR 0.52, p = 0.02), but detected no prognostic role for T2, ADC or FET signal intensity. **Conclusions:** Efficacy outcomes and exploratory imaging analyses of the ARTE trial do not support the notion that benefit from BEV is more pronounced in elderly glioblastoma patients. Clinical trial information: NCT01443676.

2015 Poster Discussion Session; Displayed in Poster Session (Board #257), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Radiomic analysis of pseudo-progression compared to true progression in glioblastoma patients: A large-scale multi-institutional study. *First Author: Srishti Abrol, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Treatment-related imaging changes are often difficult to distinguish from true tumor progression. Treatment-related changes or pseudoprogression (PsP) subsequently subside or stabilize without any further treatment, whereas progressive tumor requires a more aggressive approach in patient management. Pseudoprogression can mimic true progression radiographically and may potentially alter the physician's judgment about the residual disease. Hence, it can predispose a patient to overtreatment or be categorized as a non-responder and exclude him from the clinical trials. This study aims at assessing the potential of radiomics to discriminate PsP from progressive disease (PD) in glioblastoma (GBM) patients. **Methods:** We retrospectively evaluated 304 GBM patients with new or increased enhancement on conventional MRI after treatment, of which it was uncertain for PsP versus PD. 149 patients had the histopathological evidence of PD and 27 of PsP. Remaining 128 patients were categorized into PD and PsP based on RANO criteria performed by a board-certified radiologist. Volumetrics using 3D slicer 4.3.1 and radiomics texture analysis were performed of the enhancing lesion(s) in question. **Results:** Using the MRMR feature selection method, we identified 100 significant features that were used to build a SVM model. Five texture features (E, CS, SA, MP, CP) were found to be most predictive of pseudoprogression. On Leave One Out Cross-Validation (LOOCV), sensitivity, specificity and accuracy were 97%, 72%, and 90%, respectively. **Conclusions:** 3D radiomic texture features of conventional MRI successfully discriminated pseudoprogression from true progression in a large cohort of GBM patients.

2016 Poster Discussion Session; Displayed in Poster Session (Board #258), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Multicenter study to demonstrate radiomic texture features derived from MR perfusion images of pseudoprogression compared to true progression in glioblastoma patients. *First Author: Nabil Elshafeey, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: To differentiate between pseudoprogression and true progression in patients with glioblastoma using MR perfusion radiomic texture analysis (TA). **Methods:** 98 patients with pathologically-proven diagnosis of GBM were retrospectively included in this IRB approved HIPAA compliant study. All patients underwent DSC and DCE Perfusion MRI as part of their routine clinical care. Images were analyzed using Nordic ICE 2.3 (Nordic-NeuroLab) ; rCBV and ktrans maps were obtained. Subsequently, 3D slicer 4.3.1(http://www.slicer.org) was used to segment the entire tumor on the different processed maps to create a volume of interest (VOI) for Radiomic TA. Multiple invariant texture features where then extracted from each VOI. 475 invariant texture features were applied to each map. Leave-one-out cross-validation (LOOCV), receiver operating characteristic (ROC), Kaplan Meier, and multivariate Cox proportional hazards regression analyses were used to assess the relationship between texture feature and pseudoprogression and true progression. **Results:** Variance and sum entropy were the two most significant radiomic features that discriminated between pseudoprogression and true progression. P value, AUC, specificity and sensitivity were 0.03, 89.26%, 81.82%, and 100% respectively. **Conclusions:** Radiomic TA derived from perfusion images can be helpful in determining true versus pseudoprogression in GBM. Further, this study illustrates successful application of radiomic TA as an advanced processing step for different MRI perfusion maps (DCE, DSC).

2017 Poster Discussion Session; Displayed in Poster Session (Board #259), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Low grade glioma patients with IDH mutation and 1p19q codeletion: To treat or not to treat? *First Author: Enrico Franceschi, Department of Medical Oncology, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Bologna, Italy*

Background: Molecular characterization of low grade gliomas (LGG) is essential for diagnosis and treatment of these diseases. LGG patients (pts) with IDH mutation and 1p19q codeletion (codel) are characterized by a median OS (mOS) longer than 10 years. Thus, the role of treatments and side effects should be carefully evaluated. **Methods:** We evaluated LGG pts from our data warehouse (n=679 pts) who received surgery and had sufficient tissue to assess biomarkers characterization. Pts with gliomatosis were excluded. IDH1/2 assessment was performed on formalin-fixed paraffin-embedded samples by qPCR. In wild type cases we performed NGS. 1p/19 codel analysis was performed by FISH. **Results:** 93 consecutive LGG with IDH mutation and codel were included. The median follow up (FU) was 96.1 months. Mean age was 40 yrs (range: 25-66); 8 pts (8.6%) underwent biopsy, 61 pts (65.6%) partial resection, 24 pts (25.8%) complete resection. 84 pts (90.3%) were considered high risk using RTOG criteria (>40 years and/or incomplete resection). Fifty pts (53.7%) received only FU, 17 pts (18.3%) received chemotherapy (CT), 18 pts (19.4%) received radiotherapy (RT), 8 pts (8.6%) received RT + CT. Median PFS (mPFS) was 59.6 months (95%CI: 41.8-77.4) and was significantly longer in pts who received postsurgical treatments (79.5 months, 95%CI: 66.4-92.7) than pts who received FU (46.3 months, 95%CI: 36.0-56.5; P=0.001). mPFS was 50.8 months (95%CI: 17.4-84.3), 103.6 months (95%CI: 11.7-195.6) and 120.2 months (95%CI: 40.5-199.8) in pts treated with CT alone, RT alone and RT + CT, respectively. Multivariate analysis showed that receiving a post-surgical treatment (P<0.001), and the extent of resection (P=0.043) were significantly correlated with PFS. **Conclusions:** Our study evaluated the role of treatments in LGG pts assessed with NGS and FISH. Post-surgical treatments are crucial to extend PFS in pts with IDH mutation and codel. The choice of post-surgical treatments seems to have a role, being CT alone less effective than RT and RT+CT. Longer FU is needed to provide information about OS.

2018 Poster Discussion Session; Displayed in Poster Session (Board #260), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Identification of novel therapeutic targets in glioblastoma with functional genomic mRNA profiling. *First Author: Cyrillo Gerardo Brahm, Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: Glioblastoma (GBM), the most common primary brain tumor in adults, universally recurs and has a dismal prognosis. Therefore, there is an unmet need for new and more effective treatment strategies. Here, we aim to discover new therapeutic targets by identifying upregulated genes in GBM with known antineoplastic drug interactions. **Methods:** Publicly available, raw microarray expression data of patient-derived GBM samples and normal brain tissue were collected from the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA). Subsequently, we applied functional genomic mRNA profiling (FGmRNA-profiling), a method that is able to correct the gene expression profile of an individual tumor for physiological and experimental factors, which are considered not to be relevant for the observed tumor phenotype. Next, the FGmRNA-profiles of healthy brain tissue and glioblastoma were used to perform a class comparison analysis. Significantly upregulated genes in GBM were prioritized based on: known interaction with antineoplastic agents and the current status of clinical evaluation in humans. **Results:** After FGmRNA-profiling 66 normal brain tissue samples and 1280 patient-derived GBM samples, class comparison identified 712 significantly upregulated genes. Of all significantly upregulated genes, 27 genes interacted with antineoplastic drugs. 17 out of these 27 druggable genes, including EGFR and VEGFA, have already been clinically evaluated in GBM, and had limited efficacy. Out of the 10 remaining druggable genes, we prioritized RRM2, MAPK9 and XIAP, as these genes are associated with biologic pathways involved in the carcinogenesis of GBM and are therefore considered as novel potential therapeutic targets. **Conclusions:** Based on data-driven prioritization, we identified three potential therapeutic druggable targets, which have not yet been explored in the context of glioblastoma. Further preclinical and clinical research on the inhibition of these druggable genes is necessary and may lead to an improvement of treatment outcomes for patients with GBM.

2019 Poster Discussion Session; Displayed in Poster Session (Board #261), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

RNA-Seq analysis of glioma tumors to reveal targetable gene fusions. *First Author: Deepa Suresh Subramaniam, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Fusions involving oncogenes have been reported in gliomas and may serve as novel therapeutic targets. We aim to use RNA-sequencing to interrogate a large cohort of gliomas for targetable genetic fusions. **Methods:** Gliomas were profiled using the ArcherDx FusionPlex Assay at a CLIA-certified lab (Caris Life Sciences) and 52 gene targets were analyzed. Fusions with preserved kinase domains were investigated. **Results:** Among 404 gliomas tested, 39 (9.7%) presented potentially targetable fusions, of which 24/226 (11%) of glioblastoma (GBM), 5/42 (12%) of anaplastic astrocytoma (AA), 2/25 (8%) of grade II astrocytoma and 3 of 7 (43%) of pilocytic astrocytoma (PA) harbored targetable fusions. In GBMs, 1 of 15 (6.7%) IDH-mutated tumors had a fusion while 22 of 175 (12.6%) IDH-wild type tumors had fusions. 46 oligodendroglial tumors were profiled and no fusions were seen, which was lower than frequency of fusions in astrocytic tumors (34/300, p = 0.0236). The most frequent fusions seen involved FGFR3 (N = 12), including 10 FGFR3-TACC3 (1 AA, 6 GBM and 3 glioma NOS); 1 FGFR3-NBR1 (AA) and 1 FGFR3-BRAP (GBM). 11 fusions involving MET were seen, 10 in GBM and 1 in AA. The most common MET fusion was PTPRZ1-MET (1 in AA and 4 in GBM), followed by ST7-MET (N = 3, GBM), CAPZA2-Met (N = 2, GBM) and TPR-MET (N = 1, GBM). 8 NTRK fusions were seen; 1 involving NTRK1 (BCAN-NTRK1, PA), 6 NTRK2 (1 NOS1AP-NTRK2 in AA; GKAP1-NTRK2, KCTD8-NTRK2, TBC1D2-NTRK2 and SOSTM1-NTRK2, 1 each in GBM and 1 VCAN-NTRK2 in grade II astrocytoma) and 1 NTRK3 (EML4-NTRK3 in GBM). EGFR fusions (2 EGFR-SEPT14 and 1 EGFR-VWC2) were seen in 3 GBMs, BRAF in 3 (1 KIAA1549-BRAF, 1 LOC100093631-BRAF in PA and 1 ZSCAN23-BRAF in glioma NOS) and PDGFRA (RAB3IP-PDGFRA, in GBM) in 1. C11orf95-RELA fusions were seen in 2 of 3 grade III ependymomas but not in the 2 grade II ependymomas. **Conclusions:** We report targetable fusion genes involving NTRK, MET, EGFR, FGFR3, BRAF and PDGFRA including novel fusions that haven't been previously described in gliomas (e.g., EGFR-VWC2; FGFR3-NBR1). Fusions were seen in over 10% of astrocytic tumors, while none was seen oligodendrogliomas. Identification of such kinase-associated fusion transcripts may allow us to exploit therapeutic opportunities with targeted therapies in gliomas.

2020 Poster Discussion Session; Displayed in Poster Session (Board #262), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Osimertinib for patients (pts) with leptomeningeal metastases (LM) from EGFR-mutant non-small cell lung cancer (NSCLC): Updated results from the BLOOM study. *First Author: James Chih-Hsin Yang, National Taiwan University Hospital, Taipei, Taiwan*

Background: LM due to NSCLC progression are associated with poor prognosis. Osimertinib is an oral, CNS-active, irreversible EGFR-TKI selective for sensitizing (EGFRm) and T790M resistance mutations. **Methods:** In the BLOOM study (NCT02228369), pts with EGFRm advanced NSCLC who had progressed on prior EGFR-TKI therapy and had LM confirmed by positive cerebrospinal fluid (CSF) cytology received osimertinib 160 mg once daily (qd). Response was assessed (by investigator) in 2 cohorts: T790M unselected and T790M positive (by central test); results are presented as a combined analysis set. Analyses were based on CSF cytology, brain MRI imaging, and neurological examination every 6 weeks (wk; relative to first dose) until progression. Adverse events (AEs) were graded according to CTCAE. EGFR-mutant DNA in CSF was determined by ddPCR. Plasma and CSF samples were collected for PK analyses. **Results:** As of 24 Sep 2016,32 pts had received treatment: 21 T790M unselected; 11 T790M positive. Max treatment duration was 17.5 months (m; median 6.0 m); 21 pts ongoing. 23/32 pts had a 12-wk brain image assessment: 10 had radiological improvement, 13 had stable disease (SD). The same 23 pts had a 12-wk neurological assessment: of 8 symptomatic pts, 7 improved, 1 had SD; of 15 asymptomatic pts, 2 worsened, 13 remained asymptomatic. The geometric mean decrease in EGFR-mutant DNA copy was 57% (95% CI 30, 74) in 22 pts with pre-dose and Cycle 2 Day 1 CSF samples. Most common AEs were skin effects (n = 20), diarrhea (n = 13), nausea (n = 11) and paronychia (n = 9). All were grade (G) 1/2 except 1 case each of diarrhea and nausea (both G3). 9 pts had dose interruptions and 4 had dose reductions to 80 mg qd. Osimertinib mean concentration in CSF was 7.51 nM (range 2.19–21.1 nM) at steady state (N = 16); CSF:free plasma ratio: 16%. Accrual is now complete (n = 41; 21 T790M unselected, 20 T790M positive) and updated data (including overall survival) will be presented. **Conclusions:** Osimertinib penetrates the blood-brain barrier. Encouraging activity and manageable tolerability in pts with LM from EGFRm NSCLC was observed at 160 mg qd, with a median treatment duration of 6.0 m; continued evaluation is ongoing. Clinical trial information: NCT02228369.

2021 Poster Discussion Session; Displayed in Poster Session (Board #263), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Final results from the dose-escalation stage of a phase 1/2 trial of TPI 287, a brain penetrable microtubule inhibitor, plus bevacizumab in patients with recurrent glioblastoma. *First Author: Samuel Aaron Goldlust, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ*

Background: Microtubule inhibitors, including taxanes, are active in preclinical models of glioblastoma (GBM), however, clinical benefit is hampered by poor blood-brain barrier (BBB) accumulation. TPI 287, a third-generation taxane designed to evade P-glycoprotein mediated efflux, readily penetrates the BBB and overcomes this limitation. CB-017 is a multi-center phase 1/2 trial designed to determine the optimal dose of TPI 287 and potential efficacy in patients treated with this drug plus bevacizumab (BEV) for treatment of recurrent GBM. Final results of the dose escalation Phase 1 stage of this trial are reported. **Methods:** GBM patients at first or second relapse after standard therapy and without prior exposure to anti-angiogenic agents were eligible for enrollment. BEV was administered at 10 mg/kg every 2 weeks and TPI 287 every 3 weeks via IV infusion. MRIs were obtained every six weeks with response assessed via RANO criteria. TPI 287 dose escalation was based on a traditional 3+3 design. **Results:** Twenty-four patients were enrolled in 7 TPI 287 dose-escalation cohorts (140-220 mg/m2) from 6 U.S. centers. Twenty and 23 patients were evaluable for response and survival, respectively. Median follow-up was 28 months. Results are shown in the table below. Of the 9 patients from which biomarker data was available, tumors from 8 patients (89%) harbored an unmethylated MGMT promoter, an established negative prognostic indicator for survival. No DLTs were reported and myelosuppression (n=3) was the only drug-related grade 3/4 adverse event. **Conclusions:** TPI 287 in combination with BEV is safe and well tolerated at doses up to 220 mg/m2. Final survival results from the Phase 1 portion of this study compare favorably with historical controls and support further investigation of TPI 287 plus BEV for treatment of recurrent GBM. Clinical trial information: NCT01933815.

# evaluable patients	23
Overall response	60% (12/20*)
CR	15% (3/20*)
PR	45% (9/20*)
SD	43% (10/23)
PD	4% (1/23)
Median PFS	5.5 months [4.1-8.2]
6-month PFS	40%
Median OS	13.4 mo. [10.9-17.9]
12-month OS	64%

* patients w/measurable disease at baseline only

2022 Poster Discussion Session; Displayed in Poster Session (Board #264), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Results of the OPARATIC trial: A phase I dose escalation study of olaparib in combination with temozolomide (TMZ) in patients with relapsed glioblastoma (GBM). *First Author: Sarah E. R. Halford, Cancer Research UK Centre for Drug Development, London, United Kingdom*

Background: Olaparib, a small molecule inhibitor of poly (ADP-ribose) polymerase (PARP), may improve GBM outcomes by enhancing cytotoxic effects of ionising radiation and TMZ. Clinical development of PARP inhibitors has been restricted by exacerbation of hematological toxicity. We investigated tumor pharmacokinetics (PK) of olaparib and safety and tolerability of its combination with TMZ. **Methods:** Dose escalation explored different schedules of olaparib (tablet formulation) with 42 day cycles of daily low dose TMZ. A dose expansion cohort evaluated the maximum tolerated schedule. PK analysis was performed on tumor and blood samples from patients undergoing neurosurgical resection, who received 4 olaparib doses pre-operatively. **Results:** 48 patients were recruited (median age 51(18-68); 29 male, 19 female) of whom 27 underwent surgery and 35 received olaparib/TMZ and were evaluable. 13 evaluable patients received expansion dose schedule (median age 54(21-67); 9 male, 4 female). Olaparib was detected in 73 of 74 tumor core specimens from 27 patients; mean conc. 588nM (97-1374nM), and in 27 of 28 tumor margin specimens from 10 patients; mean conc. 500nM (97-1237nM). Margin: core ratios ranged from 0.2–3.9(mean 1.2); tumor: plasma ratios ranged from 0.01 to 0.9 (mean 0.25). Olaparib dosing on days 1-5 was hindered by myelosuppression. Expansion cohort dose was defined as TMZ 75 mg/m^{2}daily plus olaparib 150 mg (OD) days 1-3 weekly. Of 13 evaluable patients receiving expansion dose-schedule, 9 completed cycle 1, 2 completed cycle 2 and 2 completed cycle 3. Currently 45% of the evaluable patients remain progression-free at 6 months, with 2 still on treatment (full data set May2017). Of 35 evaluable patients, 24 experienced AE Grade ≥3 (see Table). **Conclusions:** Olaparib penetrates both core and margins of recurrent GBM despite failing to penetrate the intact brain barrier in pre-clinical heathy rodent models. Combination with extended low dose TMZ is safe and well tolerated, yielding encouraging 6 month progression-free survival rates. Clinical trial information: NCT01390571.

	Evaluable patients experiencing AE	
Most frequent AEs	**n**	**%**
Lymphopenia	18	51
Neutropenia	9	26
Thrombocytopenia	6	17
Anaemia	5	14
Fatigue	2	6

2023 Poster Discussion Session; Displayed in Poster Session (Board #265), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

NCCTG N1174: Phase I/comparative randomized phase (Ph) II trial of TRC105 plus bevacizumab versus bevacizumab in recurrent glioblastoma (GBM) (Alliance). *First Author: Evanthia Galanis, Mayo Clinic, Rochester, MN*

Background: TRC105 is a humanized antibody targeting CD105 (endoglin), a member of the TGFβ receptor superfamily. CD105 is expressed in glioma stem cells and circulating endothelial cells (CECs) in GBM patients (pts), increasing following VEGF inhibition. N1174 was conducted in recurrent bevacizumab (bev) naïve GBM pts to investigate the hypothesis that CD105 blockade+bev can delay development of bev resistance. **Methods:** After a ph I cohort (15 pts) established the ph II dose of TRC105 as 10 mg/kg IV over 4 hours every 7 days in combination with standard dose bev, the ph II trial used 1:1 randomization with 90% power and 0.10 type I error to detect a 3 month (mo) difference in progression-free survival (PFS) between the two arms. CECs including CD105 positive subsets were measured by flow cytometry at baseline and multiple time points. **Results:** Based on 101 evaluable ph II pts, there was no significant difference in PFS between TRC105+bev and bev only (2.9 vs 3.2 mo, respectively; HR=1.14, 95% CI 0.73-1.77, p=0.57), or overall survival (10.0 vs 7.4 mo; HR 1.02 95% CI 0.63-1.65, p=0.93). Response rate (complete or partial) was 12.2% (6/49) for TRC105+bev and 11.6% (5/43) for bev only. Overall incidence of grade (gr) 3+ toxicity was higher for TRC105+bev (67.3% vs 32.7%, p<0.001) mainly due to 14 pts with gr 3 anemia in the TRC105+bev arm vs 0 in the bev only pts. Gr 3+ non-heme toxicities were higher in pts receiving TRC105+bev vs bev only (50% vs 30.6%, p=0.07), mainly due to headache (6 vs 1 pts) and hyperglycemia (3 vs 0 pts). CECs remained stable in combination treated pts, suggesting a possible impact of the anti-CD105 blockade, but increased at progression in the bev only arm. There was no association between PFS and initial changes in CEC values, independent of treatment received. **Conclusions:** TRC105 plus bev did not prolong median PFS vs single agent bev in recurrent GBM pts, although it was associated with a non-significant prolongation of OS. These data and associated correlative analysis of CECs from study pts point against endoglin being a clinically significant factor for the development of bev resistance. Support: U10CA180821, U10CA180882. Clinical trial information: NCT01648348.

2024 Poster Session (Board #266), Mon, 1:15 PM-4:45 PM

SHADOW study: Comparison of conventional clinical follow-up with clinician led video follow-up in newly diagnosed patients with intermediate and high grade glioma receiving adjuvant temozolomide therapy. *First Author: Vijay Maruti Patil, Tata Memorial Centre, Mumbai, India*

Background: In patients with gliomas, nurse led telephonic follow-up was associated with high satisfaction rates and was a valid alternative approach to conventional hospital based follow-up. However, other alternative forms of follow-up have not been studied in patients on active treatment. **Methods:** SHADOW was a prospective, randomized trial (CTRI/2017/01/007626). Adult intermediate to high grade glioma patients on adjuvant temozolomide with facilities for live video call were invited. After their consent, patients underwent a video follow-up (VF) 4 days prior to clinical follow-up (CF). The decisions taken during the VF and CF were noted in 5 domains, relating to temozolomide decisions (primary endpoint), concurrent medications, need for imaging, molecular testing and rehabilitation. Clinicians performing VF or CF were randomly assigned and were blinded for the other arm decisions. Patients satisfaction and costs incurred in each type of follow-up was documented. The planned sample size was 65, assuming an alpha of 0.05, a kappa coefficient of 0.9 with a one sided CI for lower limit of 0.6 and assuming a 20% lost to follow up rate. Agreement analysis was performed for calculation of Cohen's kappa coefficient. Results: 112 patients were screened and 65 were accrued. All patients underwent both VF and CCF. The concurrence in decision of administering temozolomide between VF and CCF was 100% (Cohen kappa = 1.0, 95%CI 1.0-1.0, $p < 0.00$). In concurrent medication domain (k = 0.66,95% CI 0.04 -1, $p < 0.00$), imaging domain (k = 1.0, 95%CI 1.0-1.0, $p < 0.00$), rehabilitation domain (k = 1.0, 95%CI 1.0-1.0, $p < 0.00$) and molecular testing domain (k = 0.65, 95% CI 0.20-1, $p < 0.00$), the agreement was substantial. The satisfaction rate was 100% post video follow up and was 98.5 % post clinical follow up. The median cost incurred in VF was 58.15 USD (IQR 43.38-91.69) while that incurred in CCF was 131.23 USD (IQR 68.8-256 ($p < 0.00$)). Conclusions: The decisions taken regarding administration of adjuvant TMZ were similar between VF and CCF. Hence, it's practical and economical to substitute CCF with VF during adjuvant TMZ administration. Clinical trial information: CTRI/2017/01/007626.

2025 Poster Session (Board #267), Mon, 1:15 PM-4:45 PM

Association of aggressive resection with survival and progression-free survival in adult low-grade glioma: A systematic review and meta-analysis with numbers needed to treat. *First Author: Timothy J Brown, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Low-grade gliomas (LGG) account for 17-22% of all primary brain tumors. Optimal surgical management consists of optimum safe resection with the goal of complete resection. We performed a systematic review and meta-analysis to quantify the association of extent of resection with likelihood of survival, expressing our results in numbers needed to treat (NNT). **Methods:** A systematic review and study-level meta-analysis to determine the association of resection with overall survival and progression-free survival in newly diagnosed, supratentorial LGG in adults was performed by querying PubMed. Data were extracted to compare gross total resection (GTR) to subtotal resection (STR) and STR to biopsy (Bx) to determine relative risks (RR) of death and progression at 2, 5, and 10 years. Data were analyzed using a random effects model. NNT were calculated from significant comparisons and rounded up to the nearest whole number. Quality of evidence was determined by American Academy of Neurology criteria. **Results:** The systematic review resulted in 283 potential studies. Ultimately 29 studies were included in at least one comparison. There were no high quality (class I and II) or prospective studies discovered in the review. Comparing GTR to STR, RR with 95% confidence intervals (CI) of death at 2, 5, and 10 years, and NNT to avoid one death at 2, 5, and 10 years (GTR vs. STR) were 0.29 [0.17-0.52, $p < 0.0001$, NNT 17], 0.39 [0.29-0.51, $p < 0.00001$, NNT 6], and 0.50 [0.35-0.70, $p < 0.0001$ NNT 4]. RR and NNT for progression (GTR vs. STR) at 2, 5, and 10 years were 0.37 [0.24-0.57, $p < 0.0001$ NNT 7], 0.50 [0.39-0.64, $p < 0.0001$ NNT 4], and 0.67 [0.53-0.84, $p = 0.0005$ NNT 4]. Comparing STR to Bx, RR of death at 2, 5, and 10 years were 0.55 [0.34-0.88, $p = 0.01$ NNT 10], 0.9 [0.61-1.34], and 0.95 [0.73-1.23]. **Conclusions:** Increasing resection thresholds appear to be associated with improved overall and progression free survival, but the body of literature consists of low quality studies. Prospective studies are required to explore whether extent of resection matters or whether resectable tumors share a favorable biology associated with better outcome.

2026 Poster Session (Board #268), Mon, 1:15 PM-4:45 PM

A phase II trial of temozolomide (TMZ) 1 week on/1 week off as initial treatment for high risk low grade oligodendroglial tumors: An AINO (Italian Association for Neuro-Oncology) study. *First Author: Roberta Ruda, Department of Neuro-Oncology, University of Turin and City of Health and Science, Turin, Italy*

Background: The efficacy of dose-dense temozolomide (TMZ, 1 week on/1 week off) in grade II gliomas is not well known and could depend on the molecular subtype. **Methods:** Between 2006 and 2010 a single arm phase II study on 60 patients with grade II oligodendroglial tumors was performed. Inclusion criteria were as follows: 1) age $\geq$ 18 years; 2) KPS $\geq$ 70; 3) biopsy-proven grade II oligodendroglioma or oligoastrocytoma ; 4) a measurable residual tumor after surgery. The primary endpoint was tumor response on MRI according to RANO criteria, while the secondary endpoints were progression-free survival (PFS), overall survival (OS), and seizure control. Most patients (65%) had seizures. Molecular factors (IDH 1-2 mutations, 1p19q codeletion, MGMT methylation) were available in 49/60 patients (81.7%). The median number of cycles was 11 (2-18). Median follow up was 64 months (7-112). **Results:** Response rate was PR in 21/60 (35%) patients, minor PR (mPR) in 14/60 (23%), SD in 21/60 (35%) and PD in 4/60 (7%). Most patients achieved the best tumor response within 6 months after the start of TMZ. Among patients with mPR and PR, 15/49 (30.6%) were IDH1-2 mutated with a PFS of 71.4% at 36 months and 28.6% at 60 months with a median value of 46 months while 11/49 (22.4%) were IDH 1-2 wild-type with a PFS of 45.8% at 36 months and 25% at 60 months with a median value of 34 months. OS was 90.5% at 36 months and 66.7% at 60 months with a median value of 76 months in the IDH1-2 mutated/1p19q codeleted subgroup, while OS was 66.7% at 36 months and 50% at 60 months with a median value of 60 months in the IDH1-2 wild-type subgroup. Responses were higher in MGMT methylated patients. Seizure improvement was achieved in 29/34 patients (85%): 17/33 (52%) patients at 12 months and 18/29 (62.1%) at 24 months were seizure-free. Time to maximal seizure response was earlier than that observed on MRI (3 vs 6 months). **Conclusions:** Dose-dense TMZ has shown a significant activity in terms of tumor and seizure control, especially in IDH1-2 mutated/1p19q codeleted patients. Seizure reduction could represent an early indicator of response to chemotherapy and maybe predict the duration of response. Clinical trial information: 2007-000386-38.

2027 Poster Session (Board #269), Mon, 1:15 PM-4:45 PM

Use of targeted next generation sequencing (NGS) to assess mutational load in glioblastoma (GBM). *First Author: Stephen Joseph Bagley, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

Background: Trials of immune checkpoint inhibitors in GBM are ongoing. Evidence from other tumors suggests that high mutational load predicts response to these agents. We estimated mutational load in adults with newly diagnosed GBM using targeted NGS and assessed its association with other clinicopathologic parameters. **Methods:** NGS was performed for all patients diagnosed with isocitrate dehydrogenase wild-type (IDH-WT) GBM at our institution since September 1, 2016. Our panel performs targeted exome sequencing of 153 cancer-related genes (+/- 10 bp at intron/exon boundaries) and detects insertions, deletions, and single nucleotide variants at an allele frequency of 2%. Polymorphisms present in $>$ 0.1% of the population according to the ExAC database and 1000 Genomes Project were filtered to reduce germline variants in the absence of matched normals. To avoid upward skewing of mutational load due to the panel's preferential detection of genes recurrently mutated in cancer, alterations with known or likely functional disruption per the COSMIC database and/or our internal variant knowledge base were also not counted. The number of mutations counted was divided by the coding region target territory of the NGS panel (~0.5 Mb) to extrapolate mutational load to the whole exome. The Mann-Whitney U test was used to compare mutational load according to sex, age ($\geq$65 vs. $<$ 65), and *MGMT* methylation status (positive vs. negative). **Results:** Of 28 patients, median age was 65, 75% were male, and 37% were *MGMT*-methylated. Mean mutational load was 3.6 mutations/Mb (range 0-8, standard deviation 2.3) and was higher in males (4.3, 95% CI 3.3-5.3) compared to females (1.4, 95% CI 0.03-2.8) ($p = 0.004$). Mutational load did not differ according to age or *MGMT* methylation. **Conclusions:** In newly diagnosed IDH-WT GBM, targeted NGS revealed an estimated mutation rate similar to that reported in whole exome sequencing studies. In addition, we detected a higher mutational load in males compared to females. The latter finding adds to recent evidence suggesting sex-specific differences in the biology of GBM, and implies that future studies should account for sex when assessing mutational load as a predictive marker of immune checkpoint inhibition.

2028 Poster Session (Board #270), Mon, 1:15 PM-4:45 PM

Comparison of high dose methotrexate treatments in CNS lymphoma patients: The Henry Ford experience. *First Author: Ranya Selim, Henry Ford Hospital, Detroit, MI*

Background: The main backbone of therapy for CNS lymphoma involves systemic treatment with high dose methotrexate (HDMTX)-based regimens, with radiotherapy reserved only for cases that fail systemic therapy due to the significant cognitive toxicity of radiation. Over the last decade, rituximab and subsequently temozolomide were added to HDMTX chemotherapy regimens. **Methods:** Patients diagnosed with CNS lymphoma between 2009 and 2015 were identified. A retrospective cohort study was conducted of patients who received HDMTX alone (Cohort A), HDMTX and rituximab (Cohort B) and HDMTX, rituximab and temozolomide (Cohort C). Data collected included treatment related adverse events along with OS and PFS. **Results:** 31 patients were diagnosed with CNS lymphoma. 11, 10 and 6 patients were in cohorts A, B and C respectively. Median PFS and OS for the entire cohort were 14 and 25 months respectively. Cohort results were compared to the respective reference trials published in the literature. Cohort A had a PFS of 11 months and OS of 12 months compared to 12.8 months and 22.8+ months in the reference Phase II trial. Cohort B had a median PFS of 25+ months and OS of 41 months compared to 21 months and 33.5 months in the reference trial. Cohort C had a 2-year PFS of 0.50 compared to 0.57 in the reference trial. 3 (9.6%), 5 (16.1%), and 2 (6.4%) patients developed renal dysfunction in cohorts A, B and C respectively. 4 (12.9), 2 (6.4%), and 0 patients developed leukopenia in cohorts A, B and C respectively. 3 (9.6), 2 (6.4%), and 1 (3.2%) patients developed anemia in cohorts A, B and C respectively. 1 (3.2%), 1 (3.2%) and 1 (3.2%) patient developed thrombocytopenia in cohorts A, B and C respectively. **Conclusions:** The addition of Rituximab to HDMTX treatment for the treatment of CNS lymphoma increased the PFS and OS compared to HDMTX alone and is in concordance with the reference phase II trials reported in the literature if not better. In addition, our data at HFH shows no increased risk of adverse events with combination therapies compared to HDMTX alone. The addition of Temozolomide to Rituximab and High Dose methotrexate treatment showed a median 2 year PFS of 0.50 which is comparable to published reports of a 2-year PFS of 0.59.

2029 Poster Session (Board #271), Mon, 1:15 PM-4:45 PM

Neurocognitive outcome in children with sensorineural hearing loss after treatment of malignant embryonal brain tumors. *First Author: Christine Dahl, Hospital for Sick Children, Toronto, ON, Canada*

Background: Neurological side effects associated with childhood brain tumors and their treatments contribute to long term neurocognitive morbidity. The aims of this study were to identify the incidence of sensorineural hearing loss (SNHL) in a large sample of children treated for malignant brain tumors, and to evaluate the potential relationship between SNHL and intellectual functioning following the completion of treatment. **Methods:** We conducted a prospective follow-up study at a single center with review of 119 patients treated for embryonal brain tumors at the Hospital for Sick Children, between 1996-2015, to analyze the impact of significant SNHL (Chang $>$ 2b) on intellectual function. Hearing was assessed post-treatment (median age: 13.5y (+4.5)) and the median age for neurocognitive testing was 12.8y (+ 4.1). The median interval from time of diagnosis was 5.8y (+ 3.7). **Results:** Severe SNHL was identified in half the patients (50.4%, n = 60/119). We identified a subset of patients (n = 61) who had assessments of intellectual function. In this cohort, intellectual function was significantly poorer in the group with severe SNHL, even after controlling for the effect of craniospinal radiation (severe SNHL 22.4 Gy + 13.3, no or mild hearing loss 20.4 Gy +12.8) and boost dose and volume. Children experiencing severe SNHL had lower overall IQ (severe SNHL 72.4 + 16.6; no/mild hearing loss 92.0 + 20.5) $p < 0.001$ and in significantly lower verbal comprehension (severe SNHL 78.7 + 15.9; no/mild hearing loss 94.7 + 13.8) $p < 0.001$, and working memory (severe SNHL 78.2+ 17.6; no/mild hearing loss 94.8 + 16.4) $p < 0.001$, scores. **Conclusions:** Hearing loss is a much more significant complication in children with embryonal brain tumors than previously estimated. We show the profound impact of hearing loss on intellectual deficit in children. Namely, patients with severe SNHL have difficulty using and understanding verbal language, and they have a reduced ability to concentrate and manipulate information in short-term memory. Our results have implications on future trial designs and follow-up of children treated for embryonal brain tumors.

2031 Poster Session (Board #273), Mon, 1:15 PM-4:45 PM

Is less more? Comparing chemotherapy alone to chemotherapy and radiation for high risk, grade II glioma—An analysis of the National Cancer Data Base. *First Author: Jaymin Jhaveri, Department of Radiation Oncology at Emory University, Atlanta, GA*

Background: Grade II glioma patients with subtotal resection (STR) or age $\geq$ 40 are considered high risk. RTOG 9802 demonstrated that for these high-risk patients, chemotherapy and radiation therapy improved overall survival (OS) compared to radiation alone. The purpose of this study is to compare the OS of high risk, grade II glioma patients treated with adjuvant chemotherapy alone (CA) to chemotherapy and radiation therapy (CRT). **Methods:** Using the National Cancer Data Base (NCDB), high risk (age $\geq$ 40 or STR) grade II glioma patients with oligodendroglioma, astrocytoma, or mixed tumors were identified. Patients receiving CA were compared to patients receiving CRT. Univariate and multivariable analyses (MVA) were performed. Propensity score (PS) matching was utilized to account for difference in patient characteristics. Kaplan Meier statistics were utilized to compare OS. **Results:** 1054 high risk, grade II glioma patients were identified, 47.1% receiving CA and 52.9% receiving CRT. Median follow up time was 55.1 months. Patients treated with CA were statistically more likely (all $p < 0.05$) to be oligodendroglioma histology (65.5% vs. 34.2%), 1p/19 co-deleted (22.8% vs. 7.5%), younger median age (47 vs. 48 years) and treated at an academic program (65.2% vs. 50.3%). MVA demonstrated treatment type was not a significant predictor for OS ($p = 0.125$), while tumor size $>$ 6cm, astrocytoma histology, and older age were predictors for worse survival (all $p < 0.05$). Utilizing 1:1 PS matching, with 662 total patients, OS was statistically similar ($p = 0.919$) for CA and CRT at 5 years (69.1% vs. 68.5%, respectively) and 7 years (55.5% vs. 60.0%, respectively). **Conclusions:** In this retrospective analysis of the NCDB, long term OS for high-risk, grade II glioma patients treated with CA appears similar to CRT. These findings are hypothesis generating, with the standard of care still remaining CRT as established by RTOG 9802. Prospective clinical trials comparing CA and CRT are warranted.

2032 Poster Session (Board #274), Mon, 1:15 PM-4:45 PM

Benefits and costs of bevacizumab in recurrent glioblastoma: A quality adjusted survival and cost analysis (EVALUATE). *First Author: Katrin Lisa Conen, University of Basel and University Hospital Basel, Medical Oncology, Basel, Switzerland*

Background: Routine clinical use of bevacizumab (Bev) in recurrent glioblastoma (rGBM) is controversial, as no large RCT has shown a survival advantage. We describe treatment algorithms, survival (OS), quality-adjusted survival (QAS) as well as costs of patients (pts) with GBM treated at an academic hospital in Switzerland, where Bev is registered and reimbursed for rGBM. **Methods:** Pts' and treatment characteristics from diagnosis until death (including neurological symptoms and toxicities) of all pts over a 5-year period were retrospectively retrieved from our GBM database. For each treatment period (1st-line, recurrence and "best supportive care") time to next treatment (TNT), OS and QAS were calculated and modelled for prognostic factors (Cox regression). QAS was evaluated as previously described (Murray *et al*). In- and out-patient costs were calculated from time of diagnosis until death in respect of Bev treatment (+Bev vs. –Bev). **Results:** 82 newly diagnosed GBM pts with a median age of 66 years (range 39-85), median KPS of 90% (range 50-100%), who were treated with 1 (n = 75), 2 (n = 36) or 3 (n = 14) lines of therapy, respectively, lived for a median OS of 11.9 (SD 9.7) months (mos). QAS was 5.3 (SD 6.9) mos i.e. 44% of the numerical survival time. 40% of patients were treated with Bev at 1st or 2nd recurrence. Pts, who were selected for BEV treatment, had a longer time from diagnosis to 2ndline treatment (median 5.2 (SD 6.3) mos) as compared to pts in the -Bev group (median 2.1 (SD 1.8) mos). Younger age and Bev treatment were associated with longer OS and QAS. QAS to OS ratio was 52% (9.4 out of 18.1 mos) for BEV treated patients and 34% (2.8 out of 8.2 mos) for the –Bev group, respectively. Bev treatment increased the overall treatment costs by 1.7x. The population adjusted incremental cost-effectiveness ratio (ICER) was CHF 75,669 per life year gained. **Conclusions:** QAS in patients with GBM is short (one third to half of OS). In our cohort, pts selected for Bev treatment had longer OS and longer QAS - at costs below the accepted threshold of 100,000 CHF per life year gained. Whether this gain of lifetime is a direct result of Bev treatment or a consequence of a selection bias needs to be addressed prospectively.

2033 Poster Session (Board #275), Mon, 1:15 PM-4:45 PM

Retrospective review of safety and efficacy of checkpoint inhibition in refractory high-grade gliomas. *First Author: Samantha Reiss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Treatment options for refractory high grade gliomas (HGG) are limited. Programmed cell death ligand-1 (PD-L1) expression has been reported in 0-61% of HGGs and therefore might be a suitable target in HGG. The purpose of this study was to describe safety and efficacy of PD-1 inhibition in patients with refractory HGGs. **Methods:** This IRB approved single center retrospective study at Memorial Sloan Kettering Cancer Center included pathologically confirmed HGG with an age ≥18 years who received a PD-1 inhibitor between 9/2014 and 10/2016 outside of a clinical trial. **Results:** Twenty five HGGs were identified. All patients received the PD-1 inhibitor pembrolizumab (pembro) as part of compassionate use. Median age was 49 years (range 30-72); 44% were men; 13 had glioblastoma (52%), 7 anaplastic astrocytoma (28%), 2 anaplastic oligodendroglioma (8%), 2 unspecified HGG (8%), and 1 gliosarcoma (4%). Patients received a median of 4 prior lines of therapy (range 1-9). Nineteen (76%) previously failed bevacizumab. Median baseline KPS was 80 (range 50-100). Concurrent treatment included bevacizumab in 17 (68%) or bevacizumab and temozolomide in 2 (8%) patients. Median number of doses administered was 3 (range 1-14). Treatment toxicity and response was assessed in 24 patients. PD-1 inhibitor related adverse events (AEs) included LFT elevations (33%), hypothyroidism (17%), diarrhea (17%), myalgias/arthralgias (13%), and rash (8%). Other common AEs were hyperglycemia, fatigue, thrombocytopenia, lymphopenia, headache, and nausea in the setting of concomitant therapy and additional supportive care (dexamethasone). Grade 3 AEs included seizure (4%), headache (4%), nausea (4%), and vomiting (4%). Best radiographic response was partial response (n = 2), stable disease (n = 5), and progressive disease (n = 17). Median progression free survival (PFS) was 42 days (range 7-282) and median overall survival was 121 days (range 15-415). Three patients (12%) had a PFS > 90 days; of these, 2 received single agent pembro. **Conclusions:** Patients with HGG had low response rates. However, a small number of patients had prolonged PFS. Pembro was tolerated with few serious AEs, even in patients receiving concomitant therapy.

2034 Poster Session (Board #276), Mon, 1:15 PM-4:45 PM

Phase I/II study of an implantable device delivering low intensity pulsed ultrasound (LIPU) to disrupt the blood-brain barrier (BBB) followed by intravenous carboplatin chemotherapy in patients with recurrent glioblastoma (GBM). *First Author: Ahmed Idbaih, Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, Paris, France*

Background: The BBB prevents the passage of most drugs from the blood to the brain and may be responsible for the limited efficacy of current chemotherapies in GBM patients. Two to four minutes of LIPU in combination with injection of micron-sized microbubbles has been shown to be a safe method for disrupting the BBB for a duration of 6 hours to increase the passage of drugs such as carboplatin by 5 to 7 fold in normal brain. **Methods:** Patients with recurrent GBM were implanted with a 1 MHz, 10-mm diameter pulsed ultrasound device in a burr hole during additional debulking surgery or during a dedicated procedure under local anesthesia. Ultrasound dose was escalated using a 3+3 Simon design. The device was activated monthly in combination with injection of a sulfur hexafluoride microbubble to transiently disrupt the BBB in 5 cm^3 of the tumor field before IV administration of carboplatin chemotherapy (AUC4-6). Patients received 150-270 seconds of pulsed ultrasound < 1 hour prior to chemotherapy. BBB disruption was visualized using contrast-enhanced T1w MRI, and patients were monitored clinically and with T2, FLAIR, DWI and SWI sequences. Tumor progression was evaluated using the RANO criteria. **Results:** Nineteen patients were treated by LIPU until tumor progression. In 65 ultrasound sessions, 52 showed BBB disruption. The median number of monthly sonications per patient was 3 and ranged from 1-10. No significant adverse events related to ultrasound sonications were observed. Six patients (31%) had long PFS (19, 20, 35, 38, 40, 52 weeks). When tumor recurrence occurred, it was predominantly outside of the ultrasound sonication field. **Conclusions:** This trial has demonstrated that LIPU is a safe modality for disrupting the BBB in GBM patients and may increase the effectiveness of drug therapies in the brain. The sonication of larger volumes of brain may further increase the effectiveness of this therapy in patients with GBM. Clinical trial information: NCT02253212.

2035 Poster Session (Board #277), Mon, 1:15 PM-4:45 PM

PD-L1 expression of high grade glial tumors at diagnosis and change of expression status at recurrence. *First Author: Basak Oyan, Acibadem University, Istanbul, Turkey*

Background: PD-L1 expression status is the main predictive factor for response to immune checkpoint inhibitors. PD-L1 status may change over time with the impact of therapies. The aim of this study is to determine if PD-L1 expression status changes in recurrent gliomas after chemoradiotherapy. **Methods:** Thirty eight patients with recurrent high grade gliomas who had surgical excision at least two times were included in this retrospective cross-sectional study. Nine patients were excluded because of the lack of appropriate pathology slides for pathologic evaluation. PD-L1 expression of 29 patients was evaluated by an expert pathologist with immunohistochemical methods. PD-L1 positivity was defined as expression in ≥1% of tumor cells. Change in PD-L1 expression status was defined as an absolute 5% difference between two resections. **Results:** Of the 29 patients, 15 patients (51.7%) had PD-L1 expression in ≥1% of tumor cells and 7 patients (24.1%) had PD-L1 expression in ≥10% of tumor cells. Tumor PD-L1 expression (defined as expression in ≥1% of tumor cells) was positive in 15 (51.7%) of 29 patients at diagnosis and at the time of recurrence. The PD-L1 status did not change in 17 patients (58.6%). 8 patients had PD-L1 negative tumors both at diagnosis and at recurrence, while 9 patients had PD-L1 positive tumors both at diagnosis and at recurrence. In 6 patients (20.7%) a negative-to-positive switch and in 6 patients (20.7%) a positive to negative switch were seen. Tumor PD-L1 expression increased in 7 of 29 patients (24.1%) and decreased in 9 of 29 patients (31.1%). PD-L1 expression remained stable in 13 of 29 patients (34.4%). The change in PD-L1 status over time was not statistically significant. **Conclusions:** More than 50% of high grade glial tumors express PD-L1 at diagnosis, so these tumors are good candidates for immune checkpoint inhibitors. The expression status changes in more than 40% of high grade glial tumors at recurrence, so immune responsiveness of glial tumors can be modified by treatments like chemotherapy and radiotherapy.

2036 Poster Session (Board #278), Mon, 1:15 PM-4:45 PM

Study of the impact of cytomegalovirus-encephalopathy on survival of brain cancer patients undergoing treatment with radio(chemo)therapy. *First Author: Nicole Lydia Goerig, Department of Radiation Oncology, Universitatsklinikum Erlangen, Friedrich-Alexander-Universitat Erlangen-Nürnberg, Erlangen, Germany*

Background: As recently demonstrated (Neurooncology, 2016), neurological decline of patients with brain cancer (high grade glioma, brain metastases) during radio(chemo)therapy (RCT) of the brain is oftentimes caused by CMV-encephalopathy but not disease progression or therapeutic complications. We examined the impact of clinical and serological CMV-status on the survival one year after the onset of radio(chemo)therapy of the brain. **Methods:** 118 patients requiring whole-brain radiotherapy for brain metastases (n = 55) or local RCT of the brain for high-grade gliomas (n = 63) were observed in the prospective GLIO-CMV-01 study. MRIs and blood samples were obtained before, halfway through, and at the end of radiotherapy. MRIs were screened for disease progression or increased intracranial pressure. Blood was tested for anti-CMV immunoglobulin (Ig)M, anti-CMV IgG, and CMV DNA. **Results:** 68 of 118 (58%) patients were positive for anti-CMV IgG before radio(chemo)therapy. 28 of those 68 (41%) developed CMV-viremia during or up to 28 days after the end of irradiation. 21 of those 28 (75%) required treatment for symptomatic CMV-associated encephalopathy. One year after the start of RCT, survival was 72% (34/47) (no encephalopathy, anti-CMV-IgG+) or 68% (34/50) (no encephalopathy, anti-CMV-IgG-) versus 38% (8/21) (encephalopathy) (p = 0.0034). **Conclusions:** Symptomatic CMV-encephalopathy all but doubles the mortality of brain cancer patients within one year of RCT, despite antiviral treatment with ganciclovir. These findings heavily underline the importance to identify patients with increased risk profile for developing CMV-encephalopathy before initiating RCT.

2037 Poster Session (Board #279), Mon, 1:15 PM-4:45 PM

Comparison of 2-hydroxyglutarate (2HG) levels in tissue and serum of isocitrate dehydrogenase (IDH)-mutated (MUT) versus wild-type (WT) gliomas. *First Author: Hao-Wen Sim, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: IDH mutations are common in low-grade gliomas and confer significantly improved prognosis. IDH catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate, and subsequently to the oncometabolite 2HG. Mutant IDH leads to preferential accumulation of the R relative to the S enantiomer of 2HG. We analyzed the ratio of R to S enantiomers (rRS) in glioma tissues and matched serum samples, and correlated findings with IDH status, 1p19q codeletion status and survival. **Methods:** Fresh frozen glioma tissues and matched serum samples were obtained from the University of Toronto Brain Tumor Bank. IDH status was determined by immunohistochemistry and confirmed by 450K methylation profile or direct sequencing. 1p19q codeletion status was determined by loss-of-heterozygosity PCR analysis. R-2HG and S-2HG levels were quantified using HPLC tandem mass spectrometry coupled with a CHIROBIOTIC column. **Results:** Glioma tissues from 70 patients were analyzed – 52 with IDH MUT and 18 WT. 30 had matched serum samples. Using glioma tissues, rRS clearly distinguished MUT vs WT (median 574 vs 1.3, $p < 1x10^{-9}$) with only three outliers. In contrast, rRS was not elevated in serum samples (median 1.5 vs 1.2, p = 0.13). Overall survival (OS) was significantly longer for MUT vs WT (median 178 vs 33 months, $p < 1\times10^{-7}$). Stratifying MUT by tissue rRS, median OS was 197, 178, 178 and 122 months for lowest to highest quartiles of rRS respectively. 1p19q codeletion status and tumor latency did not explain this trend, given rRS was similar in codeleted vs non-codeleted MUT, and similar in MUT operated < 3 vs ≥3 months from diagnosis. Progression-free survival results corresponded to OS. **Conclusions:** rRS from glioma tissues effectively differentiated MUT vs WT, whereas serum samples were unreliable. Unlike current methods, tissue rRS enables real-time determination of IDH status, and thus may guide clinical practice such as extent of surgical resection intraoperatively and upfront selection of adjuvant therapy. rRS potentially stratifies survival within MUT patients, providing detailed correlative information.

2038 Poster Session (Board #280), Mon, 1:15 PM-4:45 PM

Clinical and molecular subgroups of ependymoma in adulthood: An analysis of the German Glioma Network. *First Author: Dorothee Gramatzki, Laboratory of Molecular Neuro-Oncology, Department of Neurology, and Neuroscience Center Zurich, University Hospital and University of Zurich, Zurich, Switzerland*

Background: Ependymoma is a subtype of glioma that is rare in adults. Its classification has remained entirely morphological until recently, and surgery and radiotherapy remain the mainstays of treatment. Here we characterized DNA methylation profiles and their clinical correlates in the prospectively assembled cohort of the German Glioma Network. **Methods:** The GGN cohort was screened for patients diagnosed with myxopapillary ependymoma, subependymoma, classic ependymoma and anaplastic ependymoma for whom clinical data and remaining tumor tissue were available. Tumors were subjected to DNA methylation profiling using the Illumina Infinium HumanMethylation450 BeadChip platform. Molecular data were correlated with morphological tumor and clinical patient characteristics. **Results:** One hundred and twenty-two ependymoma patients with available tumor tissue were identified. Each adult tumor could be assigned to one of the previously defined methylation classes of ependymoma. Molecular entities of ependymal brain tumors display distinct copy-number variations. PF-EPN-B and ST-EPN-RELA tumors tend to have a worse prognosis than other ependymal subtypes in adults. **Conclusions:** Molecular classification of adult ependymal methylation subclasses should be implemented in routine diagnostics. Patients with PF-EPN-B and ST-EPN-RELA subtypes might benefit from early treatment beyond surgery.

2039 Poster Session (Board #281), Mon, 1:15 PM-4:45 PM

Overall survival (OS) by line of therapy (LOT) in Medicare-enrolled glioblastoma multiforme (GBM) patients (pts). *First Author: Abdalla Aly, Pharmerit International, Bethesda, MD*

Background: In clinical trials, the median OS of elderly GBM pts on standard treatment (tx) is ~9 months (mos) from diagnosis (dx), but has not been described in the real world (RW). This analysis describes RW OS for US Medicare GBM pts by LOT. **Methods:** GBM pts aged ≥66 years (y) were identified in SEER-Medicare (2007–2011). Pts were followed from dx to death, Medicare disenrollment or 12/31/2013. Systemic tx patterns were characterized as untreated (0L), ≥first line (1L+) and ≥second line (2L+). OS was estimated by the Kaplan-Meier method from dx for 0L, and from LOT start for 1L+ and 2L+. **Results:** Among 2533 eligible GBM pts (median age: 74 y; Charlson comorbidity index [CCI] ≥2: 13%), 49.9% received 1L+ and only 16.3% received 2L+. Median (1-year) OS for all pts was 5.3 mos (26%), range 1.6–10.7 mos (3–45%) depending on LOT, surgical resection (R) or Biopsy alone (B), tumor size, age, and CCI (Table). **Conclusions:** Receipt of tx has a significant impact on OS in Medicare GBM pts. This RW study shows that only 50% of pts receive tx, even though each LOT is associated with additional OS benefit. This suggests an unmet need for more efficacious therapies to allow additional treatment and improve outcomes.

	Median OS, mos (1-year OS, %)							
	All (N = 2533)		0L (N = 1269)		1L+ (N = 1264)		2L+ (N = 412)	
	R (n = 1839)	B (n = 694)	R (n = 822)	B (n = 447)	R (n = 1017)	B (n = 247)	R (n = 362)	B (n = 50)
All Pts	5.5 (26)	2.7 (8)	3.6 (11)	2.4 (4)	8.8 (38)	3.5 (16)	8.1 (31)	6.9 (23)
Tumor size (cm)								
< 5	6.5 (32)*	3.1 (10)*	3.8 (15)*	2.5 (5)*	10.7 (45)*	5.9 (20)	8.4 (34)	8.1 (18)
5–7	5.5 (25)*	2.7 (8)*	3.6 (10)*	2.4 (3)*	8.6 (37)*	3.3 (16)	8.1 (31)	6.9 (26)
> 7	3.2 (8)*	1.7 (5)*	1.9 (0)*	1.6 (3)*	5.6 (20)*	2.5 (7)	5.3 (22)	1.7 (0)
Age								
66–70	8.1 (36)*	2.8 (9)*	4.2 (17)*	2.6 (4)*	10.6 (45)*	3.8 (18)	8.3 (34)	8.1 (31)
71–75	6.1 (28)*	3.1 (8)*	4.2 (15)*	2.7 (7)*	8.5 (37)*	3.6 (10)	8.1 (29)	6.2 (19)
76–80	4.7 (19)*	2.6 (11)*	3.3 (7)*	2.3 (3)*	7.0 (31)*	4.1 (26)	6.9 (26)	7.7 (19)
80+	3.6 (12)*	2.4 (5)*	3.0 (4)*	2.3 (2)*	5.6 (29)*	3.2 (13)	8.6 (38)	5.7 (25)
CCI								
0	6.3 (29)*	2.7 (9)	3.7 (12)*	2.3 (4)	9.9 (42)*	3.5 (17)	8.1 (32)	8.2 (24)
1	4.7 (21)*	2.5 (6)	3.4 (8)*	2.3 (3)	7.5 (33)*	3.0 (12)	8.1 (31)	4.8 (14)
2+	3.7 (13)*	2.8 (9)	3.0 (9)*	2.5 (4)	4.9 (19)*	5.4 (19)	6.9 (28)	6.3 (22)

2040 Poster Session (Board #282), Mon, 1:15 PM-4:45 PM

Changes in survival of primary central nervous system lymphoma based on a review of national databases over 40 years. *First Author: Joe Sammy Mendez, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There has been significant improvement in treatment outcomes of Primary Central Nervous System Lymphoma (PCNSL) at specialized centers over past decades, and it is unclear if these changes have translated to benefits in the general population. In this study, we utilized national databases to examine survival trends over time. **Methods:** Incidence rates were obtained from the Central Brain Tumor Registry of the United States (CBTRUS, 2000 – 2013) and 18 Surveillance, Epidemiology and End Results (SEER, 1973 – 2013) registries. Data for survival analysis was obtained from SEER and analyzed using SEER*STAT. To focus on non-HIV-associated PCNSL, patients with "other infectious and parasitic diseases including HIV" as cause of death and follow up were excluded. CBTRUS identified 19,027 patients over 13 years and SEER 6,765 over 40 years. **Results:** The annual incidence of PCNSL in 2013 was 0.4 per 100,000 population (CBTRUS/SEER). Incidence increased from 0.1 per 100,000 in the 1970s to 0.4 per 100,000 in the 1980s, correlating with an increase in the diagnosis of elderly patients, ≥70 (1973:0.2 vs 2013:2.1 – SEER). Incidence rates differed greatly between young and elderly patients (20-29: 0.08 vs 70-79: 4.32 – CBTRUS). The median overall survival (mOS) of all patients is 17 months (m) with no survival benefit based on sex. Survival doubled from 12.5 m in the 1970s to 26 m in the 2010s. There was a significant difference in survival based on age: < 50: 83 m vs 50-69: 25 m vs ≥70: 6 m (p-value < 0.0001). In patients < 50, mOS increased from 35.5 m in the 1970s to 134 m in the 2000s (mOS not achieved in 2010s). In patients 50-69, mOS increased from 8 m in the 1970s to 35 m in the 2010s. However, mOS in the elderly population, ≥70, has not changed in the last 40 years (6 m in the 1970s vs 7 m in the 2010s, p-value = 0.1). **Conclusions:** PCNSL is a disease that more frequently affects the elderly. Although overall survival has increased over the past 4 decades, reflecting current literature in PCNSL, survival in the elderly has not changed since the 1970s. Identification of this vulnerable patient population highlights the need for clinical trials targeting the elderly in hopes of improving treatment strategies and ultimately outcomes.

2042 Poster Session (Board #284), Mon, 1:15 PM-4:45 PM

Phase 2 study to evaluate safety and efficacy of MEDI4736 (durvalumab [DUR]) in glioblastoma (GBM) patients: An update. *First Author: David A. Reardon, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

Background: DUR is a human IgG1 monoclonal Ab against PD-L1. PD-1/PD-L1 blockade has shown benefit in solid tumors. PD-L1 is expressed by many GBM tumors while cytotoxic lymphocytes infiltrating GBM tumors often express PD-1; thus, there is a rationale for exploring PD-1/PD-L1 blockade in GBM. Bevacizumab (BEV) is a VEGF-specific angiogenesis inhibitor approved for recurrent GBM. PD-L1 blockade and angiogenesis inhibition may be synergistic. **Methods:** This ongoing Phase 2, multicenter, open-label study (NCT02336165) evaluates safety/efficacy of DUR (10 mg/kg every 2 wks) in 5 GBM cohorts. Secondary endpoints are safety/tolerability, median PFS/OS, overall response rate and quality of life measures. Exploratory endpoints: neurologic function and immunocorrelative biomarkers. **Results:** Enrollment as of 16 Dec 2016: Cohort A = 35, B = 31, B2 = 34, B3 = 34, and C = 20 pts. Enrollment is ongoing for Cohorts A and C. This is an update to the interim analysis that was reported for Cohort B (male: 83.9%; mean age: 54.0 [24-77] years; baseline ECOG PS0: 51.6%, PS1: 48.4%; baseline measurable lesions: 77.4%). Incidences of treatment-related adverse events (TRAEs) by max CTCAE grade (Gr) were Gr1: 35.5%; Gr2: 41.9%; Gr3: 9.7%; and Gr4/5: 0%. Most common TRAEs (≥3 pts): fatigue, headache, hemiparesis, gait disturbance, increased AST, and decreased platelets/WBCs/lymphs. Six of 30 evaluable pts were progression free at 6 months (Kaplan-Meier, 20.0% [90% CI: 9.7, 33.0]); best overall response: partial response, 4 (13.3%) pts and stable disease, 14 (46.7%). At 1 year, 4 pts remained progression free (longest PFS ongoing at 80 wks, n=2). OS-6 and OS-12 are 59.0 and 44.4%, respectively. As of 16 Dec 2016, 7 pts remain alive (longest OS ongoing at 86 wks). **Conclusions:** DUR monotherapy appears to be well tolerated and shows durable activity in a subset of BEV-naïve recurrent GBM pts. Study is ongoing. Clinical trial information: NCT02336165.

GBM Population	Cohort (planned n)	Concomitant Therapy	Primary Endpoint
Newly diagnosed + unmethylated MGMT	A (37)	Radiotherapy	12-month overall survival (OS-12)
BEV naïve recurrent	B (30)	none	6-month progression-free survival (PFS-6)
	B2 (32)	BEV 10 mg/kg	
	B3 (32)	BEV 3 mg/kg	
BEV refractory recurrent	C (17)	BEV 10 mg/kg	OS-6

2043 Poster Session (Board #285), Mon, 1:15 PM-4:45 PM

Radiomics method to predict loss of heterozygosity on chromosome 1p/19q of oligodendroglial tumor. *First Author: Jingwei Wei, Chinese Academy of Sciences, Beijing, China*

Background: Oligodendroglial tumor (OT) is one of the main types of gliomas, which is incurable in current situation. As a tumor-specific genetic alteration of OTs, loss of heterozygosity (LOH) on chromosome 1p/19q indicates a preferable response to chemo/radiotherapy and a better survial, which could be used as a key molecular signature for personalized treatment decision making. However, 1p/19q LOH status is now commonly obtained by fluorescence in situ hybridization after the tumor resection, which is highly likely to lead functin deficit with tumor locating on eloquent area. Thus, a non-invasive predicition on 1p/19q LOH is required. Here, we used a "Radiomics" method to achieve the prediction based on magnetic resonance imaging in this study. **Methods:** A cohort of 113 OT patients was collected from Beijing Tiantan Hospital. 593 three-dimensional imaging features were extracted on T2-weighted images including textural and non-textural features. We used "minimum redundancy maximum relevance" and "iterative backward elemination and forward inclusion" algorithms to pick up the most effective features with a p-value < 0.05. With the selected features as the input, support vector machine algorithm was adopted to predict the 1p/19q LOH status with 10-fold cross validation. Comparisons were made between the traditional clinical predictors and the established model. **Results:** The prediction accuracy for 1p/19q LOH turned out to be 86.6%. The top three features contributing most to the prediction were respectively: GlobalUniformity, GaborBankD4GLRLMLGRE and GaborBankD4GLRLMSRLGE. The predictive performance of the radiomics model was proved to be far more valid than the clinical predictors (indistict tumor border and heterogeneous signal intensity) with the higher area under curve (AUC). Compared with the best single feature (GlobalUniformity, AUC: 0.749), this combined-feature model has the best diagnostic performance with an AUC of 0.898. **Conclusions:** This study reveals the intrinsic association between the imaging features and 1p/19q LOH status, meanwhile, realizes the high precision prediction, providing reliable basis for the pre-operative treatment regime.

2044 Poster Session (Board #286), Mon, 1:15 PM-4:45 PM

Expanded phase I study of intratumoral Ad-RTS-hIL-12 plus oral veledimex: Tolerability and survival in recurrent glioblastoma. *First Author: E. Antonio Chiocca, Brigham and Women's Hospital, Boston, MA*

Background: Glioblastoma (GBM) is an aggressive brain tumor affecting ~74,000 people worldwide annually. Recurrent GBM patients have a median OS (mOS) of 6-7 months. OS in patients who have failed temozolomide, bevacizumab or equivalent salvage chemotherapy, is ~3-5 months. New therapies are urgently needed. Ad-RTS-hIL-12 (Ad) is a novel gene therapy expressing IL-12 under the control of an oral activator ligand, veledimex (V), through the RheoSwitch Therapeutic System. Intratumoral administration of Ad results in targeted tumor cytotoxicity and induction of systemic T cell memory. Ad + V is a treatment strategy to extend the IL-12 therapeutic window. **Methods:** In a multicenter Phase I dose escalation trial and expansion cohort, subjects with recurrent or progressive Grade III or IV glioma undergoing resection were injected intratumorally with Ad 2 x 10^{11} viral particles and daily oral V for 15 doses, beginning prior to surgery. The primary endpoint is safety and tolerability of Ad + V; secondary endpoints include OS. **Results:** 25 subjects were dosed in 3 dose escalation cohorts: 20 mg (n = 7), 30 mg (n = 4), and 40 mg (n = 6) and an expansion cohort of 20 mg (n = 8). Results show V crossed the blood brain-barrier with 35±5% of plasma levels detected in the brain tumor. The 20 mg dose (n = 15) had better drug compliance (86%) than the 30 mg (63%) or 40 mg (52%) cohorts and the 20 mg cohort shows better survival (mOS 12.7 months) compared to other cohorts. The frequency of related ≥Grade (G)3 AEs in the 20 mg cohort was significantly lower: 20% in 20mg, 50% in 30mg and 40 mg. In the 20 mg cohort, the most frequent AEs were transient mild flu-like symptoms seen in 12/15, G3 cytokine release syndrome in 2/15, G3 elevated ALT/AST in 1/15 and G3 lymphopenia in 3/15. All AEs reversed promptly upon discontinuing V. **Conclusions:** Overall, Ad + 20 mg V is well tolerated; toxicities were predictable and reversible upon discontinuing V. There is a correlation between V dose, BBB penetration and drug related AEs. The tolerability and encouraging survival observed to date warrant further investigation in a pivotal trial. A stereotactic arm and a pediatric trial in diffuse intrinsic pontine glioma patients are planned. Clinical trial information: NCT02026271.

2045 Poster Session (Board #287), Mon, 1:15 PM-4:45 PM

Assessment of tumor hypoxia in BEV resistant GBM using FMISO ^{18}F-PET and MRI. *First Author: Yichu Liu, The University of Texas at San Antonio, San Antonio, TX*

Background: Glioblastoma (GBM) is the most common malignant brain tumor in adults, and is characterized by poor survival and marked resistance to treatment. Hypoxic volume is directly correlated with poor outcome in GBM, with structural and functional tumor vasculature changes regarded as a primary driver of tumor hypoxia. As part of an ongoing clinical trial with a hypoxia activated prodrug, we sought to explore the correlation between abnormal tumor vasculature and hypoxia in bevacizumab (BEV) resistant GBM. **Methods:** MRI and ^{18}F-FMISO PET scans were acquired at study entry. The MRI protocols include standard anatomical sequences as well as Dynamic Susceptibility Contrast (DSC/perfusion) imaging. Enhancing tumor ROIs were determined from Delta T1 maps, non-enhancing tumor ROIs were obtained from FLAIR images, ratio between enhancing and non-enhancing volumes were calculated, values from standardized rCBV maps were extracted from corresponding enhancing ROIs. Decay correction was applied to ^{18}F-FMISO images and converted to SUV units. After registration to MR images, cerebellar regions were used as surrogates for blood activity. The FMISO images were then normalized to generate tissue to blood ratio (TB). A threshold of TB > 1.2 was used in discriminating the hypoxia volume (HV). Correlation between parameters was assessed using Pearson correlation. **Results:** 7 patients from University of Texas Health Science center and 7 patients from Dana-Farber Cancer Institute had evaluable MR and PET imaging. We compared MRI parameters (enhancing and non-enhancing tumor volumes, srCBV) with hypoxia (HV and maxSUV). There was a positive correlation between HV and enhancing volume ($R = 0.732$, $p = 0.0029$) as well as between HV and ratio ($R = 0.644$, $p = 0.013$. The correlation between other pairs were not statistically significant (HV vs srCBV: $p = 0.862$, T1 vs maxSUV $p = 0.492$, srCBV vs maxSUV: $p = 0.393$, ratio vs maxSUV = 0.178). **Conclusions:** The hypoxic volume following bevacizumab failure correlates with both the volume of enhancement and the fraction of enhancement within the mass. The clinical implications of this is being assessed in an ongoing phase 2 study. Clinical trial information: NCT02342379.

2046 Poster Session (Board #288), Mon, 1:15 PM-4:45 PM

A two-part safety and exploratory efficacy randomized double-blind, placebo-controlled study of a 1:1 ratio of the cannabinoids cannabidiol and delta-9-tetrahydrocannabinol (CBD:THC) plus dose-intense temozolomide in patients with recurrent glioblastoma multiforme (GBM). *First Author: Chris Twelves, University of Leeds and St. James's Institute of Oncology, Leeds, United Kingdom*

Background: Several plant-derived cannabinoids have shown efficacy in animal models of GBM, particularly when co-administered with temozolomide, a commonly-used treatment in both primary and recurrent disease. **Methods:** We conducted a two-part study in patients with recurrent GBM following standard chemo-radiotherapy treatment as described by Stupp et al. In Part 1 of the study, 6 patients were treated to an MTD of 1:1 CBD:THC oro-mucosal spray, as an adjunct to dose-intense temozolomide (DIT), to assess the safety of the combination. Part 2 was a double blind, randomized, placebo-controlled study in a planned 20 patients receiving either their individualized dose of 1:1 CBD: THC or placebo plus DIT. The primary endpoint was tolerability of 1:1 CBD: THC plus temozolomide. **Results:** There were no Grade 3 or 4 toxicities in Part 1 of the study. In Part 2, 12 patients were randomized to CBD:THC and 9 to placebo. Mean age was 58 years in both treatment groups, but there were more males in the placebo group (5 of 12 and 8 of 9, respectively). Baseline median Karnofsky score was 90 in both groups and median time from diagnosis of recurrence to start of treatment (day 1) was similar (3.6 and 3.0 weeks in the CBD:THC and placebo group, respectively). The median number of days of dosing with CBD:THC or placebo was similar (155 days [range: 50-356] and 134 days [range: 13-359]). Median survival in the placebo group was 369 days, and $>$ 550 days in the CBD:THC treatment group (NS) and 1 year survival was 83% and 56% in the CBD:THC and placebo groups, respectively ($p = 0.042$). PFS6 was 42% in the CBD:THC group and 33% in the placebo group (NS). Overall, the commonest treatment related toxicities were dizziness (in 11/18 patients) and nausea (in 7/18 patients). Results of biomarker analyses are awaited. **Conclusions:** This randomized study provides preliminary evidence that 1:1 CBD:THC offers some efficacy in patients with recurrent GBM when used as an adjunct to dose-intense temozolomide and confirms the safety and feasibility of individualized dosing. Clinical trial information: NCT01812603.

2047 Poster Session (Board #289), Mon, 1:15 PM-4:45 PM

***TERT* promoter mutations in progressive treatment-resistant meningiomas.** *First Author: Tareq A. Juratli, University Hospital Dresden, Dresden, Germany*

Background: Recurrent meningiomas often undergo a grade-progression to become atypical or malignant upon recurrence. Detailed study of progressive meningioma has been hampered by the lack of available paired specimens. Here, we sequenced the *TERT* promoter (*TERT*p) in a large series of patients with treatment-resistant meningiomas at initial diagnosis as well as their sequential recurrences. **Methods:** We scored 77 meningiomas from 36 patients for *TERT*p mutations. All patients in this study developed recurrences during the median follow-up of 13.3 years (range 6.4 - 25.5 years) and underwent three surgeries on average (range 2-8). Additionally, we screened geographically distinct sites of all *TERT*p-mutant meningiomas to interrogate intratumoral heterogeneity. **Results:** *TERT*p mutations were detected in 18 tumor samples (18/77 = 23.3%) from 12 patients, but not in any of the matched blood sample DNAs, excluding germline mutations. Notably, the *TERT*p mutations were absent in the initial lower-grade tumor and were present in the subsequent recurrent tumors. Moreover, we observe emergent spatial heterogeneity in the form of mixed populations of recurrent tumor cells containing different mutation status of the *TERT* promoter gene in three cases. Patients with emergence of *TERT*p-mutant meningiomas had a significantly shorter overall survival than their *TERT*p wild-type counterparts, when measured from the time of initial diagnosis (2.4 vs 11.1 years, 95% CI 0.25-4.54 vs 9.3- 16.8 years $p = 0.007$). **Conclusions:** Our data confirm the high frequency of *TERT*p mutations and the emergence of *TERT* promoter mutation in recurrent progressive meningiomas, strongly indicating the presence of ongoing evolution impacting the natural history of these tumors. *TERT*p mutations are mostly associated with poor outcome. Finally, our study provides important insight into the complexity of tumor heterogeneity and has important implications for targeted therapy in treatment-resistant meningiomas.

2048 Poster Session (Board #290), Mon, 1:15 PM-4:45 PM

A novel MGMT methylation-based prognostic score in patients with glioblastoma. *First Author: Lorenzo Gerratana, Department of Medicine, University of Udine and Department of Oncology, University Hospital of Udine, Udine, Italy*

Background: The methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter has been associated with improved outcome in glioblastoma (GBM) patients (pts). Pyrosequencing (PSQ) has been reported to be an accurate method for quantitative detection of CpG islands (CpGs) methylation, but the role of methylation heterogeneity among different CpGs sites is still unclear. Aim of this study was to evaluate on a large multicentric cohort a novel prognostic score based on the evaluation of the MGMT promoter methylation at 10 different CpGs sites. **Methods:** We retrospectively analyzed a series of 185 pts with GBM treated at the University Hospital of Udine and Istituto Oncologico Veneto in Padua between 2006 and 2015. The methylation level of 10 CpGs (74 – 83) was determined by PSQ. The cut-off point of 9% was used to define a CpG as methylated. One point was assigned to each methylated CpG, with a total score from 0 (all CpGs $<$ 9%) to 10 (all CpGs $\geq$ 9%). A threshold capable to detect a favorable outcome (Overall Survival, OS $>$ 24 months) has been identified through ROC analysis as 6 by a previous study conducted at our center. The prognostic impact was explored through Cox regression. **Results:** After a median follow-up of 59 months, the median OS and Progression Free Survival (PFS) in the whole population were 16.41 and 9.67 months, respectively. A score $\geq$ 6 identified pts with a considerably better median OS (24.85 vs 12.99 months, $p < .0001$) and PFS (11.44 vs 8.22 months, $p < .0001$). On multivariate analysis, it remained independently associated with a favorable prognosis (HR 0.38, 95% CI 0.27-0.55, $p < 0.0001$) after adjustment for IDH1 mutational status (HR 0.42, 95% CI 0.20-0.87, $p = .02$), age ($>$ 70 vs $\leq$ 70 years HR 2.20, 95% CI 1.48-3.28, $p = .0001$) and ECOG performance status (2-3 vs 0-1 HR 2.35, 95% CI 1.59-3.49, $p < .0001$). The score's prognostic value was maintained in all the explored subgroups. **Conclusions:** Combining methylation data from multiple CpGs increases the prognostic value of the MGMT promoter methylation assessment. The study confirmed the independent prognostic value of a novel score system based on the evaluation of the MGMT promoter methylation at 10 different CpGi sites.

2049 Poster Session (Board #291), Mon, 1:15 PM-4:45 PM

Number of tumor-infiltrating lymphocytes in breast cancer brain metastases compared to matched breast primaries. *First Author: Jessie Narloch, Clinical Research Training Program, Duke University Medical Center, Durham, NC*

Background: Breast cancer brain metastasis (BCBM) is frequent in advanced disease, has limited therapies, and is associated with poor prognosis. Increased stromal tumor infiltrating lymphocytes (sTILs) are prognostic in triple-negative breast cancer (TNBC) and predictive of therapeutic response in early breast cancer (BC). However, little is known about sTILs in the metastatic setting. We compared %sTILs between the largest known cohort of matched primary tumors and BCBM and correlated the results with clinical endpoints. **Methods:** We retrospectively investigated 37 matched primary tumors and BCBM tissue from three institutions. In addition, we identified 29 primary tumors from patients later diagnosed with BCBM. H&E-stained sections were manually measured for %sTILs using standard criteria. Wilcoxon signed rank tests assessed for changes in %sTILs between primary and metastatic lesions. A Cox proportional hazards model was used to determine if %sTILs in the breast tissue predicts time from primary tumor biopsy to diagnosis of brain metastasis (TTDBM) while adjusting for clinicopathologic features. **Results:** Average age at time of BCBM diagnosis was 53.6 (SD 12.3). 52% (34/66) of primary tumors were hormone receptor (HR) positive. Of 60 patients with known HER2 status, 28% (17) were HER2 positive and 40% (24) TNBC. Median %sTILS was significantly different between all primary tumors (15, IQR 5-20) and brain metastases (10, IQR 5-10), $p = 0.001$. The TNBC subtype ($n = 11$) showed the largest decrease in % sTILs between primary tumors (20, IQR 10-20) and brain metastases (5, IQR 5-10), $p = 0.022$. Comparing primary tumors and brain metastases, there was a 5% decrease in %sTILs in HR-/HER2+ ($n = 5$, $p = 0.13$) and HR +/HER2- ($n = 7$, $p = 0.13$), and a 5% increase in %sTILs in the HR+/Her2+ subtype ($n = 9$, $p = 0.69$). Percent sTILs in the primary tumors was not a significant predictor of TTDBM, when adjusting for race, age, HR status, and HER2 status, $p = 0.87$. **Conclusions:** BCBM have a significantly decreased %sTILs compared to their primary tumors, most prominent in TNBC. These results suggest altered tumor immunogenicity in the metastatic setting which has broad implications for the development of immunotherapy.

2050 Poster Session (Board #292), Mon, 1:15 PM-4:45 PM

Characterizing glioma microenvironment with ultra-high gradient diffusion MRI. *First Author: Ina Ly, Massachusetts General Hospital, Boston, MA*

Background: The infiltrating nature of gliomas, particularly into the peritumoral area, is a major barrier to improving clinical outcome as microscopic disease remains even after apparent gross total resection. Conventional T1 post-contrast and T2/FLAIR MRI do not capture full tumor extent. A better imaging biomarker is needed to improve differentiation between tumor, peritumoral area and normal brain. **Methods:** 4 pre-surgical patients with non-enhancing, FLAIR-hyperintense lesions suspicious for glioma underwent ultra-high gradient diffusion MRI on the Connectome MRI scanner, a unique scanner with maximum gradient strength of 300 mT/m enabling mapping of cellular microstructures on a micron-level scale. The FLAIR area was defined as the tumor region of interest (ROI). Radiographically normal appearing brain up to 1 cm around the FLAIR area was defined as the peritumoral ROI. Using a novel 3 compartment diffusion model (Linear Multiscale Model), the volume fraction of water (VFW) was calculated within restricted (intracellular), hindered (extracellular) and free (CSF) spaces. VFW in the tumor, peritumoral ROI, contralateral normal white matter (WM) and cortex were compared. **Results:** Within the tumor ROI, the median VFW in the restricted compartment was decreased vs. the peritumoral ROI (↓ 34%), WM (↓ 46%) and cortex (↓ 18%) while median VFW in the hindered compartment was increased vs. the peritumoral ROI (↑ 26%), WM (↑ 54%) and cortex (↑ 25%). Within the peritumoral ROI, median VFW in the hindered compartment was increased compared to WM (↑ 23%). 3 patients had available histopathology revealing isocitrate dehydrogenase-mutant gliomas. **Conclusions:** Using ultra-high gradient diffusion MRI and a novel diffusion model, we detected distinct diffusion patterns in the tumor and peritumoral area not seen on conventional MRI. Lower VFW in the restricted compartment within the tumor may reflect decreased intracellular water mobility due to enlarged nuclei. Higher VFW in the hindered compartment in the tumor and peritumoral area may reflect higher degree of tissue permeability and edema. MRI-pathology and larger cohort validation studies are underway to elucidate microenvironment changes in response to treatment.

2051 Poster Session (Board #293), Mon, 1:15 PM-4:45 PM

Whole exome sequencing and copy-number variation analysis of 20 NF2-associated spinal and cranial meningiomas. *First Author: Ramita Dewan, University of Maryland School of Medicine, Baltimore, MD*

Background: Neurofibromatosis type 2 is a heritable tumor predisposition syndrome characterized by the growth of multiple tumor types in the nervous system, including bilateral vestibular schwannomas, meningiomas and ependymomas. Recent genomic sequencing studies have revealed that *NF2* inactivation is the most frequent genetic event in sporadic meningiomas. In line with Knudson's hypothesis, it is accepted that somatic inactivation of the wildtype *NF2* allele initiates tumor growth in NF2 patients, but little is known of what other genes or pathways influence meningioma tumorigenesis. **Methods:** To investigate this question, we performed whole exome sequencing (WES) (Illumina Hi-Seq 2500 platform, 96 Mb SeqCap EZ Exome + UTR Library, NimbleGen) and SNP-array analysis (HumanOmniExpressExome-8, v1.2 arrays, Illumina) of twenty spinal and cranial meningioma samples from seven NF2 patients. Mutation validation was completed via orthogonal sequencing (IonTorrent, ThermoFisher). **Results:** We identified *NF2* germline mutations in all patients, including five nonsense, one splice site and one likely pathogenic intronic mutation. We found that the predominant mechanism of somatic *NF2* inactivation in the tumors was loss of heterozygosity (LOH): we identified large chromosome 22 deletions containing *NF2* in nineteen out of twenty meningiomas. The second most frequent chromosomal aberration was a deletion within chromosome 1p, followed by entire chromosome X deletion and rearrangements in chromosome 17q. The remaining samples exhibited normal diploid genomic architecture. Somatic mutations included about twenty point substitutions and small indels. **Conclusions:** Our study revealed that somatic inactivation of *NF2* is the most frequent and only recurrent genetic event in NF2-associated meningiomas. Large LOH events are the most prevalent second hit mechanism and may also represent a common path of meningioma progression. Somatic single nucleotide substitutions and small indels are rare in these tumors. Interestingly, we did not identify mutations in *TRAF7*, *KLF4*, *AKT1*, or *SMO,* which have been found to be critical for non-NF2 meningioma growth.

2052 Poster Session (Board #294), Mon, 1:15 PM-4:45 PM

Bevacizumab (Bev) to reduce the negative impact of glioblastoma (GBM) tumor size on survival from first recurrence. *First Author: Huy Tram N. Nguyen, University of California Los Angeles Neurology, Los Angeles, CA*

Background: Bev was FDA approved for recurrent GBM in 2009. However, the survival benefit from Bev in GBM remains to be demonstrated. **Methods:** We retrospectively identified 168 primary GBM patients diagnosed between 2001-2015 at UCLA and Kaiser Permanente LA, who received upfront radio-chemotherapy, followed with Bev and/or Lomustine (CCNU) at 1st recurrence. We measured tumor size at 1st recurrent treatment initiation, using bi-dimensional (2D) and volumetric (3D) techniques. We analyzed overall survival (OS) from 1st recurrence by Kaplan-Meier analysis. **Results:** Three groups of patients diagnosed from 2009-2015 were identified: patients treated with Bev alone (n = 49), CCNU alone (n = 36), and concurrent Bev/CCNU (n = 53). Patients were statistically different in performance status at 1st recurrence and tumor size; the CCNU alone group had smaller tumor sizes at diagnosis compared to the Bev groups. The CCNU group showed substantially greater survival (median OS (mOS) = 14.1 mo) compared to the Bev and Bev/CCNU groups (mOS = 6.9 and 7.1 mo, respectively), which may be explained by the imbalance in tumor sizes among the groups, and high rate of crossover (69%) to Bev in subsequent recurrences. To minimize selection bias, we identified another control group (n = 30) diagnosed from 2001-2004 who received CCNU only (CCNU 01-04). These patients had tumor size and KPS more comparable to both Bev groups, and a low rate of crossover (7%). OS for CCNU 01-04 (mOS = 5.7 mo) was similar to the Bev groups. Across all patients, we observed poor OS associated with larger 2D size vs. those with small tumors (mOS = 6.7 vs. 8.8 mo; p = 0.003). In separate stratification of each treatment group by tumor size, this association was retained in the CCNU 01-04 group (mOS = 4.0 vs. 8.4 mo, $p < 0.001$), but not in either Bev (mOS = 6.7 vs. 7.3 mo) or BEV/CCNU (mOS = 7.0 vs. 8.8 mo). Analysis of effect of tumor size by 3D measurement yielded similar results. **Conclusions:** Bev appears to reduce the negative impact of large tumor size on GBM patient survival from 1st recurrence. 2D and 3D measurements were correlated, suggesting the adequacy of use of conventional tumor bi-dimensional measurement to predict benefit of Bev in patients based on tumor size.

2053 Poster Session (Board #295), Mon, 1:15 PM-4:45 PM

A cellular platform to enable targeted brain delivery of T cells to glioblastoma. *First Author: Heba Samaha, Texas Children's Hospital, Houston, TX*

Background: Poor T cell homing hinders the development of effective cell therapy for central nervous system (CNS) malignancies. Lessons learnt from inflammatory brain diseases can give insight into how to overcome the blood brain barrier (BBB) blockade created by cancer. Activated Leukocyte Cell Adhesion Molecule (ALCAM; CD166) is a pathological adhesion molecule upregulated in the endothelium of a number of inflammatory/infiltrative CNS diseases, such as multiple sclerosis. Antibodies blocking ALCAM decrease leukocyte access to the brain and are currently being tested in a clinical trial for MS. **Methods:** We studied the difference in the dynamic signature of adhesion molecules in the "anergic" brain tumor endothelium and that of infiltrative brain conditions. Consequently, we mapped the ALCAM minimal binding region to domain 3 (D3) of CD6 and created an artificial molecule with the intent of creating a novel cellular platform to reverse endothelial anergy, through ALCAM specific binding. **Results:** GBM endothelium fails to launch the second wave of adhesion molecules necessary for firm T leukocyte capture and effective BBB transmigration. Engineered D3 on the T cell crosslinked to ALCAM on endothelial cells in proximity ligation assays (PLA; < 40nm) during TEM. Under shear stress, D3 T cells showed a global improved ALCAM specific trafficking kinetics: higher capture on ALCAM+ endothelium, rolling with slower velocity, and better TEM. In an ex vivo model of BBB, D3 T cells exhibited higher transmigratory ability. We discovered that signaling through the D3 endodomain phosphorylated pZAp70 recruiting Talin that enables LFA-1 (ICAM-ligand) open confirmation, mediating effective TEM. Lastly, in an orthotopic model of GBM, D3 T cells homed more and accumulated at the tumor site compared to NT controls. And, testing Her2 CAR T cells on D3 platform showed an advantageous homing after IV administration which was reflected in tumor control and better survival. **Conclusions:** We created a cellular platform that enables targeted brain delivery of T cells. This platform serves as a gateway to the effective cellular therapeutics for brain malignancies but potentially as a delivery system for complex biologics for other pathological conditions.

2055 Poster Session (Board #297), Mon, 1:15 PM-4:45 PM

Treatment through progression with ofranogene obadenovec (VB-111), an anti-cancer viral therapy, significantly attenuates tumor growth in recurrent GBM: Individual phase 2 patient data. *First Author: Andrew Jacob Brenner, The University of Texas Health Science Center, San Antonio, TX*

Background: Ofranergene obadenovec (VB-111) is a viral cancer-therapy with a dual mechanism: vascular disruption and induction of a tumor directed immune response. Prolongation of overall survival (OS) has been shown in recurrent glioblastoma (rGBM) patients treated through progression with VB-111 in combination with bevacizumab (BEV) compared to historical controls and to patients with limited exposure (LE) to VB-111. Here we present individual patient tumor growth data. **Methods:** VB-111 was administered at $1x10^{13}$viral particles bimonthly until progression, followed by BEV standard of care (LE cohort). The protocol was amended to allow treatment through progression (TThP) with VB-111 bimonthly, with the addition of BEV 10mg/Kg biweekly, until further progression (TThP cohort). Tumor dimensions were assessed q2 months by MRI locally and by an independent central lab. The slope of the log tumor measurement over time was calculated for each patient, average slopes were compared across therapy groups using the Wilcoxon Rank Sum test. **Results:** 46 patients received up to 13 doses of VB-111. All started with VB-111 monotherapy. 22 were included in the LE cohort; 24 in the TThP cohort. Cohorts were comparable by measures of age, performance status, prior lines of therapy, baseline tumor dimensions and progression-free-survival. Spider diagrams demonstrate similar rapid tumor growth in both LE and TThP cohorts during the VB-111 monotherapy period (local site data; median % increase (MPI) per 30d: 14.8 vs 14.1, p = 0.98). In the TThP cohort, growth was attenuated after the 1stprogression, compared to the preceding VB-111 monotherapy period (MPI: 0.6 vs 14.1, p = 0.0032); responses were seen, including 2 complete responses (CR), one patient remaining in CR over 3 years. A similar attenuation was seen in central lab tumor measurements. **Conclusions:** Treatment through progression with VB-111 in combination with BEV induced durable tumor growth attenuation, which was associated with prolonged OS of 15 months in patients with rGBM. The GLOBE phase 3 randomized controlled trial of VB-111 in rGBM is currently underway. Clinical trial information: NCT01260506.

2056 Poster Session (Board #298), Mon, 1:15 PM-4:45 PM

Activity of cabazitaxel in temozolomide refractory glioblastoma: Final results of a phase 2 study (C-GBM study; EudraCT 2013-001550-98 NCT 01866449). *First Author: Bernhard Heinrich, Hematological-Oncological Practice, Augsburg, Germany*

Background: Following progression on Temozolomide (TMZ) glioblastoma (GBM) is a therapeutic challenge with a 6 month survival rate of only ~20-30% and no well-established 2nd line treatments. **Methods:** We designed a phase II study to assess the efficacy of cabazitaxel, a second generation taxoid, in TMZ-refractory GBM pts (pts). Primary enpoint was response at 12 weeks of treatment. Secondary endpoints were overall survival (OS), quality of life, and pharmacokinetics. The study population were pts with progressive GBM during or within 6 months after TMZ treatment, in whom radiotherapy and surgery was no treatment options. Exclusion criteria were signs of inflammation, an ECOG performance score (PS) $>$ 2, as well as impaired organ function. Patient characteristics: In total, between 2014 and 2016 8 female and 16 male pts were included with a median age of 55 years (range 32-76 years) and a median of 3 previous therapies (range 1-9). Treatment: Cabazitaxel was given at 25mg/m^2 q3w with G-CSF prophylaxis. Every two cycles response assessment was performed (MRI). Treatment was discontinued in case of i) progressive disease (RANO criteria), ii) PS$\geq$3, or iii) persistent toxicity. **Results:** Five pts went off study prior to the first MRI assessment due to progressive disease, while 19 of 24 of pts could be evaluated for response after 2 cycles. We did not observe any objective response (i.e. complete or partial remission). In 7 pts a stable disease (SD) was obtained; 12 pts had progressive disease. Of the 7 SD pts, 4 progressed after 4 cycles of treatment and the remaining pts remained in SD for 6, 10 and 12 cycles, respectively. The median OS was 155 days. Toxicity was manageable by G-CSF application in pts with CTC grade 3/4 neutropenia/leukopenia in 12 pts. Non-hematological toxicity CTC grade 3/4 comprised infection (n = 2), diarrhea (n = 2), vaginal bleeding (n = 1) and hypokalemia (n = 1). **Conclusions:** Cabazitaxel shows only marginal activity in TMZ refractory GBM with a disease stabilization rate following 4 cycles of only 12.5% in heavily pretreated GBM pts and median OS of 155 days. Clinical trial information: NCT 01866449.

2057 Poster Session (Board #299), Mon, 1:15 PM-4:45 PM

Quantifying the benefit of chemotherapy and radiation in low-grade glioma: A systematic review and meta-analysis of numbers needed to treat. *First Author: Timothy J Brown, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: The optimal role of chemotherapy and radiation (RT) in adult low-grade glioma (LGG, WHO grade 1 & 2) is unclear. We conducted a systematic review and study-level meta-analysis of the literature on overall survival (OS) and progression free survival (PFS) in patients with LGG. **Methods:** Pubmed was queried with MeSH terms. All comparative studies of adults with newly diagnosed, supratentorial LGG were included. Comparisons of interest were OS and PFS at 2, 5, and 10 years in chemotherapy versus no chemotherapy and early RT versus delayed or no RT. Data were extracted from studies and synthesized with a random effects model. Quality of evidence was determined by American Academy of Neurology criteria and further analysis was performed, separating high quality (class I and II) from low quality (class III and IV) evidence. Numbers needed to treat (NNT) were determined from the risk difference. **Results:** 1531 articles were screened; 18 studies were included. Chemotherapy was not associated with a significant survival advantage compared to control. However, an analysis of high quality data revealed a survival advantage at 10 years associated with chemotherapy compared to control with NNT 5 (relative risk death chemo vs control 0.69 [0.56-0.86] p = 0.0006). Furthermore, NNT to prevent one progression with chemotherapy at 5 and 10 years was 6 and 3, respectively. Early RT was not associated with an OS advantage compared to control. However, early RT had progression benefit at all time points, with NNT of 10, 6, and 5 at 2, 5, and 10 years. **Conclusions:** Further study will be needed to confirm the optimal role of chemotherapy and RT. Caution must be used in interpretation as much of the literature consists of low-quality studies.

	N (studies)	N (participants)	RR progression (intervention vs control)	Lower 95% CI	Upper 95% CI	P	NNT (95% CI)
5 Year Progression, Chemo vs Control	3	431	0.69	0.55	0.87	0.001	6 (4-12)
10 Year Progression, Chemo vs Control	3	431	0.58	0.39	0.87	0.008	3 (2-10)
2 Year Progression Early RT vs Control	6	1473	0.66	0.51	0.86	0.002	10 (5-50)
5 Year Progression Early RT vs Control	6	1473	0.73	0.61	0.88	0.0008	6 (4-15)
10 Year Progression Early RT vs Control	4	1114	0.74	0.60	0.91	0.005	5 (3-17)

2058 Poster Session (Board #300), Mon, 1:15 PM-4:45 PM

Association of SDF1 inhibition with local control and relative cerebral blood volume of glioblastoma. *First Author: Reena Parada Thomas, Stanford University Hospital, Palo Alto, CA*

Background: Glioblastoma is the most common and aggressive primary brain tumor, with 75-85% of patients historically having recurrence within the original tumor site. We have shown in preclinical studies that inhibition of the SDF1/CXCR4 pathway by the CXCR4 inhibitor Plerixafor increases tumor response to irradiation by inhibition of the recovery of tumor blood vessels. **Methods:** Newly diagnosed glioblastoma patients were enrolled to the clinical trial using the investigational agent Plerixafor after standard radiation therapy and temozolomide (NCT01977677). To date, 28 patients out of the planned accrual of 29 have been enrolled to this study. Normalized relative cerebral blood volume (rCBV) ratios were calculated by the mean rCBV within the 95% isodose radiation field one month post-radiation as compared to contralateral white matter outside of the radiation field. Our imaging analysis compares patients treated with Plerixafor compared to a control group receiving standard therapy (chemo-RT). **Results:** There was a significant reduction in rCBV measured by DSC-MRI within the 95% isodose field one month after radiation therapy in patients receiving Plerixafor compared to control ($p < 0.02$). The rCBV out of the radiation field was similar between patients receiving Plerixafor compared to control patients one-month post radiation therapy. As of February 7, 2017, only 2 of the total of 9 recurrences occurred within the irradiated field. The rate of out of field recurrence (77%) was therefore much higher than expected (20%), with statistical significance ($p < 0.03$, Fisher's exact test). **Conclusions:** We show that Plerixafor has a meaningful impact on local control of glioblastoma. Furthermore, DSC-MRI could be a useful biomarker of its efficacy.

2059 Poster Session (Board #301), Mon, 1:15 PM-4:45 PM

Immunological targeting of CD133 in recurrent glioblastoma: A multi-center phase I translational and clinical study of autologous CD133 dendritic cell immunotherapy. *First Author: Jeremy David Rudnick, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: A hallmark of glioblastoma is the high incidence of tumor recurrence, thought to be triggered by cancer stem cells. These tumorigenic cells are resistant to irradiation and chemotherapeutic agents. The target antigen, CD-133, was chosen because it has been reported as a cancer stem cell antigen overexpressed in glioblastoma tumors and associated with shorter survival. Recent clinical trials suggest that the mean overall survival for these patients is roughly 5-9 months, emphasizing the important unmet medical need in this disease requiring additional strategic approaches. Dendritic cell immunotherapies such as ICT-121 could provide benefit to patients by educating their immune systems to induce the formation of cytotoxic T cells that attack tumor cells bearing the target antigen. In addition to immediate attack on tumor cells present at dosing, a long-term memory response effective against tumor recurrence might be induced. Immunotherapy, such as ICT-121, that targets cancer stem cells could be an important treatment for this disease. **Methods:** This Phase I multi-center trial of ICT-121 targeting CD133 was designed to assess safety and tolerability (primary endpoint) and to monitor overall survival and progression-free survival (secondary endpoints). ICT-121 is comprised of autologous dendritic cells that are loaded with two HLA-A2 restricted epitopes of the CD133 antigen. CD133 is overexpressed on glioblastoma cancer stem cells. The HLA-A2 patients that had undergone resection for recurrence of glioblastoma were treated with ICT-121 once a week for 4 weeks during the induction phase and then once every 2 months during the maintenance phase until disease progression, death, ICT-121 depletion or discontinuation. **Results:** A total of 20 patients were treated and eight of these patients are still alive. Immune response data with cytokine mRNA expression demonstrated a response to the CD133 epitopes. A total of 20 patients were treated and eight of these patients are still alive. **Conclusions:** The results from this Phase I trial suggest that ICT-121 is both safe and well-tolerated with an immune response seen in a subset of patients. Clinical trial information: NCT02049489.

2060 Poster Session (Board #302), Mon, 1:15 PM-4:45 PM

Phase I trial of dimethyl fumarate, temozolomide, and radiation therapy in glioblastoma multiforme. *First Author: Danielle A. Shafer, Virginia Commonwealth University, Richmond, VA*

Background: Evidence is increasing for altered immune responses in malignant gliomas. Tumor-associated microglia/macrophages infiltrate human glioma tissue and produce cytokines that promote glioma growth, invasion and angiogenesis. Dimethyl fumarate (DMF), approved for relapsing-remitting multiple sclerosis, is toxic to in vitro activated microglial cells. Based on pre-clinical data demonstrating synergism with radiation (RT) and temozolomide (TMZ), we conducted a phase I study of DMF in patients with newly-diagnosed glioblastoma (GBM) in combination with RT and TMZ. **Methods:** Using a standard 3+3 dose escalation design (3 dose levels: 120 mg bid, 240 mg bid and 240 mg tid), newly-diagnosed GBM patients received daily DMF with RT (60 Gy) and concurrent TMZ 75 mg/m2 daily, followed by adjuvant DMF (continuously) and TMZ for up 6 maintenance cycles (150-200 mg/m2 on days 1-5 of each 28 day cycle). The maximum tolerated dose (MTD) was defined as the dose with $\leq$ 1/6 dose-limiting toxicities (DLT). The MTD was determined by evaluation of DLTs during the first 6 weeks of therapy. **Results:** Twelve patients were treated at the three dose levels, and no DLT was identified. There were no unexpected toxicities. The most common toxicities were lymphopenia (11 grade 3/4 events) and thrombocytopenia (2 grade 3/4 events). The only grade 3/4 non-heme toxicity was a grade 3 hemorrhoid event. Of the 12 evaluable patients, one remains on active treatment in maintenance phase. Three patients completed all treatment (concurrent and maintenance) with stable disease. Two patients had a partial response (RANO criteria) but then experienced disease progression during maintenance. Five patients had disease progression during study treatment and one patient chose to withdraw from the study during maintenance. **Conclusions:** These data suggest that DMF may be safely combined with RT and TMZ in GBM patients. A phase II study is under consideration. Clinical trial information: NCT02337426.

2061 Poster Session (Board #303), Mon, 1:15 PM-4:45 PM

VXM01 phase I study in patients with resectable progression of a glioblastoma. *First Author: Wolfgang Wick, Neurology Clinic, DKFZ, DKTK, Heidelberg, Germany*

Background: VXM01 consists of an attenuated *Salmonella typhi* Ty21a carrying a plasmid encoding for VEGFR-2. The bacterium is serving as a vector *via* the oral route of administration carrying the plasmid into the Peyer's plaques. The vaccine construct elicits a systemic T-cell response targeting VEGFR-2. This trial was set up to examine safety and tolerability, clinical and immunogenic response to VXM01 after treatment with at least four vaccinations [10^6 or 10^7colony-forming units (CFU)] in patients with recurrent glioblastoma who have failed at least radiochemotherapy with temozolomide. **Methods:** Patients with progressive resctable glioblastoma were subjected to single oral administration of VXM01 each on day 1, 3, 5, and 7. In addition, VXM01 was allowed to be administered in 4-weekly single doses every 4 weeks during the tumor follow-up period after reoperation. Follow-up was done by weekly safety laboratories and physical examinations in the treatment period and 4-weekly thereafter, MRI including perfusion maps (days 15 and 30 and six-weekly thereafter), 12-weekly T-cell immunomonitoring in the peripheral blood, and brain tumor immunohistochemistry. **Results:** Eight patients have been treated according to the schedule and surgery has been performed in seven of them. Under VXM01 treatment 47 adverse events, mostly unrelated to VXM01, were observed after a median of 7 doses per patient. Four out of eight patients (50%) showed a VEGFR-2 specific T cell response. In four patients there was a relevant increase in cerebral blood volume and apparent diffusion coefficient on post-vaccination MRI. In one patient there was an objective and durable T1 response, whereas three further patients remained stable prior to surgery and thereafter. Evaluation of infiltrating T cells in the tissue from re-operation revealed an increase in CD8+ T-cells in 5 out of 7 patients relative to the primary tumor tissue. **Conclusions:** VXM01 was safe and produces specific peripheral immune responses as well as enumeration of tumor-infiltrating T-cells in post-vaccine tumor tissue. Post treatment MRI imply vascular normalization and there was one patient with an objective response. As a consequence of this data, an expansion cohort of this trial has been launched. Clinical trial information: NCT02718443.

2062 Poster Session (Board #304), Mon, 1:15 PM-4:45 PM

Effect of treating glioblastoma with a cytokine inhibitor, ibudilast, in combination with temozolomide on survival in a patient-derived xenograft model. *First Author: Kerrie Leanne McDonald, University of NSW, Kensington, Australia*

Background: Recurrence in patients with glioblastoma (GBM) is inevitable, even in patients with *O-6-Methylguanine-DNA Methyl Transferase* (*MGMT*) methylation. We identified increased expression of the inflammatory cytokine, Macrophage Inhibitory Factor (MIF) and its receptor CD74 in patients with recurrent tumors. High levels of MIF and CD74 were associated with poor overall survival in GBM patients. This study aims to determine efficacy of Ibudliast (MN-166; 3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine) to block MIF expression and decrease tumor burden. Ibudilast is an anti-inflammatory drug that was developed for the treatment of bronchial asthma. **Methods:** The patient derived cell lines (PDCLs) RN1 (*MGMT* unmethylated), BAH1 (*MGMT* methylated), and HW1 (*MGMT* methylated) were treated *in vitro*with different concentrations of ibudilast in combination with temozolomide (TMZ). Patient derived xenograft (PDX) models of GBM were developed and treated with the combination of ibudilast and TMZ. Overall survival was calculated. **Results:** Regardless of MGMT status, significant synergism between ibudilast and TMZ was observed in the PDCLs. Efficacy was associated with significantly decreased expression of its targets, MIF and CD74. Downstream proteins such as Src and Akt were also significantly inhibited. The combination induced apoptosis. RN1 tumors were established intracranially in Balb/c nude mice. Significant increases in survival times of the mice were recorded when treated with the combination. **Conclusions:** Ibudilast in combination with TMZ resulted in significant blockage of MIF expression, increased apoptosis and longer survival *in vivo*. A human pilot study for recurrent GBM patients is underway.

2063 Poster Session (Board #305), Mon, 1:15 PM-4:45 PM

Heterogeneous spectrum of childhood and adult SHH medulloblastoma: Clinical, radiogenomic features, patterns of failure and survival. *First Author: Rakesh Jalali, Tata Memorial Hospital, Mumbai, India*

Background: To present SHH pathway driven medulloblastoma (MB) diversities in pediatric and adult patient populations. **Methods:** 60 patients with SHH-MB seen at our institute during 2009-2015. We assigned 22 predefined radiological features for all MB subgroups including SHH. Outcome data was retrieved from a prospectively maintained database. **Results:** Median age of entire cohort was 14 years (1-48 years). 29 were adults (a-SHH) and 31 were pediatric SHH (p-SHH). Radiological data available for 39 patients showed a-SHH having lateralised location in 72% cases. Distinct MRI features to predict SHH include mild/moderate contrast enhancement (90%), cystic changes (82%), edema (92%); identical in two age groups. We could predict SHH accurately 95% times. p-SHH were seen to have higher frequency of p53 mutations (70% vs 45%). At median follow-up of 37 months, 25 patients failed [isolated tumor bed (TB) in 10, TB and supratentorially in 2, cranium outside TB in 1, craniospinal in 5 (along with TB), extraneuraxial (ENM) in 5, second primary in 2 (lymphomas)]. 1 and 3 year DFS was 74% (p-SHH) vs 96% (a-SHH) and 58% vs 73% respectively (p-0.19). The failures seen in a-SHH were typically late (10/11 failed $>$ 22 months) as compared to p-SHH (12/14 failing $<$ 24 months). Also location of recurrences was different, with 7 of a-SHH failing at TB and rest 3 developed ENM. Ten of 13 in p-SHH failed beyond TB. Post- recurrence salvage was better in a-SHH compared to p-SHH, 1-year survival of 50% vs 19% (p-0.08). Overall survival at 1 and 3 year 84% and 55% for p-SHH and 100% and 88% for a-SHH respectively ($p = 0.04$). Histology and tumor location significantly correlated with OS. No significant correlation was seen with CSI dose or chemotherapy. **Conclusions:** SHH medulloblastoma have unique MRI features and can be predicted up to 95% times pre-operatively. Adult and pediatric SHH MB form extreme diverse groups with different patterns of failure reflecting different tumor kinetics. Adults fail primarily over TB after initial 2 years. Paediatric SHH follow aggressive course with early disseminated recurrences in 1st year. Different treatment modalities may be needed for pediatric and adult SHH MB.

2064 Poster Session (Board #306), Mon, 1:15 PM-4:45 PM

Comprehensive assessment of *ATRX* mutation, protein expression, and alternative lengthening of telomeres (ALT) phenotype in grade II and III gliomas. *First Author: Aline P. Becker, The Ohio State University, Columbus, OH*

Background: *ATRX* mutations are key molecular markers for classification of gliomas. We aimed to evaluate *ATRX*mutations and protein expression and the ALT phenotype as potential biomarkers for grade II and III gliomas. **Methods:** Retrospective analysis of 156 adult gliomas, with long-term follow up. Gene sequencing (*IDH1/2* and *ATRX*), Oncoscan array (1p19q co-deletion), FISH assays (1p19q co-deletion and ALT phenotype) and immunohistochemistry (IDH1 R132H and ATRX) were performed and the results were correlated with OS and PFS. **Results:** Twenty-six out of 94 samples (27.7%) had *ATRX* mutations, commonly related to *IDH1/2* mutant-1p/19q intact tumors (22/26 cases – $p < 0.0001$), however, 3 (11.5%) mutant tumors had concurrent 1p/19q co-deletions. ATRX loss of expression occurred in 66/150 cases (44%), consistently related to *ATRX* mutations ($p < 0.0001$). Intriguingly, 4/25 *ATRX* mutant tumors (2 frameshift and 2 point mutations with low/medium functional impact) showed weak/heterogeneous expression, while 18/65 (27.7%) *ATRX* wild type tumors had loss of protein expression. ALT phenotype was detected in 50/150 cases (33.3%), strongly related to *ATRX* mutations (23/32 cases), loss of protein expression (45/50 cases), and to *IDH1/2* mutant-1p/19q intact tumors (35/41 cases). Two *ATRX* mutant tumors were ALT negative, while nine *ATRX* wild type tumors with loss of expression had ALT phenotype. *ATRX*mutations, loss of protein expression, and ALT phenotype were strongly related to longer OS in grade III gliomas ($p = 0.006$, 0.023 and 0.003, respectively). Further subset analyses were not completed due to small sample sizes. **Conclusions:** *ATRX* mutations and loss of protein expression as well as ALT phenotype are potential prognostic factors for grade III gliomas. Importantly, this study highlights possible discrepancies (although infrequent) between *ATRX* sequencing, immunohistochemistry, and FISH (ALT). In addition, other mechanisms of *ATRX* gene silencing should be further investigated in grade II and III gliomas. FUNDING: R01CA108633, R01CA169368, RC2CA148190, U10CA180850-01 (NCI), Brain Tumor Funders Collaborative Grant, and The Ohio State University CCC (all to AC).

2065 Poster Session (Board #307), Mon, 1:15 PM-4:45 PM

Apparent diffusion coefficient (ADC) decrease to predict longer survival in glioblastoma patients treated by dendritic cell immunotherapy plus standard of care. *First Author: Marica Eoli, Molecular Neuroncology Unit, Carlo Besta Institute - IRCCS, Milano, Italy*

Background: The MRI follow –up of patients affected by glioblastoma (GBM) and treated with immunotherapy may be difficult, as immune responses may mimic tumor progression. To explore the potential contribution of quantitative MRI to the identification of patients with clinical benefit benefit, we used advanced MRI to study GBM patients treated with dendritic cell (DC) immunotherapy added to standard treatment (surgery, radiotherapy with concomitant temozolomide (TMZ) followed by adjuvant TMZ; DENDR1 trial, EUDRACT N° 2008-005035-15). **Methods:** A retrospective analysis was performed on longitudinal MRIs obtained soon after radiotherapy, within two days before the first vaccination (basal MRI) and every two months, in 22 patients enrolled in DENDR1. The following parameters were collected: tumor volume of contrast–enhanced lesions, mean rCBV, maximal rCBV, mean ADC, minimal ADC, ADC skewness. Receiver Operating Characteristic (ROC) curves were used to determine optimal sensitivity and specificity in differentiating patients as responder or not responder. Association with PFS (as per RANO criteria) and OS was analyzed using log-rank test and Cox regression. **Results:** Ten patients with PFS $>$ 12 months were defined as responders Their basal mean ADC was significantly higher than in non responders (1.34 ± 0.17 vs 1.14 ± 0.34, $p = 0.03$). After four DC vaccinations mean ADC significantly decreased in responders only from 1.34 ± 0.17 to 1.23 ± 0.23 ($p = 0.028$); the decrease persisted during immunotherapy. A basal mean ADC value $\geq$ 1.07 and a decrease in mean ADC value $\geq$ 0.13 were significant predictors of longer PFS (15.4 vs 9 m $p = 0.0006$; 17.2 vs 10.2 $p = 0.04$) and OS (29 vs 12.5 mo $p = 0.002$; 33 vs 19.9 $p = 0.04$ No significant correlations between the other parameters and the outcome were observed. **Conclusions:** Association with prolonged survival may suggest that in DENDR1responders decreased ADC is partly contributed by immune cells infiltrating the tumor.

2066 Poster Session (Board #308), Mon, 1:15 PM-4:45 PM

Initial phase 1 study of WT2725 dosing emulsion in patients with advanced malignancies. *First Author: Siqing Fu, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: WT2725 is a Wilms' tumor (WT1)-derived-oligopeptide vaccine intended to induce WT1 specific cytotoxic T-lymphocytes against WT1 positive tumors in HLA-A*0201+ or HLA-A*0206+. This first in human study of WT2725 was conducted to evaluate the safety, tolerability, and efficacy. **Methods:** Subjects with progressive or recurrent glioblastoma (GBM), acute myeloid leukemia (AML) (patients in morphologic remission with minimal residual disease determined by WT1 RT-PCR were allowed), non-small cell lung cancer (NSCLC), or ovarian cancer despite standard therapy were treated with 0.3, 0.9, 3, and 9 mg of WT2725 subcutaneously (s.c.) every week for 4 weeks, then every other week for 6 weeks, and every 4 weeks thereafter until progression or other discontinuation event (part 1); and with 18 mg and 27 mg of WT2725 s.c. every week for 8 weeks, then every other week for 10 weeks, and every 4 weeks thereafter until progression or other discontinuation event (part 2). Responses were evaluated by Immune-related Response Criteria (irRC) for solid tumors and modified International Working Group (IWG) for AML. **Results:** 62 subjects were dosed, the most frequent adverse events were grade 1 injection site reactions (no grade 3 injection site reactions or dose limiting toxicities observed). Of the 21 GBM subjects who were dosed, seven survived for $\geq$ 1 year (33%). Of these seven subjects, three survived for $\geq$18 months (14%), and two for $\geq$2 years (both in complete radiologic remission, 9.5%). One of the seven subjects with $\geq$1 year survival had previous treatment with bevacizumab. Two subjects continue dosing (1 complete response with no measurable disease $>$3 years and 1 partial response $>$ 13 months on study). Results in subjects with non-GBM tumors (12 subjects with AML, 21 with ovarian CA, 7 with NSCLC, and 1 other cancer) are not presented here. WT1-specific CTLs and tumor burden was monitored. WT1 specific CTLs were associated with decrease of tumor burden in two patients with low tumor burden. Some patients with high disease burden did not respond. **Conclusions:** Preliminary data suggests WT2725 is well tolerated with potential antitumor activity in GBM patients, supporting future development of WT2725 for treatment of GBM in selected subjects. Clinical trial information: NCT01621542.

2067 Poster Session (Board #309), Mon, 1:15 PM-4:45 PM

Epidemiologic study of risk factors for meningioma in the Mayo Clinic Study of Aging. *First Author: Alissa Butts, Mayo Clinic, Rochester, MN*

Background: An estimated 2% of the general population has a meningioma (Vernooij et al. 2007), which accounts for about 36% of all primary intracranial tumors (Ostrom et al. 2015). The most established risk factors are older age and female gender. One small study identified gender but no other risk factors with meningioma (Krampla et al 2004). A larger study using the Iowa Women's Health study data found lower levels of physical activity, greater body mass index (BMI), greater height and uterine fibroids were associated with meningioma (Johnson et al. 2011). We sought to replicate these findings and to identify additional risk factors related to meningioma in a large population-based sample. **Methods:** Study participants were enrolled in the Mayo Clinic Study of Aging (MCSA), a population-based sample of Olmsted County, Minnesota residents used to study prevalence, incidence, and risk-factors for Mild Cognitive Impairment and dementia and includes a variety of medical factors. Using a text search of radiologists' notes of 2,402 MCSA individuals, mean age 77±8 years and scanned between 2004-2014.We identified 52 subjects who had at least one meningioma. We estimated the association of selected potential risk factors with presence of meningioma using odds ratios and 95% confidence intervals from logistic regression models adjusted for age and gender, which informed the multivariable models. **Results:** In the initial models, significant risk factors identified included BMI (as a continuous variable) (OR = 1.06 95%CI 1.01 to 1.12), taking NSAIDS (OR = 2.11, 95%CI 1.13 to 3.95), aspirin (OR = 1.90, 95%CI 1.04 to 3.46), and blood pressure lowering medication (OR = 2.06, 95%CI 1.07 to 3.99). Protective factors included male gender (OR = 0.51, 95%CI 0.29 to 0.90), coronary artery disease (CAD; OR = 0.46, 95%CI 0.22 to 0.97) and higher Beck Anxiety Inventory (BAI) total score (OR = 0.88, 95%CI 0.78 to 0.98). Simultaneous adjustment for these factors in a multivariable model did not attenuate these associations. **Conclusions:** Findings reveal gender and BMI as risk factors for meningioma. Additionally, certain medications such as NSAIDS and BP lowering medications warrant follow up as potential factors related to development of meningioma.

2068 Poster Session (Board #310), Mon, 1:15 PM-4:45 PM

Pituitary carcinoma: The University of Texas MD Anderson Cancer Center experience. *First Author: Fernando Santos Pinheiro, MD Anderson Cancer Center, Houston, TX*

Background: Pituitary carcinoma (PC) is a rare and aggressive neuroendocrine tumor diagnosed once a pituitary adenoma (PA) becomes metastatic. Although no standard treatment currently exists, surgery, radiation (XRT) and/or chemotherapy are most commonly used. Recently, treatment with temozolomide (TMZ) has shown promising results, although the lack of prospective trials limits accurate outcome assessment. **Methods:** We describe a single-center multidisciplinary team experience in managing PC patients over a 13-year period (Oct, 2003 to Jan, 2017). **Results:** A total of 17 patients (9 males) were seen. Median age at diagnosis of PC was 44 years (range 16-82 years) and the median time from PA to PC conversion was 6 years (range 1-29 years). Median follow-up time: 28 months (range 8-158 months) with 7 reported deaths. The majority of PC was hormone-secreting (HS) subtype (n = 12): ACTH (n = 5), PRL (n = 4), FSH/LH (n = 2), GH (n = 1). After PC diagnosis, all pituitary tumors were locally invasive, all underwent at least one resection (mean 2.3) and all received at least one course of XRT alone (IMRT = 76%, SRS = 29%, IMPT = 12%) or concurrent with chemotherapy (18%). Immunohistochemistry showed high Ki-67 labeling index ($>$ 3%) in 9 (53%) cases. Most cases (n = 14) had metastases to the CNS, 35% of those had combined CNS and systemic foci. Ten (59%) cases underwent focal treatment of metastases, 90% of which underwent XRT. The most common chemotherapy used was TMZ [n = 14 (82%): single agent (n = 10); TMZ+capecitabine (n = 5); concurrent TMZ+XRT (n = 3); concurrent TMZ+XRT with adjuvant TMZ (n = 1)]. The median longest progression-free survival (LPFS) was 18 months (range 4-45 months). TMZ was associated with the chemotherapy-related LPFS in 9 (75%) cases. The 2, 3 and 5 year survival rate was 65%, 53% and 35%, respectively. All patients surviving $>$ 5 years were treated with TMZ (n = 5, 2 survived $>$ 10 years). Two refractory cases are currently on PD-1 inhibitor agent. Eighty percent of non-functioning PC were alive at last follow-up (HS-PC, 58%). Recurrence occurred in 11 (65%) cases. **Conclusions:** Treatment of PC requires a multidisciplinary approach. Multimodality therapy with surgery, radiation and TMZ was associated with higher survival rates and longer PFS.

2069 Poster Session (Board #311), Mon, 1:15 PM-4:45 PM

Phase I study (BLOOM) of AZD3759, a BBB penetrable EGFR inhibitor, in EGFRm NSCLC patients with leptomeningeal metastasis (LM) who progressed after other anti-cancer therapy. *First Author: Byoung Chul Cho, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea*

Background: AZD3759 is the first EGFR inhibitor primarily designed to effectively cross the blood brain barrier (BBB) to treat central nervous system (CNS) metastases. A phase I study is ongoing to assess AZD3759 in EGFRm NSCLC patients with leptomeningeal metastasis (LM) who progressed after other treatment (NCT02228369). **Methods:** The primary objective is safety and tolerability, and secondary objectives include anti-tumor efficacy. Two dose levels of AZD3759, 200 mg and 300 mg BID, were assessed. **Results:** As of24 September, 2016,38 patients were recruited into the expansion cohorts of this phase I study. Of those, 18 were TKI pre-treated EGFRm NSCLC patients with LM. 10 and 8 patients were in the 300 and 200 mg BID cohorts, respectively. No DLTs were observed at either dose, while AZD3759 was better-tolerated at 200 than 300 mg BID during $>$ 2 month treatment. The longest duration on treatment was $>$ 9 months. Most common AEs included skin rash and diarrhea. 67% (12 out of 18) patients had drug-related dose interruption and/or reduction, however, there were no drug-related discontinuations.The C_{trough} free plasma and CSF exposure were above pEGFR IC_{90}at the two doses. 40% of patients (4 out of 10) had $>$ 50% inhibition of pEGFR in CSF tumor cells at C1D8, and 70% of patients (7 out of 10) had reduced EGFR copy numbers in CSF at C3D1. 53% of evaluable patients (9 out of 17) had confirmed improved/stable LM MRI imaging. 2 out of 3 patients with concomitant measurable BM lesions achieved confirmed/unconfirmed partial CNS response. Among 18 patients with measurable extracranial lesions, 6 (33%) had confirmed stable extracranial disease as best response. 3 patients achieved clearance of tumor cells in CSF by two consecutive assessments. After 6 months follow-up, 29% patients (5 out of 17 evaluable) were still surviving, plus 5 surviving patients with less than 6 months follow-up. **Conclusions:** AZD3759 was well-tolerated, achieved sufficient CNS exposure for target inhibition and demonstrated promising anti-tumor activity in patients with LM who progressed after multiple lines of treatment. Updated clinical data will be shared at the meeting. Clinical trial information: NCT02228369.

2070 Poster Session (Board #312), Mon, 1:15 PM-4:45 PM

Detection of tumor-derived DNA mutations in cerebrospinal fluid of patients with primary or metastatic brain tumors. *First Author: Jianfei Wang, Genecast Precision Medicine Technology Institute, Beijing, China*

Background: Because detecting tumor-derived cell free DNA (cfDNA) in the blood of patients with primary or metastatic brain tumors is challenging, here we studied whether cerebrospinal fluid (CSF) could be serve as an alternative "liquid biopsy" by enabling measurement of circulating DNA within CSF to characterize tumor specific mutations. **Methods:** The paired cfDNA in CSF and plasma were collected from 20 patients with brain tumors and was subjected to enrichment for a 1.15M size panel cover exon regions from 1,086 genes. Followed by next generation sequencing on an Illumina X10 platform, the captured sequencing data was further processed using bioinformatics analysis to identify somatic mutations, including single nucleotide variants (SNV) and short insertions/deletions (indels). **Results:** The mutation profiles of 48 tumor associated genes in cfDNA were compared between the CSF and plasma. Our results showed that both average somatic mutation number and frequency identified in the cerebrospinal fluid was much higher than that in the corresponding plasma samples (25 vs. 18 & 1.39% vs. 0.55%). Among the twenty cases, one more potential actionable mutation, EGFR exon 19 deletion mutation with a 25.38% allele frequency variation, was only detected in the CSF cfDNA of a patient with brain metastasis lung cancer. **Conclusions:** Tumor mutations were detectable in CSF cfDNA of patients with different primary and metastatic brain tumors. Thus cerebrospinal fluid cell free DNA analysis could be a potential alternative analysis for patients with primary or metastatic brain tumors.

2071 Poster Session (Board #313), Mon, 1:15 PM-4:45 PM

What drives patient outcomes in brain metastases: Number, volume, or biology? *First Author: Rupesh Kotecha, Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH*

Background: To delineate the prognostic importance of number of brain metastases (BM), lesion volume, and biology on overall survival. **Methods:** Patients treated for BM with whole-brain radiation therapy (WBRT), surgery, and/or stereotactic radiosurgery (SRS) at a single tertiary care institution from 1997-2015 were reviewed. The primary outcome was overall survival. Multivariable proportional hazards regression was used to adjust for confounding factors. **Results:** 3,955 patients with 16,189 BM were included in the analysis. There was a reduction in median survival with increasing number of lesions [1 lesion, 10.2 months; 2-4 lesions, 7.2 months, Hazard Ratio (HR) 1.36; 5-10 lesions, 5.6 months, HR: 1.69; > 10 lesions, 5.5 months, HR: 1.57, $p< 0.001$]. Among 1,651 patients (35%) who underwent SRS, there was a similar reduction in median survival with increasing lesion number [1 lesion, 12.2 months; 2-4 lesions, 10.1 months, HR 1.20; 5-10 lesions, 8.4 months, HR 1.41; > 10 lesions, 6.9 months, HR 1.19], $p< 0.001$). Among patients who underwent upfront SRS, increasing number of BM did not adversely affect survival in those with the smallest intracranial disease volume (≤0.4 cc, 10th percentile, $p= 0.39$), but was associated with inferior survival in patients with larger disease volumes (≤1.1 cc, 25th percentile, $p= 0.05$; ≤2.6 cc, 50th percentile, $p= 0.005$; ≤6.3 cc, 75th percentile, $p= 0.006$, and ≤12.2 cc, and 90th percentile, $p =0.004$). After partitioning the cohort into molecular subsets, patients with *ALK+* disease had no difference in survival based on either lesion number or volume. Patients with *EGFR+*, *HER2+*, and luminal B disease had no difference in survival based on number of metastases, while patients with *BRAF V600+*and luminal A disease had no difference in survival based on intracranial disease volume. **Conclusions:** Number of BM closely correlates with survival in the majority of patients and intracranial disease volume impacts survival independent of number of metastases. For patients with certain tumor subtypes (*ALK+*), intracranial disease burden appears to have no correlation with survival. Molecular profile characterization is important to identify patients with favorable subtypes given available treatment options.

2072 Poster Session (Board #314), Mon, 1:15 PM-4:45 PM

Examination and prognostic implications of the unique microenvironment of breast cancer brain metastases. *First Author: Grace Prince, University of North Carolina, Chapel Hill, NC*

Background: Brain metastases (BM) are an increasingly common consequence of breast cancer (BC). Knowledge of the microenvironment in primary BC and its impact on prognosis is evolving. A similar understanding of the microenvironment of BC metastases is lacking, particularly for the brain, where unique immune regulation governs stroma composition. Such features of the peri-tumoral landscape, i.e. high immune infiltrate and low hemorrhage, offer prognostic value in BM from melanoma. This study reports on 4 biomarkers, gliosis (glio), immune infiltrate (immune), hemorrhage (hem) and necrosis (nec), and their prognostic significance in BCBM. **Methods:** A biobank of 203 patients (pts) who underwent craniotomy between 1989-2013 was created across 4 sites. Glio, immune, and hem (grouped 0 v 1-3) and nec (0-2 v 3) were scored via H&E stain (0-3). Overall survival (OS (years)) from craniotomy was estimated using the Kaplan-Meier method; log-rank tests compared OS. Cox proportional hazards regression was used to evaluate prognostic value of the 4 biomarkers. **Results:** Mean age at primary BC diagnosis was 48 years (range 26-77). BCBM subtype (n = 158) was 36% HER2+, 26% HR+/HER2-, 38% HR-/HER2- (TN). Across all samples, expression was 82% glio, 45% immune, 82% hem, and 13% nec. Subtype differences were seen for nec (higher in TN, $p < 0.01$). Across all pts, expression of glio, immune, and hem was associated with improved OS (years): 1.08 v 0.62 (p = 0.03), 1.31 v 0.93 (p = 0.03), 1.07 v 0.92 (p = 0.1), respectively. Nec was associated with inferior OS: 0.38 v 1.12 (p = 0.01). The association with improved OS was maintained for glio in TN (p = 0.02), and immune (p = 0.001) and hem (p = 0.07) in HER2+. In a multivariable model for OS, adding the 4 biomarkers to traditional clinical variables (age, race, subtype) significantly improved the model fit ($p < 0.001$). **Conclusions:** Nec is a poor prognostic finding in BCBM across all subtypes. Glio confers superior prognosis in TN, while immune and hem correlate with superior prognosis in HER2+. A deeper understanding of the rich BCBM microenvironment both refines prognostic considerations for this pt population and may lead to future investigations of targeted immunotherapies in select subtypes of BCBM.

2073 Poster Session (Board #315), Mon, 1:15 PM-4:45 PM

Neurocognitive function testing and health related quality of life in stage IV lung cancer patients with and without brain metastases. *First Author: Grainne M. O'Kane, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Survival in stage IV lung cancer (S4LC) patients (pts) continues to improve, highlighting the importance of assessing health related quality of life (HRQoL). Lung cancer, involvement with brain metastases (BM), and systemic or brain-specific treatment can all impact neurocognitive function (NCF) and HRQoL. We evaluated the relationship between NCF and HRQoL in S4LC pts by BM status. **Methods:** S4LC pts with BM (BM+) were frequency distributionally-matched to pts without BM (NBM). NCF was measured using the Hopkins Verbal Learning Test – Revised (HVLT-R), the Controlled Oral Word Association Test (COWAT) and Trail Making Tests (TMT-A/B); scores were correlated with health utility score (HUS) data from EQ5D-3L surveys (Pearson Coefficient, R). **Results:** BM+ (n = 54) and matched NBM (n = 40) pts had similar demographics. The overall median age was 61years; 59% were female; of 89% that were adenocarcinomas, half had *EGFR/ALK* alterations; mean time since diagnosis was 2.6 years; mean time since BM were diagnosed in BM+ pts was 0.5 years. Mean HUS (mHUS) were similar between groups: 0.77 for BM+ vs. 0.78 for NBM; p = 0.86. However, pts with stable BM had higher HUS than those with progressive BM (mHUS: 0.80 *vs* 0.69; p = 0.045). Of BM+ pts, 44% had received whole brain radiation (WBRT). Correlations of NCF and HUS specific for BM+ pts were observed for several HLVT scores, including Total Recall (TR), which was correlated with HUS in BM+ (R = 0.35, p = 0.01) but not in NBM (R = 0.04, p = 0.84) and Recognition Discrimination Index (BM+: R = 0.32, p = 0.03 *vs* NBM: R = 0.13, p = 0.51). In contrast, TMT-A/B NCF test results had slightly stronger associations with HUS in NBM pts. COWAT was least associated with HUS in BM+ or NBM pts. In BM+ pts treated *vs* untreated with WBRT, HLVT scores were better in untreated patients (TR, p < 0.0001; delayed recall, p = 0.006; retention, p = 0.089), associations not seen with either TMT-A/B or COWAT. Mutation status had no bearing on these associations. **Conclusions:** NCF impacts HUS in S4LC pts and should be considered in treatment planning. HVLT scores are useful to assess specifically the impact of BM and WBRT in S4LC pts, and is reflected in associations with HRQoL.

2074 Poster Session (Board #316), Mon, 1:15 PM-4:45 PM

Planned interim analysis of PATRICIA: An open-label, single-arm, phase II study of pertuzumab (P) with high-dose trastuzumab (H) for the treatment of central nervous system (CNS) progression post radiotherapy (RT) in patients (pts) with HER2-positive metastatic breast cancer (MBC). *First Author: Nancy U. Lin, Dana-Farber Cancer Institute, Boston, MA*

Background: There is currently no clear standard of care to address the management of recurring/multiple intracranial metastases post RT in HER2-positive MBC. The ongoing PATRICIA study (NCT02536339) is evaluating the safety and efficacy of P in combination with high-dose h for patients with HER2-positive MBC with CNS metastases who have CNS progression following RT. Reported herein are results from the protocol-specified interim analysis of PATRICIA. **Methods:** All eligible patients must have measurable (≥10 mm) CNS progression post RT, and stable non-CNS disease. Patients receive P (840-mg loading dose, then 420 mg every 3 weeks) and high-dose h (6 mg/kg weekly). The primary efficacy endpoint is objective response rate (ORR) in the CNS per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. The interim analysis was planned after 15 patients were enrolled and had ≥2 left ventricular ejection fraction (LVEF) measurements, 2 cycles of study drugs, and 2 response measurements. The study would proceed to full enrollment (n=40) if objective response or stable disease in the CNS was observed in ≥1 of 15 patients and <2 of 15 patients develop congestive heart failure (CHF) related to P or H. **Results:** As of Sept 6, 2016, 15 patients had been enrolled across 9 sites. Median treatment duration was 4.4 (range 1.2−8.3) months. Six patients discontinued treatment (5 for disease progression; 1 for symptomatic deterioration). Range for duration of response was 1.4−3.3 months. There were no new safety signals for P combined with high-dose h treatment. No patients had CHF or a clinically significant drop in LVEF. **Conclusions:** Based on early evidence of clinical benefit (ORR 20%) and a lack of new safety signals, the safety and futility boundaries for PATRICIA have been passed and study enrollment continues. Clinical trial information: NCT02536339.

Efficacy within CNS per RANO-BM criteria	n (%)
Complete response (CR)	0
Partial response (PR)	3 (20)
Stable disease (SD)	9 (60)
Disease progression	3 (20)
ORR[a]	3 (20)
95% CI	4.3−48.1
CR + PR + SD ≥4 months	6 (40)
95% CI	16.3−67.7

[a]CR or PR.

2076 Poster Session (Board #318), Mon, 1:15 PM-4:45 PM

The value of ^{18}F-fluordesoxyglucose positron emission tomography (FDG-PET/CT) in the detection of the primary lesion and for staging in brain metastasis (BM) patients with cancer of unknown primary site (CUPS). *First Author: Emilie Le Rhun, Lille University Hospital, Lille, France*

Background: Brain metastasis (BM) are the first clinical presentation of cancer in around 30% of patients. They are then referred as BM from cancer of unknown primary site (BM-CUPS). The value of ^{18}F-fluordesoxyglucose positron emission tomography (FDG-PET)/CT has not yet be determined for the management of these patients. **Methods:** A total of 566 patients were operated for BM at the University Hospital Zurich between 2004 and 2014, of whom 127 were identified as BM-CUPS patients. Two cohorts from other independent centers (n = 100 and 120) were used for the validation of data. **Results:** No difference in determining the localization of the primary lesion was observed between FDG-PET/CT and CT (FDG-PET/CT: 73/78, 93.6%; CT: n = 70/78, 89.7%; p = 0.25, McNemar's test). The same pattern of primary lesion and other extracranial lesions was observed in 36 of 64 patients (56.3%). Additional suspicious extracranial metastases were identified by FDG-PET/CT in 28 patients (43.7%). The median graded prognostic assessment (GPA) scores were 2.5 determined according to FDG-PET/CT and 3 according to CT alone ($p = 3.8x10^{-5}$), resulting in predicted survival times of 3.8 versus 5.3 months ($p = 6.1x10^{-5}$; Wilcoxon's test). **Conclusions:** A similar sensitivity of FDG-PET/CT and chest CT was observed for the detection of the primary tumor in BM-CUPS, however, FDG-PET/CT significantly improved the accuracy of staging. FDG-PET/CT should be preferred for the management of BM-CUPS and may help to avoid redundant CT imaging.

2077 Poster Session (Board #319), Mon, 1:15 PM-4:45 PM

Linac-based radiosurgery for multiple brain metastases: A quality assurance and feasibility study. *First Author: Raphael M. Pfeffer, Assuta Medical Center, Tel Aviv, Israel*

Background: The classical treatment for multiple brain metastases is whole brain radiotherapy (WBRT). For patients with 1-3 brain metastases stereotactic radiosurgery (SRS) results in better response, similar survival and less short and long term toxicity such as neurocognitive dysfunction than WBRT. For patients with $>$ 3 metastases there is little prospective data of SRS partly due to the technical and logistic difficulties of delivering SRS to multiple metastases. We present a new SRS planning program (MMM) that allows the planning and delivery of linac-based SRS to up to 10 brain metastases simultaneously in less overall time than for WBRT. **Methods:** Between August 2014 and August 2016, patients referred for RT with 2 or more brain metastases were offered treatment with MMM. System QA included ArcCheck diode array and film dosimetry and gel dosimetry based on a patient derived phantom. Individual QA included replanting treatment arcs on an independent system. **Results:** 94 patients with 2-10 (median 5) metastases and a combined volume of 0.01-8.64 cc were treated. Planning time including image fusion, target delineation and RT plan generation required on average 20 minutes minutes. SRS was delivered using 4-5 (is more 7-10 since return arcs do not address the same targets) non-coplanar arcs and a single isocenter at the center of mass of the metastases. Treatment time to deliver 18-24 Gy to all metastases was 25 mins (beam on time ~6 minutes) for a total time of 45 minutes. This is the same as the time for each individual metastasis on earlier planning systems and compares to 20 minutes planning time and 12 mins delivery time for each of 10 fractions for a conventional 2 field WBRT plan WBRT (total 140 minutes). At 6 months follow up, 88% of treated metastases had decreased in size, 10% were stable and 2% grew. Acute toxicity was mild except for one patient with intractable seizures. **Conclusions:** Linac based SRS for multiple brain metastases is efficient, requiring the same resources as for treatment of a single metastasis and less resources than for WBRT, with a high rate of local control. Appropriate equipment is available in most radiotherapy departments which will allow more prospective studies of SRS for multiple metastases.

2078 Poster Session (Board #320), Mon, 1:15 PM-4:45 PM

Outcomes from 735 patients with breast cancer brain metastases (BM) according to biological subtype, number of BMs, and systemic treatment after local therapy. *First Author: Anna Niwinska, Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland*

Background: To assess survival when BM is detected according to the biological subtype of breast cancer, number of BMs and systemic treatment after local therapy. **Methods:** Subjects were 735 consecutive breast cancer patients with BM treated during 2003-2015. Whole brain radiotherapy was undertaken in 97%, neurosurgery -19% and systemic therapy was performed in 74% cases. The biological subtypes: triple-negative (TNBC), HER2+ER/PR-, HER2+/ER/PR+ and ER/PR+HER2- (Luminal) were determined in 714 subjects. Survival after BM detection was assessed in the entire group, in patients with a single BM (1 brain lesion regardless of metastases in other organs) and those with a solitary brain metastasis (1 brain lesion but no metastases in other organs). Factors influencing survival upon detecting BM were assessed by Cox multivariate analysis. **Results:** The median survivals for all patients with TNBC, HER2+ER/PR-, HER2+/ER/PR+ and Luminal breast cancer BM were respectively 4, 8, 10 and 9 months ($p < 0.001$). In those both treated and untreated systemically within the TNBC, HER2+ER/PR-, HER2+/ER/PR+ and Luminal subtypes survivals were correspondingly 6, 10, 14, 11 and 2, 3, 2, 2 months ($p < 0.001$). Median survivals of 171 patients with a single BM treated and untreated systemically were respectively 15 and 5 months ($p < 0.001$). Median survivals of 70 patients with solitary BM treated and untreated systemically were respectively 28 and 6 months ($p < 0.001$). In patients with solitary brain metastasis, median survival within the TNBC, HER2+ER/PR-, HER2+/ER/PR+ and Luminal subtypes, with systemic treatment was respectively 16, 28, 28, 28 months and without systemic treatment 6, 7, 7 and 7 months ($p < 0.001$). **Conclusions:** Patients with TNBC and BM had the worst prognosis. Systemic treatment performed after local therapy is an important factor prolonging survival of patients with breast cancer BM, even in those with solitary brain metastasis. Based on the present evidence and our recent publication, systemic treatment should be performed in all patients with BM after local treatment, even those with brain metastases as an isolated recurrence.

TPS2079 Poster Session (Board #321a), Mon, 1:15 PM-4:45 PM

Individualized screening trial of innovative glioblastoma therapy (INSIGhT). *First Author: Brian Michael Alexander, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA*

Background: Patient with glioblastoma (GBM) with unmethylated *MGMT* promoters derive limited benefit from temozolomide (TMZ) and have dismal outcome. Prioritizing the numerous available therapies and biomarkers for late stage testing requires an efficient clinical testing platform. INSIGhT (NCT02977780) is a biomarker-based, Bayesian adaptively randomized, multi-arm phase II platform screening trial for patients with newly diagnosed GBM and unmethylated MGMT promoters. **Methods:** INSIGhT compares experimental arms to a common control of standard concurrent TMZ and radiation therapy (RT) followed by adjuvant TMZ. The primary endpoint is overall survival (OS). Patients with newly diagnosed, unmethylated GBM that are IDH R132H mutation negative, and with genomic data available or who consent to whole exome sequencing through the ALLELE companion study for biomarker grouping are eligible. Two experimental arms consist of concurrent RT/TMZ followed by adjuvant neratinib (EGFR, HER2, and HER4 inhibitor) or abemaciclib CDK 4/6 inhibitor), respectively, in place of TMZ. The other experimental arm is CC-115 (TORC1/2 and DNA PK inhibitor), which replaces TMZ in both the concurrent and adjuvant phases. Biomarker groups include: EGFR + patients with EGFR amplification/mutation; PI3K + patients with PIK3CA mutation/amplification, PIK3R1 mutation, AKT3amplification, PIK3C2B $>$ 1 copy gain, or PTEN dual loss; CDK: + patients with wild-type RB1 and CDK4 amplification, CDK6 amplification, or CDKN2A $>$ 1 copy loss. Given the lack of pretrial biomarker data and the anticipated overlap of the groups, randomization will initially be equal. As the trial progresses, randomization probabilities will be adapted based on the Bayesian estimation of the probability of treatment impact on progression-free survival (PFS). These randomization probabilities can vary among the biomarker groups so predictive biomarkers will be identified and utilized if present. Treatment arms may drop due to low probability of treatment impact on OS, and new arms may be added. Experimental arms are compared only with control and should be thought of as discrete experimental questions, with INSIGhT being open to new investigators with proposed therapeutic hypotheses. Clinical trial information: NCT02977780.

TPS2080 Poster Session (Board #321b), Mon, 1:15 PM-4:45 PM

A phase 2 study to determine the efficacy and safety of TVB-2640 in combination with bevacizumab in patients with first relapse of high grade astrocytoma. *First Author: Adolfo Enrique Diaz Duque, University of Texas Health San Antonio - MD Anderson Cancer Center, San Antonio, TX*

Background: The mainstay of treatment for Glioblastoma Multiforme (GBM) remains surgical removal followed by combined chemotherapy with temozolomide and radiation therapy. Second line Bevacizumab (Bev) is indicated upon progression, but unfortunately the responses are not very long lasting, and there are no therapeutic options available at that point. We have learned that antiangiogenic resistance in GBM is promoted by hypoxia; moreover, metabolomic profile of GBM under such conditions reveals an increased presence of long chain fatty acids. On second hand, tumor cells compared to normal cells depend more on palmitate, and is Fatty Acid Synthase (FASN) the enzyme capable of catalyzing its biosynthesis. Further studies have shown how GBM overexpress FASN and how its inhibition selectively inhibits growth and viability of tumor cells by inducing tumor cell apoptosis. TVB-2640 emerges as a novel agent that selectively inhibits FASN. This study represents a phase 2 clinical investigation of TVB-2640, which is to be conducted in patients with Recurrent High Grade Astrocytoma. **Methods:** This is a prospective, randomized, phase 2 study of TVB-2640 in combination with Bev or Bev alone in patients with GBM in first relapse. Primary end point is progression free survival (PFS). Patients 18 years or older, with ECOG 0 to 2 and GBM progression following standard combined modality treatment will qualify for the study. Patients will be randomized into 2 separate arms. Patients in arm number one will receive Bev every 2 weeks in combination with TVB-2640 while patients in arm number two will receive Bev alone every 2 weeks. MR-Spectroscopy will be obtained on all patients at day 1 and 28 of first cycle. Starting on cycle 2 day 1, all patients will converge to a single arm and will continue to receive Bev in combination with TVB-2640. A total sample size of 24 patients will provide 90% power to detect a 4 months difference in PFS (3 months for Bev alone (historic controls) versus 7 months for TVB-2640 in combination with Bev, i.e., a hazard ratio of 0.43) using a one-sided log-rank test with alpha = 0.1. The trial is open and enrollment will begin in Feb 2017. Clinical trial information: NCT03032484.

TPS2081 Poster Session (Board #322a), Mon, 1:15 PM-4:45 PM

STELLAR: A phase 3, randomized, open-label study of eflornithine with lomustine vs lomustine for patients with first recurrence of anaplastic astrocytoma after RT and adjuvant temozolomide. *First Author: Victor A. Levin, Orbus Therapeutics, Inc, Greenbrae, CA*

Background: Eflornithine irreversibly inhibits ornithine decarboxylase an enzyme that catalyzes the biosynthesis of putrescine, one of 3 polyamines in mammalian cells. Over 390 patients with anaplastic gliomas (AG) received eflornithine alone, with a nitrosourea, or the PCV combination in past clinical trials. A phase 3 randomized study of adjuvant chemotherapy with PCV vs eflornithine-PCV in 228 patients with AG found a median overall survival (mOS) increase from 61.1 to 75.8 months in the eflornithine-PCV arm. **Methods:** Patients must have histologically proven diagnosis of WHO grade 3 anaplastic astrocytoma (AA) with unequivocal evidence of first AA tumor progression or recurrence $\leq$ 3 months prior to randomization following surgical resection or biopsy, RT and temozolomide chemotherapy. Patients must have RT $\geq$ 6 months prior to randomization and have a KPS of $\geq$ 70. Randomization of 280 patients will be 1:1 with stratification to: Age ($\leq$ 45 yrs, $>$ 45 yrs), region (US, Ex-US), IDH1 status (wild, mutant), and prior surgeries (biopsy, 1-2 resections). Patients will receive eflornithine 2.8 g/m^2 orally every 8 h on a 2 week on, 1 week off schedule, and lomustine 110 mg/m^2 orally once every 6 weeks, or lomustine alone dosed at 110 mg/m^2 orally once every 6 weeks. Lomustine will be limited to 6 cycles or 12 months of therapy. Eflornithine can be given up to 24 months in the combination arm. The primary endpoint will be OS. Secondary objectives include PFS and objective response rate (ORR) based on MRI. The study sample size was calculated by assuming true mOS of 12 months for lomustine monotherapy and true mOS of $>$ 18 months for the eflornithine plus lomustine arm. Such an improvement represents a true hazard ratio of 0.667 (investigational arm/control arm). Inferential comparisons of OS will be performed using a stratified log-rank test with 137 patients per arm and total information of 194 deaths with 80% power to detect a 33% reduction in the OS failure hazard rate. The study is open at 55 sites in the USA, Germany and Italy with an additional 10-15 sites being evaluated in 3 additional countries. Study enrollment is expected through 2018. Clinical trial information: NCT02796261.

TPS2082 Poster Session (Board #322b), Mon, 1:15 PM-4:45 PM

Clinical trials of VAL-083 in patients with chemo-resistant glioblastoma. *First Author: Jeffrey A. Bacha, DelMar Pharmaceuticals, Vancouver, BC, Canada*

Background: Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard of care includes surgery, radiation and treatment with temozolomide (TMZ), however nearly all tumors recur and the prognosis for recurrent GBM is dismal. Most GBM tumors have unmethylated promoter status for O6-methylguanine-DNA-methyltransferase (MGMT); a validated biomarker for TMZ-resistance. Second-line treatment with anti-angiogenic agent bevacizumab has not improved overall survival (OS) and 5-year survival is less than 3%. Dianhydrogalactitol (VAL-083) is a bi-functional alkylating agent targeting N7-Guanine and inducing interstrand DNA cross-links, double-strand breaks and cell death in GBM cell lines and GBM cancer stem cells, independent of MGMT status *in vitro*. VAL-083 readily crosses the blood-brain barrier and accumulates in brain tumor tissue. Our recent phase I/II clinical trial in recurrent GBM patients failing both TMZ and bevacizumab, suggested that VAL-083 offers clinically meaningful survival benefits for patients with recurrent GBM and pinpointed a new dosing regimen (40 mg/m^2/d on days 1,2,3 of a 21-day cycle) which was well-tolerated and was selected for study in subsequent GBM trials. **Methods:** These trials include i) an ongoing single-arm, biomarker driven, Phase 2 study to determine if VAL-083 treatment of *MGMT*-unmethylated adult GBM patients at first recurrence/progression, prior to bevacizumab improves overall survival at 9 months, compared to historical control with lomustine (clinicaltrials.gov identifier: NCT02717962). ii) A pivotal Phase 3 study in recurrent GBM after failing both TMZ and bevacizumab. The control arm will consist of a limited number of salvage chemotherapies currently used in bevacizumab-failed GBM. If successful, this study will serve as the basis for a New Drug Application (NDA) submission for VAL-083. iii) A single arm, biomarker driven, Phase 2 study to confirm the tolerability and efficacy of VAL-083 in combination with radiotherapy in newly diagnosed *MGMT*-unmethylated GBM patients whose tumors are known to express high MGMT levels. The results of these studies may support a new treatment paradigm in chemotherapeutic regimens for the treatment of GBM. Clinical trial information: NCT02717962.

TPS2083 Poster Session (Board #323a), Mon, 1:15 PM-4:45 PM

A phase 0/II study for ribicoclib in patients with recurrent glioblastoma. *First Author: Nader Sanai, Barrow Neurological Institute, Phoenix, AZ*

Background: Disruption of CDK4/6-dependent G1-S cell cycle regulation is a hallmark of glioblastoma (GBM) progression in 78% of cases. Newly-developed CDK4/6 inhibitors have shown promise in non-CNS cancer trials and glioma animal models. To explore the utility of Ribociclib, a specific CDK4/6 inhibitor, in treating recurrent GBM patient, we designed a phase 0/II clinical trial to examine the pharmacokinetic (PK) and pharmacodynamics (PD) of Ribociclib. **Methods:** 24 adult patients are allocated to 3 time-escalation arms and receive 5 days of daily Ribociclib prior to planned GBM resection. Eligible patients are selected based on intact Rb expression and loss of Ink4a/Arf locus. Intensive PK sampling of blood, CSF, and tumor is performed intraoperatively and Ribociclib concentrations are determined by a validated LC-MS/MS method. PD endpoints, including RB phosphorylation and FoxM1 expression, are compared to matched archival tissue. Patients exhibiting positive PK and PD outcomes will graduate to a therapeutic regime of Ribociclib as part of the Phase II component of the study with a primary endpoint of progression-free survival, as determined by Response Assessment in Neuro-Oncology (RANO) criteria. Clinical trial information: NCT02933736.

TPS2084 Poster Session (Board #323b), Mon, 1:15 PM-4:45 PM

Nivolumab combined with hypofractionated stereotactic irradiation (HFSRT) for patients with recurrent high grade gliomas: A phase I trial (NCT02829931). *First Author: Solmaz Sahebjam, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: Nivolumab is an IgG4 monoclonal antibody that targets the PD-1 immune checkpoint pathway and prevents binding of PD-1 with PD-L1 and PD-L2. Expression of PD-1 and PD-L1 is found in the microenvironment of high grade gliomas and correlates with worse outcome providing a rationale for investigating nivolumab in this group of patients (pts) with very limited treatment options. Nivolumab monotherapy is well tolerated in recurrent glioblastoma pts. Preclinical studies have demonstrated that radiotherapy synergizes with anti PD-1/PD-L1 blockade and produces tumor regression and long-term survival in orthotopic murine models of glioma. This report describes an ongoing phase I trial of nivolumab in combination with HFSRT in pts with recurrent WHO grade III or IV gliomas. **Methods:** This phase I study includes a safety cohort of 6 pts followed by dose expansion cohort of 20 pts (NCT02829931). Pts with bevacizumab naïve recurrent WHO grade III or IV gliomas (maximum diameter of enhancing brain lesion $\leq$ 4 cm) are eligible. An interval of at least 6 months after the end of prior radiation therapy is required unless there is a new recurrence outside of the previous radiotherapy treatment field. Eligible patients will be treated with HFSRT to the recurrent tumor (30 Gy delivered in 5 fractions). Nivolumab will be started 5 days after HFSRT. It will be administered intravenously every 2 weeks (at 240 mg flat dose) for 4 months. After 4 months, nivolumab will be administered every 4 weeks at 480 mg flat dose. The primary study objectives are to determine safety and tolerability of nivolumab administered in combination with HFSRT to recurrent high grade gliomas. Secondary endpoints include determination of the preliminary antitumor activity (response rate, 6-months survival and 9-months survival rates), and exploring tissue and imaging biomarkers. Study Progress: At deadline for abstract submission, 5 patients have been treated on this study. Clinical trial information: NCT02829931.

TPS2085 Poster Session (Board #324a), Mon, 1:15 PM-4:45 PM

REGOMA: A randomized, multicenter, controlled open-label phase II clinical trial evaluating regorafenib (REG) activity in relapsed glioblastoma (GBM) patients (PTS). *First Author: Giuseppe Lombardi, Department of Clinical and Experimental Oncology, Medical Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy*

Background: GBM is the most common and malignant form of primary brain tumor with a high recurrence rate after surgery, radiation therapy and temozolomide. Currently, there is no established regimen for the treatment of recurrent GBM. GBMs are highly vascularized tumors with high expression of pro-angiogenic factors and activation of multiple signaling pathways in the tumor microenvironment, including the receptor tyrosine kinases, VEGFR, FGFR, and PDGFR, which control the tumor vasculature. REG, an oral multikinase inhibitor, inhibits these angiogenic kinases and the mutant oncogenic kinases KIT, RET and B-RAF. REG was demonstrated to be safe and effective in metastatic colon-rectal cancer, hepatocellular carcinoma and GIST PTS. It was shown that REG inhibits tumor angiogenesis and tumor cell proliferation in rat GBM tumor xenografts (Wilhelm S.M, et al. Regorafenib: a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int. J. Cancer:129,245-255.2011). **Methods:** Primary aim of the study is to assess the role of REG activity in prolonging the overall survival in relapsed GBM PTS after surgery and Stupp regimen; secondary aims are to analyze progression free survival, objective response rate, disease control rate and quality of life. Eligible PTS with ECOG PS 0-1, documented progression of disease (after Stupp treatment) as defined by RANO criteria, adequate bone marrow, liver and renal function are randomized in a 1:1 ratio to REG 160 mg/die (3 weeks on, 1 week off) or lomustine 110 mg/m2 (every 6 weeks). A total of 112 PTS will be randomized ($\alpha = 0.20$, $\beta = 0.20$) and stratified based on surgery at recurrence. Disease evaluation is performed with gadolinium brain MRI every 8 weeks according to RANO criteria. Additional exploratory objectives include analysis of specific angiogenic and metabolic biomarkers in tissue as possible predictors of response to REG. The trial started in Nov 2015; as of Jan 2017, 105 PTS have been enrolled. Final analysis is planned in Dec 2017. Clinical trial information: NCT02926222.

TPS2086 Poster Session (Board #324b), Mon, 1:15 PM-4:45 PM

Cognitive support program for patients with brain metastases. *First Author: Nadine M. Richard, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Brain metastases occur in ~30% of cancer patients. While treatment options continue to evolve, prognosis remains poor in both morbidity and survival, and quality of life (QOL) is increasingly emphasized. Most patients will experience cognitive dysfunction. Deficits in executive and self-regulatory functions, memory, and communication interfere with patients' functional independence, participation in valued activities, relationships and QOL; they also affect families and caregivers. There are currently no established interventions for oncology and supportive care teams to address cognitive dysfunction and its impact on patient and family QOL. This study targets this gap in knowledge and clinical practice through development and piloting of a novel cognitive support program (CSP) for brain metastasis patients and their primary caregivers. **Methods:** Building on relevant neuroscience and behavioral research in other cognitively-impaired populations, we designed the CSP as a brief, structured, client-centered program. Using a prospective longitudinal design, 24 cognitively-impaired patients are being recruited from an outpatient multidisciplinary brain metastasis clinic. Each patient, together with their primary caregiver, attends 3 weekly individual sessions to learn strategies for memory, communication and executive functions. At-home practice between sessions applies the strategies in daily activities. Feasibility will be assessed through retention and adherence. Preliminary efficacy will be assessed by reliable change on cognitive, functional and QOL measures completed by patients pre-, post-, and 3 months following the CSP intervention. Caregivers will complete ratings of patient functioning and their own QOL at the same intervals. Analyses of variance will examine CSP intervention effects, with regression analyses to explore moderating effects of participant demographics, baseline levels of cognitive impairment, disease and treatment factors (e.g., volume and location of brain lesions, CNS-directed treatments received). Results of this pilot trial will lay the groundwork for a future randomized trial and further development of cognitive supports for brain metastasis patients and their families.

2500 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Debio 1347, an oral FGFR inhibitor: Results from a first-in-human, phase I dose-escalation study in patients with FGFR genomically activated advanced solid tumors. *First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Oncogenic alterations in fibroblast growth factor receptors (FGFR) are seen across multiple solid tumor malignancies. Debio 1347 is an orally available, highly selective panFGFR inhibitor with potent antitumor effect in preclinical models bearing FGFR1-3 genetic alterations. **Methods:** Patients harboring defined FGFR 1, 2 or 3 alterations received escalating doses of Debio 1347 starting from 10 mg once daily. Dose escalation followed a 3+3+3 algorithm based on a modified Fibonacci sequence. The MTD was defined as the level where ≥ 3/9 patients suffer a DLT. Pharmacokinetics (PK) and pharmacodynamic were serially evaluated in blood, skin and/or tumor tissue. **Results:** Fifty-six patients were enrolled, including patients with mutations (n = 17), amplifications (n = 28) and fusions (n = 11). The dose was escalated up to 150 mg over 8 cohorts. DLTs were experienced by 4/56 patients, including G2 intolerable dry mouth + eyes at 60 mg, G3 hypercalcemia + hyperamylasemia at 80 mg, and G3 bilirubin increase at 110 mg. At data cut-off, the most common treatment-emergent adverse events (TEAE) were hyperphosphatemia (73%), fatigue (41%), diarrhea (39%), nausea (37%), and inappetence (32%). Fifteen patients (27%) experienced a grade ≥ 3 related TEAE. Twenty-five patients (47%) required dose modification, primarily due to hyperphosphatemia and cutaneous toxicity. An MTD has not been reached. PK appeared overall linear, with a half-life of 14 hours; hyperphosphatemia was dose-dependent. Among the 54 response-evaluable patients, 4 confirmed and 1 unconfirmed partial responses were observed in patients with cholangiocarcinoma (FGFR2 mutant), uterine (FGFR2 and FGFR1 amplified), colon (FGFR2 fusion), and urothelial cancer (FGFR3 fusion); an additional 10 patients had target regression < 30%. **Conclusions:** Debio 1347 had a tolerable and manageable safety profile. Encouraging antitumor activity was seen in several tumor types, mainly in patients with FGFR2 or 3 gene alterations, including fusion events, treated at 80 mg and 110 mg daily. Efficacy will be further explored in disease-specific and molecularly defined expansion cohorts. Clinical trial information: NCT1948297.

LBA2501 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers. *First Author: David Michael Hyman, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, June 3, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

2502 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Ceritinib plus nivolumab (NIVO) in patients (pts) with anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer (NSCLC). *First Author: Enriqueta Felip, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Induction of PD-L1 expression due to constitutive oncogenic signaling has been reported in NSCLC models harboring EML4–ALK rearrangements. Here we explore whether the combination of ALKi (ceritinib) and PD1-inhibitor (NIVO) will provide sustained clinical benefit to pts with ALK+ NSCLC. **Methods:** This phase 1 dose escalation study enrolled previously treated (ALK inhibitor [ALKi] or chemotherapy) or tx-naive pts with stage IIIB/IV ALK+ NSCLC; who received NIVO 3 mg/kg IV Q2W + ceritinib with low-fat meal, at 450 mg/day (group 1) or 300 mg/day (group 2) until progression/unacceptable toxicity. Primary objective: MTD/recommended dose for expansion. Dose escalation was guided by Bayesian logistic regression model with overdose control. **Results:** Median follow-up: group 1 (n = 14) 13 mos (10-15); group 2 (n = 22) 6 mos (2-10). As of 9 Sep 2016, 16/36 (44%) pts discontinued tx: disease progression (11 [31%] pts), AE's (3 [8%] pts), and death (2 [6%] pts). In group 1, 4 pts experienced DLT: pancreatitis (n = 2), lipase and transaminase increase (n = 1), and autoimmune hepatitis (n = 1). In group 2, 2 pts experienced DLT: G3 ALT increase. Both dose levels met Bayesian criteria for dose expansion. Overall most frequent (≥40%) AEs (n = 36), were diarrhea (64%), ALT increase (56%), AST increase (44%) and vomiting (42%). Most frequent (> 10%) grade ≥3 AEs were increases in ALT (22%), GGT (17%), amylase (11%), and lipase (11%), and maculopapular rash (11%). Incidence of rash (grouped term) was 61%; similar in both groups. Grade 3 rash was reported in 29% pts in group 1 and 14% pts in group 2. Preliminary ceritinib steady state PK ($AUC_{0\text{-}24}$ and C_{max}) suggested that 300 mg/day exposure was ~ 70-75% of 450 mg/day. Confirmed (c)/unconfirmed (u) ORR: ALKi-pretreated pts (group 1 [n = 8], group 2 [n = 12]) was 63% (4 cPR,1 uPR; 95% CI: 25%, 92%), and 33% (4 uPR) 95% CI: 10%, 65%) respectively; ALKi-naïve pts, (group 1 [n = 6], group 2 [n = 10]) was 83% (5 cPR; 95% CI: 36%, 100%), and 70% (1 cCR, 3 cPR 3uPR; 95% CI: 35%, 93%) respectively. **Conclusions:** Ceritinib + NIVO is an active combination in ALK+ NSCLC. However, the protocol will be amended to address observed toxicities. Data will be updated for presentation. Clinical trial information: NCT02393625.

2503 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

An investigator-initiated phase I study of ONX-0801, a first-in-class alpha folate receptor targeted, small molecule thymidylate synthase inhibitor in solid tumors. *First Author: Udai Banerji, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: ONX-0801 is a first-in-class alpha folate receptor (AFR) targeted thymidylate synthase inhibitor, engineered to differentially accumulate 6000-fold in AFR overexpressing cancer cells. **Methods:** A 3+3 dose escalation design was used and two IV schedules were explored. Schedule A, weekly dosing (QW) and schedule B, once every 2 weeks dosing (Q2W). A cycle consisted of 4 weeks and treatment was stopped after 6 cycles in both schedules. An expansion cohort to evaluate clinical activity in patients with AFR overexpressing high grade serous ovarian cancer (HGSOC) was planned. **Results:** 21 patients each were treated in schedule A and B exploring doses ranging from 1-6 mg/m^2 and 2-12 mg/m^2, respectively. The dose limiting toxicity on schedule A was G3 cellulitis; no dose limiting toxicity was seen on schedule B. The most common toxicities were fatigue 15/42 (36%), nausea 9/42 (21%) and dysgeusia 5/42 (12%). Within schedule A at 4 mg/m^2, 2 patients developed suspected drug-related changes on pulmonary function tests (drop in Dlco > 15%) at cycles 5 and 6, respectively. No cases of suspected drug-related drop in Dlco were noted in patients treated in schedule B. No grade 3-4 diarrhea, mucositis or neutropenia were seen in either cohort. The Cmax, AUC and half-life at 12 mg/m^2 were 4952 ng/mL, 85170 h*ng/mL and 26 h, respectively. Pre-clinical PK-PD modelling aimed to achieve concentrations between 0.05-1 μM and this was achieved for periods of 48 h at doses of 4 mg/m^{2}and above. Based on safety and PK, the recommended phase II dose (RP2D) of ONX-0801 was 12 mg/m^2 Q2W and an expansion in patients with HGSOC is ongoing. 5 patients with HGSOC had partial responses (PRs) in the dose escalation cohort. In the current expansion cohort in patients with HGSOC, 5/11 patients had PRs. Archival samples have been analyzed from 8/11 patients in the expansion cohort. 4/4 AFR+ve and 4/4 AFR-ve patients did and did not have a PR following treatment with ONX-0801, respectively. **Conclusions:** The RP2D of ONX-0801 is 12 mg/m^2 Q2W. At the RP2D, multiple patients with AFR overexpressing HGSOC have had PRs and further randomized biomarker prespecified phase II trials are warranted. Clinical trial information: NCT02360345.

2504 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Phase I first-in-man trial of a novel bromodomain and extra-terminal domain (BET) inhibitor (BI 894999) in patients (Pts) with advanced solid tumors. *First Author: Philippe Georges Aftimos, Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*

Background: The BET family (BRD2, BRD3, BRD4) regulates transcription, epigenetic memory and cell growth, emerging as a novel therapeutic strategy. BI 894999 is a highly potent and selective orally available BET inhibitor. **Methods:** BI 894999 was given once a day, continuously (1 cycle = 3 weeks; Arm A). An intermittent schedule was explored: once a day, D1-14 Q21 days (1 cycle = 3 weeks; Arm B). Bayesian Logistic Regression Model was used to guide dose escalation. HEXIM1, HIST2H2BF and CCR2 gene expressions were used as pharmacodynamic (PD) markers. **Results:** 28 pts were treated: 21 in Arm A, 7 in Arm B. Median number of cycles was 2 (range: 1-12). Pts were treated at 6 dose levels in Arm A (0.2-5 mg) and 2 dose levels in Arm B (1.5 and 2 mg). The maximum tolerated dose (MTD) was exceeded at 2 mg in Arm A. In Arm B, dose escalation was halted due to the observation of ECG changes in 3 pts and raised serum troponin in 8 pts, pending cardiology review. MTD in Arm A was defined as 1.5 mg. The most frequent (≥10%) treatment-related adverse events were: fatigue (50%), thrombocytopenia (29%), decreased appetite (21%), diarrhea (18%), increased troponin T (18%), dysgeusia (14%), nausea (14%), stomatitis (14%), increased CK (11%), neutropenia (11%) and vomiting (11%). DLTs included: thrombocytopenia grade (G) 4 (n=3), increased troponin G3 (n=1), hypophosphatemia G3 (n=1), multiple G2 events in 1 pt preventing adequate dose intensity in cycle 1. Of 27 evaluable pts, 3 had partial response (PR; one was confirmed) and 1 had stable disease (SD) lasting >4 cycles. C_{max} and AUC increased with dose in a greater than linear fashion particularly at higher dose levels. Mean terminal $T_{1/2}$ was ~1 day with high interpatient variability. PD analyses showed target engagement in all 3 genes at doses ≥1 mg in both schedules. **Conclusions:** BI 894999 showed target engagement at doses ≥ 1 mg and demonstrated clinical activity (3 PRs and 1 SD lasting >4 cycles). Thrombocytopenia prevented continuous dosing and 1.5 mg was defined the MTD for Arm A, whilst dose escalation was halted in Arm B due to cardiac findings. Mitigating hematological toxicity of BI 894999 via synergistic drug combinations should be explored. Clinical trial information: NCT02516553.

2505 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Phase I trial of a novel stapled peptide ALRN-6924 disrupting MDMX- and MDM2-mediated inhibition of *WT p53* in patients with solid tumors and lymphomas. *First Author: Funda Meric-Bernstam, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ALRN-6924 is a cell-penetrating stapled alpha-helical peptide designed to equipotently disrupt the interaction between the p53 tumor suppressor protein and its endogenous inhibitors, murine double minute X (MDMX) and 2 (MDM2). For TP53 wild-type (WT) tumors, pharmacological disruption of this interaction offers a means to restore p53-dependent cell cycle arrest and apoptosis, resulting in antitumor efficacy via a novel mechanism. **Methods:** The study evaluated safety, PK, PD and anti-tumor effects of ALRN-6924 in patients (pts) with advanced solid tumors or lymphomas in a standard 3+3 design. Pts received ALRN-6924 IV once weekly for 3 consecutive wks on a 28-day cycle (arm A), or 2/wk for 2 consecutive wks on a 21-day cycle (arm B). **Results:** As of Dec 2016, 69 pts were enrolled with median age 61 yrs (25-78). Pts received a median of 2 (1-19) cycles in arm A [0.16-4.4 mg/kg] and 3 (1-19) cycles in arm B [0.32-2.7 mg/kg]. ALRN-6924 showed a $t_{1/2}$ of 5.5 hours, dose-dependent PK, and an increase in serum macrophage inhibitory cytokine-1. Treatment-related AEs seen in 96% of pts were primarily grade 1 and 2; most frequent were GI side effects, fatigue, anemia, and headache. DLTs were G3 fatigue at 3.1 mg/kg, and G3 hypotension, G3 alkaline phosphatase elevation, G3 anemia and G4 neutropenia at 4.4 mg/kg all in 5 pts in arm A. No G3/4 thrombocytopenia was observed. All DLTs resolved with dose hold. Infusion-related reactions were seen in 7 pts, with 3 treatment discontinuations. The RP2D was determined to be at MTD: 3.1 mg/kg QW for 3 wks every 28 days. In 55 pts evaluable for efficacy, disease control rate (DCR) was 45%, including 2 CR (Peripheral T-cell Lymphoma [PTCL], Merkel Cell Carcinoma), 2 PRs (Colorectal Cancer, Liposarcoma) and 21 pts with SD. In WT TP53 pts who initiated ALRN-6924 at ≥0.8 mg/kg, DCR was 57%. 9 pts remain on treatment post data cutoff including 3 pts exceeding 1 year of treatment. **Conclusions:** ALRN-6924 was well tolerated and demonstrated intriguing anti-tumor activity in this first-in-human phase I trial. An expansion phase IIa cohort in PTCL opened in August 2016 using 3.1 mg/kg (arm A) and is currently enrolling. Clinical trial information: NCT02264613.

2506 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Results from the biomarker-driven basket trial of RO5126766 (CH5127566), a potent RAF/MEK inhibitor, in RAS- or RAF-mutated malignancies including multiple myeloma. *First Author: Maxime Chenard-Poirier, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: RO5126766 is a potent RAF and MEK inhibitor with activity in xenografts models of RAS and RAF-mutated cancers. We present data from the RAS/RAF-mutated advanced solid tumor cohort and the initial results for the multiple myeloma (MM) cohort. **Methods:** Patients with *KRAS*, *NRAS* or *BRAF*-mutant tumours were treated with RO5127566 using a novel schedule: 4mg twice weekly in 4-week cycles. For MM patients, it was given 3 weeks out of 4 and co-administration of weekly dexamethasone was authorised. Response assessment was completed using RECIST 1.1 criteria for solid tumours and the International Myeloma Working Group (IMWG) criteria were used for MM. **Results:** A total of 20 patients with solid tumours (10 NSCLC, 5 gynaecological cancers and 5 miscellaneous cancers) and 1 MM patients were evaluable. Among the 10 *KRAS*-mutant NSCLC patients, tumour regression was seen in 6/10 (60 %), of which 3/10 (30 %) were partial responses. Two of these patients had maintained response for over 1 year and one patient is still on study after 30 cycles. Of the gynaecological cancers, 3/5 patients (60%) achieved a partial response (*KRAS*-mutant endometrial and ovarian cancer and *BRAF*-mutant ovarian). Of these patients, 1 of the *KRAS* mutants had received 2 previous lines of MEK inhibitors and the *BRAF* mutant had previously received a BRAF inhibitor. In the miscellaneous group, 4 patients with colorectal cancer (2 BRAF and 2 NRAS) and 1 patient with *NRAS*-mutant melanoma were treated and none responded. Two patients with MM have been treated so far (1 *KRAS*, 1 *KRAS+NRAS*). The one evaluable patient has had an IMWG partial response (PR) after 1 cycle (FLC-λ from 324 mg/L to 161mg/L, ratio 0.03 to 0.08) without concomittant dexamethasone. This patient was previously treated with an immunomodulatory drug, a proteasome inhibitor and two ASCTs. **Conclusions:** RO5126766 has shown exciting preliminary activity across a wide range of *RAS*- and *RAF*-mutated malignancies, with significant response rates in lung and gynaecological cancers. To our knowledge, the PR seen in our MM patient represents one of the first responses to a single-agent RAF/MEK inhibitor in multiple myeloma in a trial context. Clinical trial information: NCT02407509.

2507 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

A first-in-human dose phase 1 study of LY3009120 in advanced cancer patients. *First Author: David S. Hong, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: LY3009120, a pan-Raf and dimer inhibitor, demonstrates inhibition of phospho-Mek/Erk and tumor growth inhibition in several non-clinical cancer models with BRAF, NRAS, or KRAS mutations. This is the first-in-human phase 1 study of LY3009120 in patients (pts) with advanced cancer. **Methods:** The safety and tolerability of LY3009120 was evaluated in pts with cancer aged 18 years or older who had an ECOG performance status ≤1, at least 1 unidimensionally measurable lesion (RECIST 1.1), and adequate organ function (NCT02014116; I6X-MC-JBDA; Eli Lilly & Co.). The study sought to determine a recommended phase 2 dose using the toxicity band method and the safety, pharmacokinetic, and preliminary efficacy of LY3009120. Pharmacodynamic (PD) biomarkers, including pERK, p27 and Ki67, were evaluated in tumor tissue. The dose escalation phase evaluated dosages from 50 mg to 500 mg by mouth twice daily in pts with advanced cancers. **Results:** 34 pts (3 at 50 mg, 4 at 100 mg, 3 at 200 mg, 15 at 300 mg, 7 at 400 mg, and 2 at 500 mg) in dose escalation and 1 pt in dose expansion (1 at 300 mg) received at least one dose of LY3009120 by January 2, 2016 (median age = 47.4 yrs, range: 26-82). Most pts had a gene mutation (BRAF, n = 7; N/KRAS, n = 18); the most common cancer types included colon (n = 9), non–small cell lung cancer (n = 8), and pancreatic (n = 5). There were 6 dose-limiting toxicities in the dose escalation phase: 2 pts at 300 mg (G3 dermatitis acneiform [n = 1] and G2 blurred vision [n = 1]); 2 pts at 400 mg (G2 increased ALT with G3 hyperbilirubinemia [n = 1] and G3 increased ALT [n = 1]); 2 pts at 500 mg: (G3 arthralgia/myalgia [n = 1] and G3 stomatitis/pain [n = 1]). Based on these data, the maximum tolerated dose for LY3009120 was determined to be 300 mg twice daily. Treatment-emergent adverse events related to LY3009120 occurring in ≥10% of pts included fatigue (34%), nausea (31%), decreased appetite (20%), and dermatitis acneiform (20%) (Grade 1,2). A dose proportional increase in exposure was observed, but not at the 400 mg dose. The best response was stable disease in 5 pts. PD effect by rtPCR was not observed in tested paired tumor samples. **Conclusions:** LY3009120 is well tolerated at doses of 300 mg twice daily. Updated data from dose expansion will be presented in the meeting. Clinical trial information: NCT02014116.

2508 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

First-in-class oral ERK1/2 inhibitor Ulixertinib (BVD-523) in patients with advanced solid tumors: Final results of a phase I dose escalation and expansion study. *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Aberrant MAPK pathway activation is known to be an oncogenic driver in many solid tumors, making ERK inhibition an attractive therapeutic strategy. Ulixertinib is an oral ERK1/2 inhibitor that demonstrated potent activity in vitro and tumor regression in *BRAF* and *RAS* mutant xenograft models. **Methods:** This multi-center phase I trial enrolled patients (pts) with advanced solid tumors. Dose escalation utilized an accelerated 3+3 design; expansion cohorts included *BRAF or NRAS* mutant melanoma and other *BRAF* or *MEK* mutant cancers. Study objectives were to characterize dose limiting toxicities (DLTs), maximum tolerated dose (MTD), toxicity profile, pharmacokinetics, pharmacodynamics and preliminary anti-tumor activity by RECIST 1.1. **Results:** A total of 135 pts were enrolled. Dose escalation enrolled 27 pts (10-900 mg BID) and established the MTD and recommended phase 2 dose (RP2D) of 600 mg BID. DLTs included rash, diarrhea, elevated AST, and elevated creatinine. Drug exposure was dose proportional up to the RP2D, which provided near-complete inhibition of ERK activity in whole blood. In the 108 pt expansion cohort, there were no drug related deaths; however, 32% of pts required a dose reduction. The most common adverse events were rash (49%), diarrhea (47%), fatigue (41%), and nausea (37%). In addition to 3 pts with partial responses during escalation (11%), an additional 9 of 83 (11%) evaluable pts at expansion had a partial response: 1 melanoma pt refractory to prior BRAFi/MEKi treatment, 3 *NRAS* mutant melanoma pts, 2 pts with *BRAF* V600E mutant lung cancers including response in brain metastases, 1 with *BRAF* V600E mutant glioblastoma multiforme, 1 with *BRAF* G469A head & neck cancer, and 1 with *BRAF*L485W gallbladder cancer. The duration of response ranged from 2 to 24+ months. **Conclusions:** Ulixertinib at 600 mg twice a day has an acceptable safety profile and has produced durable responses in pts with *NRAS* mutant melanoma, *BRAF* V600 and non-V600 mutant solid tumors including melanoma, glioblastoma multiforme, lung cancers with brain metastases, gallbladder and head & neck cancers. These data support further clinical development of ulixertinib. Clinical trial information: NCT01781429.

2509 Poster Discussion Session; Displayed in Poster Session (Board #1), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Phase I study of ABBV-399, a c-Met antibody-drug conjugate (ADC), as monotherapy and in combination with erlotinib in patients (pts) with non-small cell lung cancer (NSCLC). *First Author: Eric Angevin, Institut Gustave Roussy, Villejuif, France*

Background: The c-Met receptor is overexpressed in ~50% of pts with NSCLC. ABBV-399 is a first-in-class ADC composed of ABT-700, an anti–c-Met antibody, conjugated to monomethyl auristatin E (a microtubule inhibitor). Preclinical data demonstrate that ABBV-399 can deliver a potent cytotoxin directly to c-Met+ tumor cells. **Methods:** ABBV-399 was administered at doses ranging from 2.4 to 3.0 mg/kg (dose expansion and combination cohorts at 2.7 mg/kg) once every 21 days to 29 pts with advanced c-Met+ (immunohistochemistry [IHC] H-score ≥150) NSCLC both as monotherapy (ABBV-399/monoT; 16 pts) and in combination with oral erlotinib 150 mg daily (ABBV-399/ERL; 13 pts) (NCT02099058). c-Met overexpression was assessed by IHC utilizing the SP44 antibody (Ventana; Tucson, AZ, USA). **Results:** As of January 9, 2017, 16 pts with c-Met+ NSCLC received ≥1 dose of ABBV-399/monoT. Monotherapy treatment-related adverse events (TRAEs) occurring in ≥10% of pts (all dose levels and all grades) were fatigue (43.8%), nausea (37.5%), neuropathy (25.0%), vomiting (18.8%), and anemia, constipation, and diarrhea (12.5% each). Three of 16 (19%) ABBV-399–treated c-Met+ NSCLC pts had a confirmed partial response (PR) with duration of response (DOR) 3, 4.5, and 10+ months. At week 12, 6 of 16 pts (37.5%) had disease control. TRAEs in ABBV-399/ERL occurring in ≥10% of pts (all grades) were neuropathy (30.8%), and acneiform rash, diarrhea, fatigue, nausea, and dry skin (15.4% each). Four of 13 (31%) evaluable ABBV-399/ERL–treated c-Met+ pts had a PR (3 confirmed, 1 unconfirmed) with DOR 1+, 2.7, 5.3+, and 11+ months. Three of the 4 pts with PR had EGFR-mutated tumor and recently progressed on TKI. At week 12, 8 of 13 pts (61.5%) had disease control. There were no treatment-related deaths as monotherapy or in combination with erlotinib. Responses were seen in both squamous and non-squamous histology. **Conclusions:** ABBV-399 is well tolerated at 2.7 mg/kg once every 21 days and has demonstrated antitumor activity in pts with c-Met+ NSCLC both as monotherapy and in combination with erlotinib. Updated efficacy/safety data and *MET* gene status will be presented. Clinical trial information: NCT02099058.

2510 Poster Discussion Session; Displayed in Poster Session (Board #2), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Preliminary results from a phase 1 study of the antibody-drug conjugate ABBV-221 in patients with solid tumors likely to express EGFR. *First Author: Emiliano Calvo, START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain*

Background: ABBV-221 is a 2nd-generation antibody-drug conjugate (ADC) targeting EGFR based on the 1st-generation ADC ABT-414. ABT-414 shows efficacy in glioblastoma (GBM) patients (pts) with EGFR amplification in ongoing studies. ABBV-221 is an affinity matured monoclonal antibody against EGFR linked to the toxin MMAE. ABBV-221 has higher affinity for overexpressed EGFR than ABT-414, potentially allowing it to target a broader range of tumor types. **Methods:** This is a Phase 1, multicenter study to determine maximum tolerated dose (MTD) and recommended Phase 2 dose (RPTD) of ABBV-221. Pts are required to have an EGFR-dependent cancer to be eligible. Starting dose of ABBV-221: 0.3 mg/kg IV infused over 3 hrs for each 21-day cycle, with alternate dosing schedules utilized (2 wks on, 1 wk off or weekly) to mitigate infusion reactions. **Results:** As of 11 January 2017, 42 pts were treated (13 colon, 5 head & neck (H&N) cancer, 5 non-small cell lung cancer, 5 GBM, 2 breast, 12 other). Ten dose escalation cohorts have been completed with the last cleared dose 4.5 mg/kg per cycle. Tumor tissue samples were evaluated for EGFR protein expression by IHC, EGFR and EGFR ligand mRNA expression by RNAseq, and the results compared to outcome. The most common adverse event (AE) was infusion reaction in 18/42 pts (43%); 3 pts experienced severe infusion reactions. Several mitigation strategies were used to permit continued dose escalation. The other most common AE was fatigue in 17/42 pts (41%). Only 1 pt had keratitis (Grade 4). Sixteen pts (38%) had stable disease (SD), including 4 pts who remained on study longer than 6 months. One H&N pt who has received 2 cycles of ABBV-221 had an unconfirmed partial response and continues to be treated. This pt had high levels of both EGFR and EGFR ligand. Preliminary pharmacokinetics (PK) analysis suggests ABBV-221 exposures are approximately dose-proportional. **Conclusions:** Safety, PK, pharmacodynamics, and preliminary efficacy data of ABBV-221 warrant further study in this population. Infusion reactions have been manageable and primarily a first dose phenomenon. The duration of SD in pts with refractory solid tumors is encouraging. Clinical trial information: NCT02365662.

2511 Poster Discussion Session; Displayed in Poster Session (Board #3), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

A phase I study of PF-06647263, a novel EFNA4-ADC, in patients with metastatic triple negative breast cancer. *First Author: Ignacio Garrido-Laguna, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: PF-06647263 is an anti-Ephrin-A4 (EFNA4) antibody drug conjugate (ADC) composed of a humanized mAb, a hydrazone cleavable linker, and calicheamicin, a potent DNA damaging agent. Higher levels of EFNA4 expression have been shown in tumor versus normal tissue, including in two thirds of triple negative breast cancers (TNBC). In vivo preclinical studies demonstrate PF-06647263 induced tumor regression in TNBC models. **Methods:** In Part 1 of a dose escalation, cohorts of 2-12 patient (pts) with solid tumors that were unselected for EFNA4 expression received escalating doses of PF-06647263 once every 3 weeks (Q3W, Cohort A) or weekly (QW, Cohort B). Escalations were based on mTPI design. An expansion cohort enrolled TNBC patients (n=12) unselected for EFNA4 expression. Efficacy, safety, EFNA4 RNA expression, pharmacokinetic (PK) and anti-drug antibody development were assessed. **Results:** Part 1 (dose escalation):A total of 48 pts (25 in A and 23 in B) wereenrolled. The most common treatment related adverse events (AE) were fatigue (65%), and nausea (60%), thrombocytopenia (40%), and decreased appetite (38%). DLTs were observed in 6 and 2 pts in the Q3W and QW regimens, respectively. One confirmed VOD and one suspected VOD were observed in two patients in the Q3W schedule. The maximum tolerated dose (and RP2D) was determined to be 0.015 mg/kg QW. Confirmed partial responses (PR) were observed in 5 pts (3 Ovarian Ca and 2 TNBC). Part 2 (TNBC dose expansion at RP2D)data are available on 10 of 12 pts treated (2 ongoing). The most common adverse events (AE) were nausea (40%), asthenia (30%), vomiting (30%) and mucosal inflammation (30%). No objective RECIST response was observed; there was no dependency with duration of treatment relative to EFNA4 expression. **Conclusions:** In Part 1 of this study, PF-06647263 was generally well-tolerated in the QW schedule and some antitumor activity was observed in heavily pretreated pts with EFNA4 unselected advanced malignancies. However, in the expansion cohort (Part 2) at RP2D in TNBC no objective responses were observed regardless of EFNA4 expression. Final safety, efficacy, expression and PK data will be reported at the meeting. Clinical trial information: NCT02078752.

2512 Poster Discussion Session; Displayed in Poster Session (Board #4), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Personalized, molecularly matched combination therapies for treatment-na. *First Author: Jason K. Sicklick, Department of Surgery, University of California San Diego, San Diego, CA*

Background: Precision medicine has been studied in patients (pts) with advanced, heavily-treated cancers by administering molecularly matched monotherapies. With increasing availability of large gene assays and cognate agents, we hypothesized that offering customized combination therapies to treatment-naïve tumors would be feasible and improve response rates. **Methods:** Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy (I-PREDICT, NCT02534675) targeted metastatic and/or unresectable, untreated lethal cancers (> 50% 2-yr mortality). Comprehensive genomic profiling (CGP, Foundation Medicine; 315 genes), and, if possible, PD-(L)1 IHC, tumor mutational burden (TMB) and circulating tumor DNA were performed. A molecular tumor board discussed results immediately upon receipt, and emphasized customized combinations. Final decisions were the treating physician's choice. **Results:** CGP was evaluable in 40/47 treatment-naïve pts (85.1%); 22 (46.8%) were treated [17 matched (36.2%); 5 unmatched (10.6%); 11 different diagnoses). The other 25 pts (53.2%) are awaiting therapy (8, 17%) or could not be treated (17, 36.2%), mainly due to patient deterioration or payor limitations. Each tumor had a unique genomic portfolio. The median (range) of genomic alterations/patient was 5 (1-12). TMB was available in 17 pts (12 low; 4 intermediate; 1 high). The median (range) Matching Score [(matches (#)/characterized genomic alterations (#)] was 33% (14-100%; 100% designated immunotherapy match or all alterations matched to targeted agents) [Reference PMID 2719717]. Nine/17 matched pts (53%) achieved SD > 6 months (N = 2) or CR (1)/PR (6). The median progression-free survival (PFS) for matched vs. unmatched pts was 4.7 vs. 1.0 months (P= 0.0019). There were no drug-related deaths. **Conclusions:** With the use of broad-based DNA sequencing assays, inclusion of pts earlier in their disease course, timely mandated molecular tumor board discussions, and increasing availability of cognate drugs for customized combinations, we report: 1) high molecular matching rates (~36%); 2) high rates of SD > 6 months/CR/PR (~53%); and 3) improved PFS. Study expansion is ongoing. Clinical trial information: NCT0253467.

2513 Poster Discussion Session; Displayed in Poster Session (Board #5), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT): An MD Anderson precision medicine study. *First Author: Apostolia Maria Tsimberidou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We present outcomes for 637 patients who were referred for phase I trials and were treated under IMPACT. **Methods:** Patients with advanced, refractory cancer who had tumor genomic analyses were treated with matched targeted therapy (MTT) when available. **Results:** Overall, 1,179 (82.1%) of 1,436 patients had ≥1 alteration (median age, 59.7 yrs; men, 41.2%); 637 had ≥1 actionable aberration and were treated with MTT (n=390) or non-MTT (n=247). Patients treated with MTT had higher rates of CR and PR (11% vs. 5%; p=.0099) (Table), longer failure-free survival (FFS) (3.4 vs. 2.9 months; p=.0015), and longer overall survival (OS) (8.4 vs. 7.3 months; p = .041) than unmatched patients. Two-month landmark analyses showed that, for MTT patients, FFS for responders vs. non-responders was 7.6 vs. 4.3 months (p<.0001) and OS was 23.4 vs. 8.5 months (p<.0001); for non-MTT patients (responders vs. non-responders), FFS was 6.6 vs. 4.1 months (p=.0005) and OS was 15.2 vs. 7.5 months (p = .43). Patients with both PI3K and MAPK pathway alterations matched to PI3K/Akt/mTor axis inhibitors alone showed outcomes comparable to unmatched patients. **Conclusions:** Matched versus unmatched patients had significantly better outcomes. For matched responders, median survival reached almost two years. However, matching patients who harbor both a PI3K and a MAPK pathway alteration to only a PI3K pathway inhibitor did not improve outcome. Clinical trial information: NCT00851032.

Response by matching (N=637).

	Treatment Group	Evaluable for response	CR+PR (%)	Odds Ratio (95% CI)	P-value	SD≥6 months + CR+PR+v(%)	Odds Ratio (95% CI)	P-value
				Group 1				
1A	MTT	381	43 (11)	2.4 (1.2, 4.6)	0.0099	111 (29)	1.3 (.9,1.9)	0.13
1B	Non-MTT	238	12 (5)			56 (24)		
				Group 2				
2A	Patients with both PI3K and MAPK alterations matched by PI3k pathway only	36	2 (6)	1.0		7 (19)		
2B	Non-MTT	238	12 (5)	1.0 (0.2, 4.6)	1.0	56 (24)	1.3 (0.5,3.1)	0.59 (comparison, 2B to 2A)
2C	MTT minus 2A	345	41 (12)	2.3 (.5, 9.9)	0.25	104 (30)	1.8 (.8,4.2)	0.12 (comparison, 2C to 2A)

2514 Poster Discussion Session; Displayed in Poster Session (Board #6), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Development and validation of a real-world clinicogenomic database. *First Author: Gaurav Singal, Foudation Medicine, Inc., Cambridge, MA*

Background: Genomic findings have diagnostic, prognostic, and predictive utility in clinical oncology. Population studies have been limited by reliance on trials, registries, or institutional chart review, which are costly and represent narrow populations. Integrating electronic health record (EHR) and genomic data collected as part of routine clinical practice may overcome these hurdles. **Methods:** Patients in the Flatiron Health Database with non-small cell lung cancer (NSCLC) who underwent comprehensive genomic profiling (CGP) by Foundation Medicine were included. EHR processing included structured data harmonization and abstraction of variables from unstructured documents. EHR and CGP data were de-identified and linked in a HIPAA-compliant process. Data included clinical characteristics, alterations across > 300 genes, tumor mutation burden (TMB), therapies and associated real-world responses, progression, and overall survival (OS). **Results:** The cohort (n = 1619) had expected clinical (mean age 66; 75% with smoking hx; 80% non-squamous) and genomic (18% EGFR; 4% ALK; 1% ROS1) properties of NSCLC. Presence of a driver mutation (EGFR, ALK, ROS1, MET, BRAF, RET, or ERBB2; n = 576) was associated with younger age, female gender, non-smoking, improved OS (35 vs 19 mo, LR p < 0.0001), and prolonged survival when treated with NCCN-recommended therapy (42 vs 28 mo, LR p = 0.001). CGP identified false negative results in up to 30% of single-biomarker tests for EGFR, ALK, and ROS1. CGP accuracy was supported by clinical outcomes. For example, 5 patients with prior negative ALK-fusion testing began ALK-directed therapy after positive CGP results. All 5 exhibited at least a partial response as recorded in the EHR by treating clinicians. Immunotherapy was used in 22% of patients (n = 353). TMB predicted response to nivolumab, including in PD-L1 negative populations. We recapitulated known associations with smoking, histology, and driver mutations. **Conclusions:** We present and validate a new paradigm for rapidly generating large, research-grade, longitudinal clinico-genomic databases by linking genomic data with EHR clinical annotation. This method offers a powerful tool for understanding cancer genomics and advancing precision medicine.

2515 Poster Discussion Session; Displayed in Poster Session (Board #7), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Pharmacokinetic-driven phase I study of DCC-2618 a pan-KIT and PDGFR inhibitor in patients (pts) with gastrointestinal stromal tumor (GIST) and other solid tumors. *First Author: Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: DCC-2618 is a potent switch control inhibitor of KIT and PDGFR kinases active in a broad range of mutations. GIST is an important disease to achieve a proof-of-concept due to the heterogeneity of KIT resistance mutations, which emerge on treatment with approved KIT inhibitors. **Methods:** This was a PK-guided dose escalation study of oral DCC-2618 (QD or BID q28 days) in advanced solid tumors. FDG-PET scans were used to assess changes in FDG uptake in GIST pts after 3 wks of therapy. Next generation sequencing (NGS) of plasma cell-free (cf) DNA was performed throughout the study to assess and quantify KIT and other molecular alterations in drug targets and potential mechanisms of resistance. **Results:** 38 pts were enrolled (30 GIST; 4 glioma; 1 mastocytosis, 3 other carcinoma) to 8 dose levels: BID doses: 20 (4 pts), 30 (4), 50 (5), 100 (6), 150 (6) and 200 mg (3); QD doses: 100 (5) and 150 mg (4). Safety of evaluable pts is as follows: G3 or G4 adverse effects (regardless of attribution and occurring in > 1 pt) included anemia (5), lipase increase (4), hypertension (2). Two of the G3/4 lipase increase at 100 mg BID and 200 mg BID were DLTs. All G3/4 lipase increase were asymptomatic. G1/2 AEs (considered at least possibly related to DCC-2618) and occurring in ≥15% (n > 5) of pts include fatigue (12), alopecia & lipase increase (7), weight decrease (6). Starting with 50 mg BID dose level, trough concentrations of total drug exceeded the IC90 of the least sentivitive KIT mutations. Plasma concentrations > 5μM were achieved starting at 100 mg BID and the selection of the expansion phase dose is being finalized. Of 18 pts with KIT mutant GIST assessed by FDG PET, 14 (78%) had partial metabolic response per EORTC criteria. RANO/RECIST partial responses (PRs) were reported in 3 patients (1 GBM with PDGFRA/KIT amplifications and 2 GIST with Ex 11 & 17 / Ex 11 & 18 mutations, respectively). NGS of plasma cfDNA revealed 44 KIT mutations in baseline samples from 19 of 21 pts with GIST. **Conclusions:** DCC-2618 is well tolerated with encouraging preliminary activity in GIST pts with a broad spectrum of mutations and prior therapies. PR was also seen in a pt with GBM with PDGFRA/KIT amplifications. Clinical trial information: NCT02571036.

2516 Poster Discussion Session; Displayed in Poster Session (Board #8), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

A first-in-human first-in-class (FIC) trial of the monocarboxylate transporter 1 (MCT1) inhibitor AZD3965 in patients with advanced solid tumours. *First Author: Sarah E. R. Halford, Cancer Research UK Centre for Drug Development, London, United Kingdom*

Background: A key metabolic alteration in tumour cells is an increased dependency on the glycolysis, resulting in the production of lactate, which is transported out of cells by MCTs. Inhibition of MCT-1 leads to a profound inhibition of cancer cell growth in preclinical models. AZD3965 is a FIC inhibitor of MCT-1, and we report results from the phase I study of this agent. **Methods:** Patients with advanced solid tumours were treated with oral (po) AZD3965 at total daily doses of 5-30mg given once (od) and twice daily (bd). Exclusion criteria included a history of retinal or cardiac disease due to preclinical toxicology findings in the eye and heart (which express MCT-1). The primary objectives were to determine the safety, dose limiting toxicities (DLT) and maximum tolerated dose (MTD) of AZD3965. Intensive pharmacokinetic (PK) profiling was performed with subsequent modelling for receptor occupancy. Pharmacodynamic profiling included imaging to detect pH changes and tumour glucose uptake; plasma/urine metabolomics and MCT-1 and MCT-4 tumour expression by immunohistochemistry. **Results:** 35 patients (20M:15F median age 65) were treated at dose levels 5, 10, 20, and 30mg od and 15 and 10mg bd. AZD3965 was generally well tolerated with nausea and fatigue (CTCAE Gr1-2) the most commonly reported side effects. A single DLT of cardiac troponin rise was observed at 20mg od. Asymptomatic, reversible retinal ERG changes were observed in all but the lowest dose levels, with DLTs observed at doses above 20mg od. PK data indicate exposures in the preclinical efficacy range. Metabolomic changes in urinary lactate and urinary ketones correlate with on-target activity. The increase in urinary ketones is likely to be attributable to the role of MCT1 in physiological ketone transport. **Conclusions:** The MCT1 inhibitor AZD3965 can be administered to patients at doses which engage the drug target, with a MTD of 20mg od po. DLTs seen were primarily dose dependent, asymptomatic and reversible changes in retinal function, which were an expected on-target effect. Investigation of the activity of AZD3965 is ongoing in tumours known to express MCT1. Clinical trial information: NCT01791595.

2517 Poster Discussion Session; Displayed in Poster Session (Board #9), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Phase 1 study of ARQ 761, a β-lapachone analog that promotes NQO1-mediated programmed cancer cell necrosis. *First Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: NAD(P)H:quinone oxidoreductase 1 (NQO1) is a two-electron oxidoreductase expressed in multiple tumor types at levels 5- to 200-fold above normal tissue. ARQ761 is a β-lapachone hydroquinone analog that exploits the unique elevation of NQO1 found in solid tumors to cause tumor-specific cell death by eliciting a futile redox cycle generating high levels of reactive oxygen species and ultimately PARP1 hyperactivation-dependent cell death. **Methods:** 3+3 dose escalation study of 3 schedules (weekly, every other week, 2/3 weeks) of ARQ 761 as a 1-hr or 2-hr infusion. Eligible patients had refractory advanced solid tumors, ECOG 0-1, adequate organ function, and central venous access. Blood samples were analyzed for ARQ761 levels and NQO1 polymorphisms. Archival tumor tissue was analyzed for NQO1 staining intensity and prevalence. After 18 patients were analyzed, enrollment was restricted to patients with NQO1-positive tumors (defined as Histo-score ≥200). **Results:** A total of 42 patients were treated. Median number of prior lines of therapy was 4. For all schedules, the maximum tolerated dose (MTD) was 390 mg/m^2 as a 2-hr infusion. DLT was hemolytic anemia. The most common treatment-related adverse events were anemia (79%), fatigue (45%), hypoxia (33%), hemolysis (17%), nausea (17%) and vomiting (17%). Transient grade 3 hypoxia, due to methemoglobinemia, occurred in 26% of patients. Among 31 evaluable patients, the best response was stable disease (n = 11) and progressive disease (n = 19). For the 18 analyzed cases analyzed prior to NQO1 enrollment biomarker, clinical benefit appeared associated with tissue NQO1 expression: disease control rate was 65% in NQO1-positive tumors and 18% in NQO1-negative tumors (P=0.06). Analysis of all 31 evaluable patients did not show a significant difference in progression-free survival (PFS) according to NQO1 status (P=0.26), but 3-mo PFS rate was numerically greater among NQO1-positive cases (40% versus 20%). **Conclusions:** ARQ 761 has clinical activity in NQO1-positive tumors. Principal toxicities include hemolytic anemia and methemoglobinemia. Combination studies are underway.

2518 Poster Discussion Session; Displayed in Poster Session (Board #10), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

A phase I trial of TRC102 (methoxyamine HCl) with temozolomide (TMZ) in patients with solid tumors and lymphomas. *First Author: Robert S. Meehan, Early Clinical Trials Development Program, DCTD, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: TRC102 inhibits BER by binding to abasic sites and acting as a topo II poison to cause DNA strand breaks; it potentiates the activity of alkylating agents including TMZ in murine models. In xenograft studies, TRC102 efficiently enhanced the antitumor effect of TMZ regardless of cell line genetic characteristics, e.g., O^6-methylguanine DNA-methyltransferase, mismatch repair (MMR), or p53 status. This is the first report for the expansion phase (the escalation phase was reported previously (ASCO2016)). **Methods:** We conducted a phase 1 trial of TRC102with TMZ in patients (pts) with refractory solid tumors. Eligibility criteria included adults that had progressed on standard therapy, ECOG PS of 0-2, and adequate organ function. TRC102 and TMZ were given orally days 1-5, in 28-day cycles. The pharmacokinetic and pharmacodynamic profile of TRC102 with TMZ was evaluated. Antitumor responses were determined using RECIST 1.1 criteria. The DNA damage response (DDR) markers γH2Ax, pNbs1, and Rad51 were evaluated in the expansion cohort at DL6, tested by previously described methods on paired tumor biopsies prior to and after the first course of therapy. **Results:** After the recommended Phase 2 Dose was defined as DL6 (TRC102 125mg, TMZ 150mg/m^2 D1-5), 15 pts were accrued to the expansion cohort between 9/2015 to 11/2016. A total of 52 pts were enrolled (37 escalation, 15 expansion). Grade 3/4 adverse events included neutropenia (13%), anemia (the DLT;10%), thrombocytopenia (7%), hemolysis (5%) or hypophosphatemia (3%). 4 pts had a partial response (PR) (NSCLC, ovarian (2), and colon); 13 pts had stable disease (SD), 29 progressive disease (PD), and 6 were not evaluable; three pts remain on study. 11/14 paired biopsies were suitable for analysis. Rad51 signal was induced in 6/11pts. One patient showed γH2Ax and 2 showed pNbs1 induction. 4/5 colon cancer specimens had evidence of DDR marker induction. **Conclusions:** The combination of TRC 102/TMZ is active with 4 PRs and 13 SDs, and the side effect profile is manageable. DDR markers were induced in 4 of 5 paired colon biopsies indicating DNA damage following treatment. A phase 2 trial of patients with colon cancer, NSCLC, and granulosa cell ovarian cancer is accruing. Clinical trial information: NCT01851369.

2519 Poster Discussion Session; Displayed in Poster Session (Board #11), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

A phase I study of PT-112 in advanced solid tumors. *First Author: Daniel D. Karp, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PT-112 is a novel platinum-pyrophosphate agent designed to avoid the toxicity and drug resistance mechanisms of conventional chemotherapy. Pre-clinical models show effects on multiple cell signaling components: p16 mediated G1/S cell cycle arrest; modulation of MDM2/p53 expression; extrinsic apoptosis initiation; and immunogenic cell death (ICD) induction. This Phase I first-in-human, multicenter, open label study assesses PT-112's safety and pharmacokinetic (PK) profile in advanced solid tumor patients (pts), to determine the RP2D and signals of activity. **Methods:** Pts with advanced solid tumors and acceptable marrow / organ function received PT-112 IV over 1-hr on days 1, 8, and 15 every 4 wks in a 3+3 dose escalation design. Intra-subject escalation was allowed. PK samples from cycles 1-2 were analyzed by ICP-MS and LC-MS/MS. **Results:** 44 pts have been treated across dose levels (DL) from 12-300mg/m^2. Cumulative dosing ranged from 1 to 60 infusions, and cumulative exposure from 96 to 5,244 mg/m^2. PK parameters were dose proportional. Target C_{max} and AUC levels were achieved, with constant V_D. DLTs were observed at 150mg/m^2 (G3 pancytopenia); 250mg/m^2 (G2 renal injury in a cervical ca pt with hydronephrosis); and 300mg/m^2 (G3 rash). The most common treatment-related AEs were G1-2 fatigue (26% pts), nausea (23%), vomiting (14%), constipation (12%), and diarrhea (12%). Numerous signals of activity were observed at DLs ≥ 125mg/m^2. These include a confirmed PR in a NSCLC pt with 6 prior lines of therapy and no response to TKI inhibition or PD-1 blockade; PFS > 6 months (7-18 months) in 3 pts; metabolic response via PET scan in bone and liver mets (basal cell and pancreatic ca.); biomarker responses in ovarian and prostate ca.; and nodal/metastatic volumetric reduction in 3 pts. **Conclusions:** PT-112 is a well-tolerated novel agent with a pleiotropic mode of action and feasibility for long-term and combination treatment. Numerous signals of anti-cancer efficacy in heavily pre-treated pts suggest lack of cross-resistance with conventional agents. MTD has not yet been reached. PT-112's profile makes it an attractive candidate for further development, including in combination with immunotherapy. Clinical trial information: NCT02266745.

2520 Poster Discussion Session; Displayed in Poster Session (Board #12), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

GMI-1271, a novel E-selectin antagonist, in combination with chemotherapy in relapsed/refractory AML. *First Author: Daniel J. DeAngelo, Dana-Farber Cancer Institute, Boston, MA*

Background: GMI-1271 is a novel antagonist of E-selectin (E-sel) that down-regulates cell survival pathways and enhances chemotherapy response. We assessed GMI-1271 plus salvage chemotherapy with mitoxantrone, etoposide, and cytarabine (MEC) for the treatment of patients (pts) with relapsed/refractory (R/R) AML. **Methods:** A phase (Ph) 1trial in pts with R/R AML escalated GMI-1271 across pharmacologically active doses from 5-20 mg/kg combined with MEC. Safety, tolerability and anti-leukemia activity were assessed. GMI-1271 was given 24 hrs prior, then every 12 hrs during and for 48 hrs post induction/consolidation. Eligible pts had an ECOG score 0-2, received ≤2 prior inductions, WBC < 20K (< 40K after 2 dose levels), no active CNS disease, and adequate renal/hepatic function. E-sel expression was assessed. After confirming safety and tolerability, a Ph 2 study of GMI-1271 at 10 mg/kg plus MEC was initiated. **Results:** To date, 47 pts have enrolled (Ph 1 = 19; Ph 2 = 28 of planned 47). The recommended Ph 2 dose is 10 mg/kg based on drug exposure, time over IC50 for E-sel binding, lack of DLT, and clinical outcomes. Ph1/Ph2 combined median age was 55yrs (range 26-84) with 70% male pts. Prior AML history included 26% primary refractory, 36% CR1 < 6 mos; 17% prior SCT; 55% unfavorable cytogenetics (by SWOG). Common Gr 3/4 AEs were febrile neutropenia (36%), sepsis (26%), bacteremia (13%), hypoxia (13%). 30 and 60 d mortality were 0 and 7%, respectively. ORR (CR/CRi/MLFS/PR) was 21/42 evaluable (50%). Remission rate (CR/CRi) was 45%. Observed/expected remission (CR/CRi) ratio was > 2.75 (Estey, Blood 1996). With a median follow-up of 11 mos, the Ph 1 median Leukemia Free Survival was not reached and Overall Survival was 7.6 mos. The median E-sel ligand binding at baseline was 35% of blasts (range, 1-75%) and was higher in those achieving remission. **Conclusions:** The addition of GMI-1271, a novel E-sel antagonist, to MEC chemotherapy is well tolerated with a high ORR, low induction mortality, and promising initial survival outcomes in pts with R/R AML. Furthermore, the baseline expression of E-sel ligand is predictive of response. Clinical trial information: NCT02306291.

2521 Poster Session (Board #13), Mon, 8:00 AM-11:30 AM

Dose escalation results from a first-in-human, phase 1 study of the glucocorticoid-induced TNF receptor-related protein (GITR) agonist AMG 228 in patients (Pts) with advanced solid tumors. *First Author: Ben Tran, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: AMG 228 is an agonistic human IgG1 monoclonal antibody that binds to GITR (CD357), a TNFSFR costimulatory molecule expressed by effector/regulatory T cells. Dose escalation of this open label, first in human, phase 1 study evaluated the safety, pharmacokinetics (PK), pharmacodynamics, and maximum tolerated dose (MTD) and recommended phase 2 dose of AMG 228 in pts with advanced solid tumors. **Methods:** Pts with refractory advanced colorectal cancer (n = 13), squamous cell carcinoma of head and neck (n = 10), non–small cell lung cancer (n = 2), urothelial transitional cell carcinoma (n = 4), and melanoma (n = 1) received AMG 228 IV Q3W. Dose escalation was in two stages: single-pt cohorts until AMG 228-related grade > 2 adverse events (AEs), efficacy, or 90 mg dose reached (4 cohorts: 3, 9, 30, and 90 mg), followed by rolling six design (n = 2 to 6) until MTD or highest planned dose of 1200 mg reached (5 cohorts: 180, 360, 600, 900, and 1200 mg). Primary endpoints included incidence of dose-limiting toxicities (DLTs) and AEs and PK. Additional endpoints were objective response (RECIST 1.1) and evidence of biological activity. **Results:** In total, 30 pts (median age 63 y) were treated (3, 9, 30, and 90 mg, n = 1; 180 mg, n = 6; 360 mg, n = 4; 600 mg, n = 6; 900 mg, n = 4; 1200 mg, n = 6). Twenty-seven (90%) pts had treatment-emergent AEs; the most common were hypophosphatemia (23%), fatigue (23%), anemia (23%), nausea (20%), and pyrexia (20%). No DLTs occurred; the MTD was not reached. AMG 228 exposure was dose-related, with PK profiles at low doses (3 to 90 mg) consistent with target mediated drug disposition; doses > 360 mg achieved serum levels needed for 95% receptor occupancy on activated PBMCs. No evidence of T cell activation was observed despite complete target coverage in both tumor and peripheral blood. Among 29 evaluable pts, none had an objective response. **Conclusions:** In this population of pts with advanced solid tumors, AMG 228 Q3W was tolerable up to the highest tested dose (1200 mg), showing favorable PK. However, no clinical or immunological activity was observed in this limited number of pts. Clinical trial information: NCT02437916.

2522 Poster Session (Board #14), Mon, 8:00 AM-11:30 AM

First-in-human phase 1/2 study of MCLA-128, a full length IgG1 bispecific antibody targeting HER2 and HER3: Final phase 1 data and preliminary activity in HER2+ metastatic breast cancer (MBC). *First Author: Maria Alsina, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: MCLA-128 is a novel IgG1 bispecific antibody with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) activity targeting HER2 and HER3 receptors. We report final phase 1 single agent escalation data, and safety and preliminary activity at the recommended phase 2 dose (RP2D). **Methods:** In the phase 1 part, patients (pts) with advanced solid tumors received MCLA-128 every 3 weeks (q3w) IV over 1-2 hr from 40 to 900 mg. In the phase 2 part, pts with selected metastatic indications were treated at the RP2D. Antitumor activity was assessed as per RECIST 1.1. Clinical benefit rate (CBR) was defined as CR + PR + SD ≥12 weeks. **Results:** As of January 2017, 28 advanced solid tumor pts were treated in the escalation part. No dose limiting toxicities were seen. The RP2D was established as 750 mg q3w (flat dose, corticosteroid premedication) based on safety and PK data. Fifteen pts with HER2 amplified tumors were treated at the RP2D (8 MBC, 4 gastric, 2 ovarian, 1 colorectal). Median age was 52 years (range 33-71), ECOG PS 0/1: 3/12, all ≥2 metastatic sites. The safety profile at the RP2D confirmed dose escalation data; the most common AEs were infusion related reactions in 6 pts (40%; G1-2 in 5 pts, G4 in 1 pt), and G1-2 diarrhea, rash, fatigue in 2 pts each (13%). No congestive heart failure or significant LVEF decreases occurred. The 8 MBC pts had a median 5.5 prior lines of metastatic therapy (range 4-14), all had progressed on 3 prior Her2 inhibitor therapies and received a median of 4.5 MCLA-128 cycles (range 2-12); 1 had a confirmed PR, 5 had SD (including 2 sustained, 11 and 12 cycles). SD was also seen in 2 evaluable MBC pts treated at 480 mg in the phase 1 part (7 and 4 cycles). Overall, CBR in these 10 MBC pts was 70%. Evaluation of other indications is ongoing. **Conclusions:** MCLA-128 showed a well tolerated safety profile. Consistent antitumor activity was seen in heavily pretreated MBC patients progressing on HER2 therapies. Further exploration of MCLA-128 based combinations with chemotherapy or trastuzumab in less pretreated MBC patients progressing after ≥2 prior Her2 inhibitors including TDM-1 is planned. Clinical trial information: NCT02912949.

2523 Poster Session (Board #15), Mon, 8:00 AM-11:30 AM

A phase I study of LY3022855, a colony-stimulating factor-1 receptor (CSF-1R) inhibitor, in patients (pts) with advanced solid tumors. *First Author: Afshin Dowlati, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: Binding of CSF-1 to the CSF-1 receptor (CSF-1R) results in proliferation, differentiation, and migration of monocytes/macrophages. Intratumoral infiltration with macrophages correlates with increased invasiveness, growth, and immunosuppression. LY3022855 (LY) is a human IgG1 antibody (mAb) targeting CSF-1R. **Methods:** Eligible pts (ECOG 0-2) with advanced solid tumors were enrolled. Mandatory pre and post-treatment biopsies were obtained. LY was given on a 6-week cycle. Two escalation regimens (Part A: weight-based dosing; Part B: flat dosing) were investigated in a 3+3 design. Primary objective was to establish the safety and characterize the pharmacokinetics (PK) of LY. Secondary objectives were to establish recommended phase 2 dose (RP2D) and to characterize pharmacodynamics (PD). **Results:** As of Sept 6, 2016, 35 cancer pts (colorectal 14; lung 4; pancreas 3; others 14) were treated (29 in Part A; 6 in Part B) with median treatment duration 4 weeks (range 1-21). Common treatment-emergent adverse events (TEAEs) were fatigue (54%), hypoalbuminemia (40%), nausea (37%), AST increase (37%), anemia (34%), anorexia (34%), creatine kinase elevation (29%), and constipation (23%). Most common grade (G) 3/4 TEAEs were anemia (11%), fatigue (11%), ascites (9%), and lymphocyte count decrease (9%). 3/28 evaluable pts had DLTs: G3 left ventricular systolic dysfunction (1), G4 rhabdomyolysis and G4 acute renal failure (1), and G3 pancreatitis (1). Eight treatment unrelated deaths were reported. One pt (adenoid cystic carcinoma) had stable disease (~3 mo as of last visit), 19 pts had progressive disease, and 15 pts were non-evaluable for response assessment. PK profile of LY was consistent with IgG1 mAbs. An interim analysis following completion of Part A demonstrated a lack of relationship between weight and clearance, prompting evaluation of non-weight based dosing. PD analyses revealed dose-dependent increases in serum CSF-1 levels as well as suppression of circulating non-classical monocytes ($CD14^{dim}$ $CD16^{bright}$), indicating biologic activity at studied doses. **Conclusions:** RP2D for LY monotherapy has been determined. Detailed PK and PD data will be presented. Clinical trial information: NCT01346358.

2524 Poster Session (Board #16), Mon, 8:00 AM-11:30 AM

Results of a phase Ib study of ARQ 092 in combination with carboplatin (C) plus paclitaxel (P), or with P in patients (pts) with solid tumors. *First Author: Nehal Lakhani, START Midwest, Grand Rapids, MI*

Background: ARQ 092 is an oral, potent AKT inhibitor with single agent antitumor activity. P or P+C is the standard therapy or the therapy of choice for pts with various solid tumors. ARQ 092 potentiated antitumor activity of P in in vivo xenograft models, providing the rationale for this study. **Methods:** This is an open-label, phase Ib study of ARQ 092+C+P (CP Arm) or ARQ 092+P (P Arm) in pts with advanced solid tumors to determine safety and tolerability of these 2 combinations. Blood samples are collected for PK. **Results:** Enrollment into CP Arm has been completed with 13 pts (15% male; median age 62 years, 4 ovarian, 9 others) being treated in 2 dose cohorts (see table and results below). Enrollment into P Arm is ongoing. Data from P Arm (80 mg/m2 weekly) will be presented during the meeting. In CP Arm, 3 DLTs were observed in 2 pts (both received ARQ 092 at 200 mg BID, 1 day/week) including grade (G) 4 neutrophil count decreased, G 4 thrombocytopenia and G 3 diarrhea. ARQ 092-related adverse events (AEs) in ≥10% pts included diarrhea 69%, fatigue 54%, hyperglycemia 31%, maculopapular rash 31%, nausea 23%, mucosal inflammation 23%, anemia 15%, platelet count decreased 15% and hypokalemia 15%. Paclitaxel- and/or carboplatin-related AEs in ≥10% pts included fatigue 77%, alopecia 62%, thrombocytopenia 39%, platelet count decreased 39%, nausea 31%, lymphocyte count decreased 31%, neutrophil count decreased 31%, white blood cell count decreased 31%, anemia 23%, mucosal inflammation 23%, hypomagnesaemia 23%, peripheral sensory neuropathy 23%, neutropenia 15%, vomiting 15% and hypokalemia 15%. Two ovarian pts previously treated with CP achieved complete response (mutant AKT) and partial response (AKT mutation unknown) respectively and 3 pts (Gastroesophageal, pancreatic, ovarian mixed mullerian) experienced stable diseases for >12 weeks. PK data will be presented during the meeting. **Conclusions:** Encouraging anticancer activity was demonstrated in heavily pretreated ovarian cancer pts, but full dose CP was not tolerated by most patients. Clinical trial information: NCT02476955.

Arm	ARQ 092	Carboplatin	paclitaxel	N
CP	200 mg BID, 1 day/week	AUC 6 Q3W	175 mg/m2, Q3W	10
CP	100 mg QD, 5 days on/5-6 days off	AUC 6 Q3W	175 mg/m2, Q3W	3

2525 Poster Session (Board #17), Mon, 8:00 AM-11:30 AM

Development of a population pharmacokinetic (PPK) model of intravenous (IV) trastuzumab in patients with a variety of solid tumors to support dosing and treatment recommendations. *First Author: Whitney Paige Kirschbrown, Genentech, Inc., San Francisco, CA*

Background: The aim of this analysis was to develop a PPK model for IV trastuzumab (Herceptin), to assess the impact of patient covariates on PK, and perform simulations to support dosing recommendations. **Methods:** Serum trastuzumab concentration data (26,040 samples) from 1582 patients with metastatic breast cancer (MBC), early breast cancer (EBC), advanced gastric cancer (AGC) or other tumor types, and 6 healthy volunteers in 18 Phase I, II, and III trials were analyzed using nonlinear mixed-effects modeling (NONMEM). Monte Carlo simulations were performed using the NONMEM PK parameter estimates (with variability) to inform dosing recommendations. **Results:** A two-compartment model with parallel linear and nonlinear elimination best described the data. Significant covariates ($P < 0.001$) influencing linear CL were baseline weight, SGOT, albumin, primary tumor type, and presence of liver metastases. MBC had similar PK parameters as EBC, with lower distributions of $C_{min,ss}$ in MBC explained by covariates. The higher linear CL in AGC patients resulted in a 30.5% lower $C_{min,ss}$. Simulations for drug washout indicated that 95% of patients with breast cancer (BC) reach trastuzumab concentrations < 1 μg/mL (~97% washout) at ≤7 months. Simulations also indicated that a missed dose of trastuzumab in BC or AGC patients of ≤1 week did not result in a long PK under-exposure (i.e. the trastuzumab concentration is within 15% of $C_{min,ss}$ by 3 weeks) but a missed dose of > 1 week took approximately 6 weeks to get back within the steady-state exposure range. **Conclusions:** Trastuzumab PK was well described by a two-compartment model with parallel linear and nonlinear eliminationacross cancer types, disease status, and regimens. No dose adjustment is required based on any of the identified patient covariates (e.g. weight, tumor type). Simulations using the PPK model informed the prescribing information for Herceptin; trastuzumab has a 7-month serum washout period during which patients should avoid an anthracycline-based therapy, pregnancy, or breastfeeding. A re-loading dose is required if a maintenance dose is missed by > 1 week to maintain serum concentrations.

2526 Poster Session (Board #18), Mon, 8:00 AM-11:30 AM

Phase I study of nab-paclitaxel, gemcitabine, and bevacizumab in advanced cancers. *First Author: Shiraj Sen, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Gemcitabine (gem) with nab-paclitaxel (nab-p) is known to have antitumor activity and a favorable toxicity profile. The addition of bevacizumab (bev) to nab-paclitaxel has also been found to enhance nab-paclitaxel cytotoxicity. **Methods:** We therefore performed a modified 3+3 dose escalation study with 15 dose levels of fixed dose gem 1000 mg/m^{2}IV (day 1, 8, 15) and escalating doses of nab-p IV (day 1,8, 15) and bev IV (day 1,15) every 28 days. The study design allowed for the possibility of multiple MTDs. Correlative studies on VEGF polymorphism and response were planned. (NCT01113476). **Results:** 103 patients (45 male) with advanced cancers were enrolled (19 ovarian, 18 pancreatic, and 18 gastroesophageal (GE) cancers among the most common). All patients were ECOG PS 0-2, median age was 60 years (range 17-85), and 51 patients (50%) were gem refractory with a median of 3 prior lines of therapy. 3 DLTs were observed during dose escalation - one with nab-p 50 mg/m^2 and bev 10 mg/m^2 (grade 3 dysphagia, dehydration), one with nab-p 75 mg/m^2 and bev 10 mg/m^2 (grade 3 cellulitis) and one with nab-p 150 mg/m^2 and bev 5 mg/m^2 (grade 3 bacteremia, hypotension). 2 DLTs were observed among the 13 patients in the nab-p 100 mg/m^2 and bev 5 mg/m^2 expansion cohort (one grade 3 diarrhea, one grade 3 fatigue) and 1 DLT among the 12 patients in the nab-p 75 mg/m^2 and bev 10 mg/m^2 expansion cohort (grade 3 rectal bleed). Dose escalation up to nab-p 125 mg/m^2 and bev 15 mg/m^{2}was well tolerated with no MTD. One patient with gem refractory peritoneal papillary carcinoma achieved a complete response, 13 patients (13%) had partial responses (PR), and 54 patients (52%) had prolonged stable disease (pSD) ≥ 12 weeks. 4 patients achieving PR and 26 patients with pSD were previously gem refractory. 3/6 (50%) small cell cancers achieved PR and all 6 of these patients had tumor shrinkage of at least 25%. 4/19 (21%) ovarian cancers achieved PR, 3/18 (17%) GE cancers achieved PR, and 1/18 (6%) pancreatic cancers achieved PR. **Conclusions:** The combination of gem 1000 mg/m^2, nab-p 125 mg/m^2 and bev 15 mg/m^2 is safe, well-tolerated, and has activity even at lower doses in advanced malignancies, including gem refractory tumors. Correlative VEGF polymorphism studies are ongoing. Clinical trial information: NCT01113476.

2527 Poster Session (Board #19), Mon, 8:00 AM-11:30 AM

A phase I study of carboplatin and talazoparib in patients with and without DNA repair mutations. *First Author: Mallika Sachdev Dhawan, University of California, San Francisco, San Francisco, CA*

Background: Talazoparib is a novel PARP inhibitor (PARPi) in clinical development. Synergistic anti-tumor effects of PARPi and chemotherapy have been observed in preclinical models. Overlapping toxicity may limit tolerability in patients with germline DNA repair defects. **Methods:** In a dose escalation Phase 1 trial, we tested the safety, tolerability, pharmacokinetics (PK), and efficacy of talazoparib and carboplatin in patients with and without germ line mutations. **Results:** 24 patients with solid tumors were enrolled in 4 cohorts evaluating talazoparib 0.75 or 1 mg daily and carboplatin AUC 1 or 1.5 mg/mL/min 2 or 3 weeks of a 3-week cycle. Dose-limiting toxicities included grade 3 fatigue and grade 4 thrombocytopenia. Other grade 3/4 toxicities included fatigue (13%), neutropenia (63%), thrombocytopenia (29%), and anemia (38%). Post cycle 2 hematologic toxicities required dose delays/reductions in all patients. One complete and two partial responses occurred in germline BRCA1/2 (gBRCA1/2) patients. Of the 4 patients with stable disease beyond 4 months, 3 had somatic BRCA mutations and 1 had a BRIP1 germline mutation suggesting greater benefit in tumors with DNA repair mutations. PK-toxicity modeling suggests that after 3 cycles of carboplatin AUC 1.5 weekly and talazoparib 1 mg daily, the percent decrease in neutrophil counts from baseline was significantly more pronounced in gBRCA carriers; -78% (95% CI: -87 to -68%) vs. non-carriers; -63% (95% CI: -72 to -55%), p-value < 0.001. This modeling also showed that 2-4 fold dose reductions for each drug are needed to improve tolerability of this combination. Pulse dosing of talazoparib may be more tolerable in gBRCA carriers. **Conclusions:** The combination of carboplatin and talazoparib showed responses in gBRCA carriers but also had increased hematologic toxicity in gBRCA carriers. PK toxicity modeling was used to determine alternate dosing strategies based on carrier status. Clinical trial information: NCT02317874.

2528 Poster Session (Board #20), Mon, 8:00 AM-11:30 AM

Effect of target lesions selection on between-reader variability of response assessment according to RECIST 1.1. *First Author: Christiane K. Kuhl, University of Aachen, RWTH, Aachen, Germany*

Background: Response-classification-systems, e.g. RECIST1.1, and dedicated oncology software-tools (DOST) are used to standardize response assessment. Expectation is that different readers should yield the same response-classification for any given patient. We investigated real-life variability between readers who, as in clinical practice, were free to select target-lesions (TL). **Methods:** Prospective study on 316 patients with metastatic disease who underwent 932 CT-studies, yielding a total 616 follow-up occasions (baseline vs. follow-up) for analysis. All CT-studies were independently evaluated by 3 radiologists who used state-of-the-art DOST (MintLesion). Readers were free to select TL in the respective baseline study, and did so independently. Kappa-statistics were used to analyse agreement for RECIST1.1 response-class-assignment depending on whether readers had selected the same or different TL.To investigate possible impact on treatment decisions, agreement was also determined after aggregating response classes into progressive (PD) vs. non-progressive (CR/PR/SD). **Results:** Readers used the same TL in 38.6 (238/616), different in 61.4% (378/616). Where readers happened to select the same TL, agreement was "almost perfect" (κ = 0.966 [96%-CI: 0.912–1.00] for assignment of individual response-classes, and 0.977 [0.898–1.0] for the distinction progressive-vs-non-progressive). Where readers had selected different TL, agreement was only "moderate" (0.583 [0.541–0.624] for individual response-class-assignment, and 0.644 [0.587 to 0.701] for distinction progressive-vs.-non-progressive). Choice of the same TL was associated with agreement for distinction between progressive-vs.-non-progressive-disease in 97.7 % [95.4%–100.0%] of patients; choice of different TL was associated with disagreement in 44.7% [37.6%–51.8%]. **Conclusions:** If different radiologists use RECIST1.1 and DOST for response assessment, they will select different TL more often than not. Just depending on whether TL selection was concordant or not, radiologists will exhibit perfect agreement, or substantial disagreement, even for distinguishing progressive vs non-progressive disease.

2529 Poster Session (Board #21), Mon, 8:00 AM-11:30 AM

Deflexifol (a novel formulation of 5FU): Phase 1 dose escalation study of infusional and bolus schedules after failure of standard treatment. *First Author: Philip R. Clingan, Southern Medical Day Care Centre, Wollongong, Australia*

Background: 5-Fluorouracil (5FU) is administered in combination with leucovorin (LV) to enhance clinical activity. However, simultaneous administration is not feasible as 5FU and LV are chemically incompatible, so the maximum possible interaction for benefit is not achieved Deflexifol, an all in one formulation of 5FU/LV with cyclodextrin (HP-β-CD 100mg/ml, 5-FU 15mg/ml & LV 1mg/ml) at physiological pH, was developed to improve efficacy and tolerance. **Methods:** A phase I dose-escalation trial to assess the safety, tolerability, MTD and DLT of Deflexifol given in two schedules has been completed. Secondary objectives included the pharmacokinetic (PK) profile and efficacy outcomes. Cohorts of patients with advanced malignancy after failure of standard treatment received Deflexifol as 46-h infusion Q2W or bolus weekly x6 in a standard 3+3 phase I design with no intra-patient dose escalation from dose level 1: 375mg/m² bolus or 1200mg/m² infusional up to dose level 5: 575mg/m² bolus or 3600mg/m² infusional. PK sampling of 5FU and dihydroFU was conducted on all patients to assess PK variability and adequacy of dosing. **Results:** 40 patients (21 infusional, 19 bolus) with breast (7), colorectal (24), other GI (6) & NSCLC (3) received a total 293 courses of treatment. No > grade 1 toxicity was noted at 375-475 mg/m^2 bolus, or at 1200-2400 mg/m^2 infusion. The DLT in bolus schedule was grade 3 diarrhea and myelosuppression at 575 mg/m^2, with no DLT in the infusion schedule at the maximum dose 3600 mg/m^2. The MTD have been established for both treatment arms: bolus 525mg/m²; 46-h infusion 3,600mg/m², with no grade IV toxicity observed. Other grade 3 toxicities were nausea, vomiting, and raised liver function tests. 5FU PK in this mixture is similar to 5FU alone. Encouraging efficacy results were seen with partial response in 1 patient and stable disease in 23 patients. Median PFS was (12.3 wks) and OS was (24.8 wks). **Conclusions:** Deflexifol has little toxicity and is effective in bolus and infusion schedules at doses equal to or greater than those feasible with 5FU and LV infused separately. A first-line phase II study in combination with oxaliplatin is planned. Clinical trial information: 044867.

2530 Poster Session (Board #22), Mon, 8:00 AM-11:30 AM

Deflexifol (a novel formulation of 5FU): Pharmacokinetics in a phase 1 trial in comparison to 5FU. *First Author: Stephen P. Ackland, University of Newcastle, Callaghan, Australia*

Background: Simultaneous administration of 5-fluorouracil (5FU) and leucovorin (LV) is generally not feasible as 5FU and LV are chemically incompatible (CaPO4 crystals), so the maximum possible interaction for benefit is not achieved. Deflexifol, an all in one formulation of 5FU/LV with cyclodextrin (HP-β-CD 100mg/ml, 5-FU 15mg/ml & LV 1mg/ml) at pH 7, was developed to overcome this problem. **Methods:** Limited sampling PK was done with dose 1 and 6 in a standard 3+3 phase I trial of Deflexifol given in two schedules (46-h infusion Q2W or bolus weekly x6) with no intrapatient dose escalation, at doses shown in Table. Sample times were infusion: 0, 2, 46h; bolus: 0, 0.2, 0.4, 1, 24h. 5FU and dihydroFU were measured as per Ackland et al, Anal Biochem 1997. 5FU AUC, clearance (CLR) and t1/2 were estimated for each patient to assess PK variability and adequacy of dosing compared to previous reports. **Results:** 40 patients were treated (21 infusion, 19 bolus, median age 67, 19 M, 21 F). The MTD(bolus) was 575 mg/m^2, with no DLT in infusion schedule to 3600 mg/m^2. PK showed substantial inter-patient variability – CLR(bolus) 21-900 L/h, t1/2 0.11-0.52 h, with intra-patient dose 6 CLR = 54-117% of dose 1, and a trend to increased AUC (mg/L.h) with dose (Table). Infusion CLR and AUC estimates were highly variable (CLR range 2-1200), with many cases with insufficient data. Compared to historical data with 5FU alone, AUC was likely subtherapeutic until 475mg/m^2 bolus and for many patients with infusion <3000mg/m^2. **Conclusions:** 5FU PK with Deflexifol is similar to 5FU alone. No evidence of saturation of kinetics over this dose range was seen, or induction of metabolism with repeated dosing. In each schedule AUC data supports the clinical impression of reduced toxicity at the same dose of 5FU. Accurate estimation of infusion PK requires more than 2 timepoints. PK in a phase II study is planned. Clinical trial information: 044867.

Bolus mg/m2	n	mean CLR	mean AUC	Infusion mg/m2	n	mean CLR	mean AUC
375	3	97	6.5	1200	3	45	461
425	3	188	5.5	1800	3	3.2	1074
475	3	200	7.1	2400	5	76	463
525	5	148	17.7	3000	2	42	618
575	4	59	18.4	3600	3	706	11

(dose 1 data only are shown)

2531 Poster Session (Board #23), Mon, 8:00 AM-11:30 AM

A phase I dose escalation study of SCB01A, a micro-tubular inhibitor with vascular disrupting activity, in patients with advanced solid tumors refractory to standard therapy. *First Author: Nai-Jung Chiang, National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan*

Background: SCB01A is a novel anti-microtubular agent with vascular disrupting activity. The Phase I study aimed to determine the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), safety, and pharmacokinetic (PK) profiles of SCB01A in patients with advanced solid tumor. **Methods:** This was an open-label, phase I clinical trial with a rapid titration followed by a 3 x 3 study design. Eligible patients would receive a 3-hr intravenous infusion of SCB01A, every 21 days as one cycle. All adverse events were classified according to the CTCAE V4.0. DLT was defined as the occurrence of grade 3 with complications and grade 4 hematoloigcal, or ≥grade 3 non-hematological toxicities. **Results:** From June 2011 to November 2015, a total of 33 eligible patients were enrolled to eight dose levels: 2 mg/m^2 (n = 1), 3 mg/m^2 (n = 1), 4 mg/m^2 (n = 6), 6.5 mg/m^2 (n = 9, with 3 additional subjects were recruited for safety concern), 10 mg/m^2 (n = 3), 16 mg/m^2 (n = 3), 24 mg/m^2 (n = 6) and 32 mg/m^2 (n = 4). Six episodes of DLTs were observed in 5 patients (each one in dose levels of 4/6.5/24 mg/m^2 and two in dose level of 32 mg/m^2), including grade 4 blood creatine phosphokinase elevation (4 mg/m^2), grade 3 gastric hemorrhage (6.5 mg/m^2), grade 2 venous thrombosis (24 mg/m^2), grade 3 peripheral neuropathy manifested as weakness of lower limbs, grade 3 aspartate aminotransferase elevation, and grade 3 hypertension (32 mg/m^2). The MTD was determined to be 24 mg/m^2. Pharmacokinetic profiles revealed a linear AUC-dose response with an average elimination half-life ($t_{1/2}$) of 2.5 hours. Partial response was observed in one subject with buccal cancer. A total of 57.6% (19/33) subjects had stable disease for at least 2 cycles. **Conclusions:** SCB01A is safe and tolerable in patients with solid tumor. The MTD of SCB01A is 24 mg/m^2 every 21 days, which deserves further development. Clinical trial information: NCT011159522.

2532 Poster Session (Board #24), Mon, 8:00 AM-11:30 AM

Phase 1/2a trial of daily oral BAL101553, a novel tumor checkpoint controller (TCC), in advanced solid tumors. *First Author: Rebecca Sophie Kristeleit, University College London, London, United Kingdom*

Background: BAL101553 (prodrug of BAL27862) is a small molecule TCC that binds microtubules and promotes tumor cell death by activation of the spindle assembly checkpoint. In a previous study (NCT01397929, Lopez et al. JCO 34, 2016; abstr 2525), 2-h IV infusion on Days 1, 8, 15 (q28d) of BAL101553 up to 80 mg/m^2 (maximum administered dose, MAD) showed vascular toxicities, including transient hypertension, which appeared to be C_{max} related. The recommended Phase 2 dose (RP2D) was 30 mg/m^2 weekly IV. Based on nonclinical models, antiproliferative effects of BAL27862 are driven by AUC. This trial explores whether once daily oral administration of BAL101553 reduces C_{max}-related toxicity and improves the therapeutic window (NCT02490800). **Methods:** Patients (pts) with advanced solid tumors who failed standard therapy, received QD oral BAL101553 (28-d cycles) in a 3+3 dose-escalation design to determine the MTD. Adverse events were assessed by CTCAEv4 grade (G); tumor response by RECIST 1.1; serial PK on Day 1 of Cycles 1 and 2. **Results:** In the ongoing study, 19 pts (9M/10F; median age 67 y) received doses of 2, 4, 8, 16 or 30 mg oral BAL101553 QD. The MAD was 30 mg with DLTs of reversible G2 hallucination and asymptomatic, reversible G3 electrolyte imbalances. No DLTs were observed at ≤ 16 mg. Dosing is ongoing between 16 and 30 mg QD to determine the MTD. BAL27862 exposures after oral QD dosing of BAL101553 compared to weekly 2-h infusions suggested high relative oral bioavailability. The BAL27862 weekly AUC at the oral MAD (30 mg QD) compared to the RP2D of 30 mg/m^2 for 2-h IV was more than 5-fold higher (19,656 vs 3,584 ng*h/mL) and C_{max} was 1.5-fold lower (171 vs 266 ng/mL). Both $C_{max}$and AUC were dose-proportional, with low/moderate variability. Oral BAL101553 had no effects on blood pressure and showed no vascular toxicity. 5 pts had stable disease (2 pts [cholangiocarcinoma, neuroendocrine pancreatic cancer] > 4 cycles). **Conclusions:** Daily oral BAL101553 enables higher weekly exposures of BAL27862 with lower C_{max} levels compared with a 2-h weekly infusion, due to the absence of C_{max} related vascular toxicity. Doses up to 16 mg QD are well tolerated. The MAD has been identified as 30 mg QD; definition of the MTD is ongoing. Clinical trial information: NCT02490800.

2533 Poster Session (Board #25), Mon, 8:00 AM-11:30 AM

Representation of minorities in oncology clinical trials: Review of the past 14 years. *First Author: Narjust Duma, Mayo Clinic, Rochester, MN*

Background: Many cancer clinical trials (CT) lack appropriate representation of specific patients populations, limiting the generalizability of the evidence obtained. Therefore, we determined the representation of ethnic minorities in oncology CT. **Methods:** Enrollment data from all therapeutic trials reported as completed in clinicaltrial.gov from 2003 to 2016 were analyzed. CT in rare cancers (< 1% incidence) or with recruitment outside of the US were excluded. Enrollment fraction (EF) was defined as the number of enrollees divided by the 2013 SEER database cancer prevalence. Chi-square test was used to estimate differences in categorical data. **Results:** Out of 1,012 CT, 310 (31%) reported ethnicity with a total of 55689 enrollees. Distribution by race and comparison with data from 1996-2002, US cancer prevalence and US census are described in the Table. Participation in CT varied significantly across ethnic groups, non-Hispanic Whites (NHW) were more likely to be enrolled in CT (EF of 1.2%) than African Americans (EF of 0.7%, $p < 0.001$) and Hispanics (EF of 0.4%, $p<0.001$). A decrease in African Americans (AA) and Hispanics (H) enrollment was observed when compared with historical data from 1996 to 2002. Hispanics were less represented in breast and prostate cancer CT contributing only to 3% and 1.5% of the study population; African Americans were less represented in lung (5.4%) and renal cell carcinoma (3%) trials. Asians were well represented and their recruitment doubled over the past 14 years (2% vs 5.3%). **Conclusions:** African Americans and Hispanics were less likely to be enrolled in CT. Comparing with historical data; we observed a decrease in minorities' recruitment in the past 14 years. This change could be attributed to the increased complexity of CT and mandatory molecular testing as many minorities lack access to institutions with genetic testing capacity. Future trials should take extra measures to recruit participants that adequately represent the U.S. cancer population.

Race/ethnicity	Trials participants No. (%)	1996-2002 trial participants %	2013 cancer prevalence %	2010 U.S. Census %
NHW	46431 (83)	85.5	79	66
AA	3270 (6)	9.2	10	12.6
H	1484 (2.6)	3.1	7	16
Asian	2982 (5.3)	2	3.3	4.8
Native American	190 (0.3)	0.2	0.3	0.6
Other	1332 (2.4)			

2534 Poster Session (Board #26), Mon, 8:00 AM-11:30 AM

Validation of RECIST 1.1 for use with cytotoxic agents and targeted cancer agents (TCA): Results of a RECIST Working Group analysis of a 50 clinical trials pooled individual patient database. *First Author: Saskia Litière, European Organisation for Research and Treatment of Cancer, Brussels, Belgium*

Background: The Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 were derived from an international collaborative effort supported by data from clinical trials (16 studies, 9147 patients) on cytotoxic chemotherapy (CT), providing a standard tool for response assessment. RECIST's role has been questioned for TCA. Using a pooled individual patient database (IPD) from clinical trials performed by industry and cooperative groups, we assessed whether modifications to RECIST are required to evaluate antitumor activity of TCA. **Methods:** Data were collected from phase 2 and 3 clinical trials testing TCA in solid tumors. To study the occurrence of mixed responses, the variability of response of lesions within patients was studied. Furthermore, response was correlated with survival through landmark analyses and time dependent Cox models. **Results:** Clinical data were obtained from 23,259 patients, mainly with lung (36%), colorectal (28%) or breast cancer (11%). 15,620 patients (67%) received a TCA, mainly transduction or angiogenesis inhibitors, either as single agent (37%) or combined with other TCAs (7%) or CT (56%); 28% received CT only and 5% best supportive care or placebo. Within-patient variability reduced as the number of lesions used for response assessment increased, and did so similarly for TCAs (+/- CT) and CT. Mixed responses seemed to occur similarly across these treatment categories as well. Landmark analyses showed improving overall survival by % tumor shrinkage and a clear distinction between the effect of tumor shrinkage and progressive disease (PD) according to RECIST 1.1. This was confirmed by time dependent analysis. In addition target lesion growth showed no marked improvement in overall survival prediction over and above the other components of RECIST 1.1 PD (new lesions, non-target PD), regardless of treatment (TCA, CT or both) received. Similar results were seen focusing on major tumor types and classes of TCA. **Conclusions:** Using a large IPD dataset we demonstrated that RECIST 1.1 performs equally well for response assessment of TCA as for CT. No modifications are required.

2535 Poster Session (Board #27), Mon, 8:00 AM-11:30 AM

Food effect studies and drug label recommendations: A review of recently approved oncology products. *First Author: Mark Farha, AstraZeneca, Waltham, MA*

Background: Evaluation of the effect of food on the pharmacokinetics of orally administered oncology drugs is a critical aspect of drug development, as food can mitigate or exacerbate toxicities and can change and influence variability in systemic exposure. Our aim in this review of approved oncology products is to describe the approaches used by sponsors to assess food effect and decide on the final dosing recommendations. **Methods:** Data for small molecule oncology drugs approved between 2003-2016 was extracted from the clinical pharmacology review in the sponsor's FDA submission package. Information on food-effect study design, outcomes, intersubject variability, exposure-response relationships for safety, and the label dosing recommendation regarding food was analyzed. **Results:** Of the 29 drugs analyzed, 19 food effect studies were conducted in healthy volunteers, and 10 were conducted in cancer patients. The ratio of population geometric means between fed and fasted treatments fell outside the 80-125 percent equivalence limit in 55% of compounds for AUC and in 69% of compounds for Cmax. 6 drugs (21%) are recommended to be given with food, 11 drugs (38%) in the fasted state, and 12 drugs (41%) can be dosed regardless of food. Label recommendations appeared to be driven by the exposure-response analysis. 80% of drugs with a fasted label recommendation despite an increase in bioavailability with food had an exposure-response relationship for safety. **Conclusions:** Optimizing study design by conducting early food effect studies designed to estimate food effect rather than confirming no food effect, and learning the impact of food early may eliminate unnecessary study arms and save sponsors money and time. Furthermore, understanding the potential of food to mitigate or exacerbate toxicities may improve patients' experience with treatments and has been shown here to be a major driver of the final dosing recommendation regarding food.

2536 Poster Session (Board #28), Mon, 8:00 AM-11:30 AM

A call for global harmonization of phase I oncology trials: Results from two parallel, first-in-human phase I studies of DS-7423, an oral PI3K/mTOR dual inhibitor in advanced solid tumors conducted in the United States and Japan. *First Author: Tomoya Yokota, Shizuoka Cancer Center, Shizuoka, Japan*

Background: The aim of this study was to determine the safety, maximum-tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of DS-7423, a novel inhibitor of PI3K/mTOR, in US and Japanese population. We further compared toxicities and recommended phase 2 dose (RP2D) of DS-7423 and approved oncology drugs in the two populations. **Methods:** We conductedparallel, first-in-human studies in US and Japan in patients with advanced solid tumors. We conducted a Pubmed search of pivotal and corresponding phase I studies to compare the RP2D and final approval doses of molecularly targeted agents (MTA) between US and Japan. **Results:** 69 patients were enrolled (n = 42 from US and n = 27 from Japan). Between populations, the only difference at baseline was body weight (BW) and body mass index (BMI). Dose-limiting toxicities included grade 3 rash (48 mg), grade 3 stomatitis (240 mg), grade 3 lung infection (240 mg), grade 4 hyperglycemia (240mg), grade 3 fatigue (320 mg), and grade 3 dehydration (320mg). The MTD and RP2D was 240 mg/d in both populations. Frequent treatment-related adverse events included diarrhea, fatigue, decreased appetite, rash, and stomatitis. No remarkable difference in AUC and Cmax were observed between populations. Prolonged stable disease was seen in cholangiocarcinoma, thymic cancer, non-small cell lung cancer, squamous cell carcinomas, carcinoid, and sarcoma. DS-7423 demonstrated PD effects on serum glucose, C-peptide and Akt phosphorylation and 18F-FDG uptake in tumors. The final RP2D of 17 MTA approved in US and Japan from 2001 to 2015 was near identical. The approved doses in both regions were identical. **Conclusions:** Despite differences in BW, BMI, and ethnicity, DS-7423 showed no difference in PK, PD, toxicity or efficacy between populations. We found near identical RP2D in phase I oncology studies and approved doses in pivotal studies. This supports increased international collaboration in the conduct of phase I oncology trials. Clinical trial information: NCT01364844, Japic CTI, 12766.

2537 Poster Session (Board #29), Mon, 8:00 AM-11:30 AM

Hormone receptor (AR/ER/PR) expression as a prognostic marker and novel candidate for drug development across multiple tumor types. *First Author: Shiraj Sen, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Hormone receptor (HR) [androgen receptor (AR), estrogen receptor (ER), progesterone receptor (PR)] expression is ubiquitous across tumor types and central to breast and prostate cancer treatment. While implicated in tumorigenesis, its role as a prognostic biomarker and therapeutic target in other tumor types has yet to be elucidated. **Methods:** We performed bioinformatic analyses of HR expression [reported as median transcripts per million (TPM)] using RNAseq from the Cancer Genome Atlas and completed Kaplan-Meier analyses to identify associations between HR expression and median overall survival (OS). **Results:** 9,743 samples from 9,674 patients across 33 tumor types were analyzed. AR was highly expressed in GBM (2 TPM), low grade glioma (2 TPM), breast (15 TPM), prostate (14 TPM), ovarian (6 TPM), renal clear cell carcinoma (4 TPM) and HCC (2 TPM) . Tumors with the highest quartile of expression had improved OS in renal clear cell [53 months (mo) vs not reached (NR), $p = 4x10^{-11}$] and adrenocortical carcinoma (45 mo vs NR, p = .03) and worse OS in low grade glioma (119 vs 64 mo, $p = 6x10^{-4}$). PR was highly expressed in uterine (12 TPM), breast (5 TPM), and renal chromophobe (2 TPM) carcinoma. PR expression was associated with improved OS in sarcoma (49 mo vs NR, p = .03), endometrial (NR, p = .02) and renal clear cell carcinoma (58 mo vs NR, p = .003) and worse OS in low grade glioma (53 vs 97 mo, p = .01), gastric adenocarcinoma (7 vs 17 mo, p = .04), and possibly pancreatic adenocarcinoma (21 vs 44 mo, p = .07). ER was highly expressed in breast (116 TPM), endometrial (87 TPM), ovarian (32 TPM), cervical (4 TPM), thyroid (4 TPM), prostate (3 TPM), and lung adenocarcinoma (2 TPM). ER expression was associated with improved OS in mesothelioma (15 vs 28 mo, p = .03) and endometrial cancer (NR, p = .001) and worse OS in squamous lung cancer (80 vs 48 mo, p = .02). **Conclusions:** HR expression may represent a novel prognostic marker in multiple tumor types and a candidate for drug development in low grade glioma, gastric adenocarcinomas, squamous cell lung cancer, and pancreatic adenocarcinomas. Protein-based IHC testing and early phase clinical trials targeting HR signaling in these tumor types is warranted.

2538 Poster Session (Board #30), Mon, 8:00 AM-11:30 AM

Large scale adverse event data mining for targeted therapies development. *First Author: Mayur Sarangdhar, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: Targeted anti-cancer small molecule drugs & immune therapies have had a dramatic impact in improving outcomes & the approach to clinical trials. Increasingly, regulatory approvals are expedited with small studies designed to identify strong efficacy signals. However, this may limit the extent of safety profiling. The use of large scale/big data meta-analyses can identify novel safety & efficacy signals in "real-world" medical settings. **Methods:** We used AERSMine, an open-source data mining platform to identify drug toxicity signatures in the FDA's Adverse Event Reporting System of 8.6 million patients. We identified patients (n = 732,198) who received either traditional and targeted cancer therapy & identified therapy-specific toxicity patterns. Patients were classified based on exposures: anthracyclines (n = 83,179), platinum (117,993), antimetabolites (93,062), alkylators (81,507), antimicrotubule agents (97,726), HER2 inhibitors (40,040), VEGFis (79,144), VEGF-TKis (90,734), multi TKis (34,457), anaplastic lymphoma Kis (7,635), PI3K-AKT-mTOR inhibitors (33,864), Bruton TKis (9,247), MEKis (4,018), immunomodulatory agents (174,810), proteasome inhibitors (44,681), immune checkpoint inhibitors (20,287). Pharmacovigilance metrics [Relative Risks & safety signals] were used to establish statistical correlation & toxicity signatures were differentiated using the Kolmogorov–Smirnov test. **Results:** To validate the use of the AERSMine to detect AEs, we focused on cardiotoxicity. It identified classic drug associated AEs (e.g. ventricular dysfunction with anthracyclines, HER2is & VEGFis; VEGFi hypertension & vascular toxicity; multi TKIs vascular events). AERSMine also identified recently reported uncommon toxicities of myositis/myocarditis with immune checkpoint inhibitors. It indicated a higher frequency of myositis/myocarditis with combination immune checkpoint therapy, paralleling industry corporate safety databases. These toxicities were reported at higher frequencies in patients > 65 yrs. **Conclusions:** AERSMine "big data" analyses provide a sensitive tool to detect potential new patterns of AEs simultaneously across multiple clinical trials & in the real-world setting.

2539 Poster Session (Board #31), Mon, 8:00 AM-11:30 AM

FDA analysis of patient enrollment by region in clinical trials for approved oncological indications. *First Author: Bindu Kanapuru, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Clinical trials are increasingly conducted on a global scale in an effort to accelerate accrual. This analysis attempts to quantify and characterize participants in trials submitted to support approval of drugs for oncology indications by the region of enrollment. **Methods:** Demographic information was extracted for patients enrolled in clinical trials submitted to the FDA from 2005-2015. Only trials submitted to support approval for malignant solid tumor or hematology indications were included. Countries were grouped into regions for further analysis. A total of 178,024 patients with information regarding age and country were included in this analysis. **Results:** Forty five percent (80,460) of clinical trial participants were enrolled from Europe, 36% (63,958) from North America (includes U.S.A and Canada) and 8.4% (14,975) from Asia. Countries in Latin America, Middle East/Africa and the Baltic States/Russia enrolled the remainder 10.5% of the patients. Among 99,556 participants < 65 years of age; 38.7% (38,538) were enrolled from North America, 40.5% (40,362) from Europe, 9.7 % (9674) from Asia and 11% from the rest of the regions. Europe enrolled the highest number of cancer patients aged 65 years or older; 51.1% (40,098) compared to 32.4% (25,420) from North America and 6.8 % (5301) from Asia. **Conclusions:** Majority of patients enrolled into clinical trials submitted for oncology drug approvals were from regions other than North America, with highest number enrolled from Europe particularly in the older age group. While it is interesting to speculate, the reasons for differential enrollment of patients between Europe and North America and the impact of these findings on interpretation of clinical trial results need additional exploration. Analysis of trends over time may be useful to address this issue.

	North America	Europe	Latin America	Middle East and Africa	Asia	Baltic states and Russia
Total N (%)	63,958 (36.0)	80,460 (45.0)	7788 (4.4)	3237 (1.8)	14,975 (8.4)	7606 (4.3)
Age < 65 yrs. N (%)	38,538 (38.7)	40,362 (40.5)	3761 (3.8)	1940 (1.9)	9674 (9.7)	5281 (5.3)
Age ≥65 yrs. N (%)	25,420 (32.4)	40,098 (51.2)	4027 (5.1)	1297 (1.7)	5301 (6.8)	2325 (3.0)

2540 Poster Session (Board #32), Mon, 8:00 AM-11:30 AM

Suitability factors of core needle biopsies for pharmacodynamic (PD) studies. *First Author: Ralph E. Parchment, Laboratory of Human Toxicology and Pharmacology, Applied/Developmental Research Directorate, Leidos Biomedical Research, Inc., Frederick National Laboratories, Frederick, MD*

Background: There are different requirements of biopsies for diagnosis vs. pharmacologic evaluation of drug mechanism biomarkers. Evaluation of core needle biopsy pairs collected pre-dose and at a defined timepoint post-dose provides insight into the pharmacodynamics of agents in early development. Adequate biopsies are key for quantifying response of the tumor cell population to molecular drug action. Tumor heterogeneity and variable tumor content make many biopsy pairs unsuitable for biomarker evaluation with any assay platform (microscopy, immunoassay, etc.). We analyzed biopsies obtained from the Developmental Therapeutics Clinic (DTC) for suitability for PD assays. **Methods:** Specimens obtained from 2010-2016 across 4 trials were analyzed. For microscopy measurements, biopsy pairs collected using image guidance are snap-frozen, thawed under fixative, and embedded in paraffin with control tissues. The likelihood of finding optimal regions for analysis is maximized by preparing a series of sections with H&E stained flanking slides, and annotation by an anatomic pathologist. **Results:** Of 112 biopsies evaluated, 26% were found to contain $<$ 5% tumor, making them inadequate for quantitative microscopy due to a mixture of factors, with the primary factor being predominantly non-neoplastic tissue, followed by extensive mucin content, necrosis, fibrosis, inadequate size and tissue artifact post-collection. Another 20% contained $\leq$25% tumor, and in this group, tumor segmentation methodology during image analysis increased the rate of evaluable biopsies. 56% of tissues had $>$ 25% tumor and were suitable for analysis. **Conclusions:** Improved communication between oncologists, radiologists and pathologists is key to a better understanding of factors that affect suitability of biopsies for robust PD biomarker analyses. NCI's DTC has implemented protocol modifications including increased tissue collection and frequent case reviews by the Phase 1 team, interventional radiologists and PD team aimed at understanding features during image guidance that relate to suitability. Implementation of a scoring system has allowed the assessment of suitability of biopsies for analysis. Funded by NCI Contract No HHSN261200800001E.

2541 Poster Session (Board #33), Mon, 8:00 AM-11:30 AM

FDA analysis of MRD data in hematologic malignancy applications. *First Author: Nicole Gormley, U.S. Food and Drug Administration, Silver Spring, MD*

Background: There is considerable interest in the use of minimal residual disease (MRD) in clinical trials of hematologic malignancies, especially as a potential surrogate endpoint to expedite drug approval. Although surrogacy has not yet been established in most hematologic malignancies (except CML), MRD data has been submitted in applications to the agency to allow for further characterization of the product's activity. Here we describe the new drug applications (NDA) or biologics licensing applications (BLA) that included MRD data and provide an analysis of the MRD data and the Agency's decisions. **Methods:** The authors reviewed internal databases for all original and supplemental NDA and BLA applications submitted to the Division of Hematology Products (DHP) between 2014 and 2016 that pertained to malignant hematologic conditions. The applications were reviewed for inclusion of MRD data. The clinical reviews and prescribing information (PI) of the identified applications were reviewed for assessment of MRD data and FDA's findings. **Results:** There were 34 NDAs or BLAs submitted between 2014-2016. Of these, 13 (38%) included MRD data, in the following diseases: CML, CLL, ALL, and MM. MRD data was added to the PI in 6 cases (46%), not included in 4 (31%), and was not proposed for inclusion in 3 (23%). Among the 6 cases in which MRD data was included in the PI, 5 used PCR testing and 1 used flow cytometry. Among the 4 in which MRD data was not included in the PI, the identified issues included: missing data among those in CR, incomplete test performance characteristics data (e.g.-limit of detection), disparate sample sources (blood, bone marrow), high amount of test failure rates (i.e.-inability to identify a clonal rearrangement), lack of test validation in the proposed disease setting, and inappropriate planned statistical analyses. **Conclusions:** Nearly 40% of applications submitted to DHP between 2014 and 2016 included MRD data. While the data submitted was deemed adequate for inclusion in the PI in 46% of cases, 31% of applications contained MRD data that the Agency deemed un-interpretable. Data collection and assay performance characteristics should be of significant rigor and completeness to allow for comprehensive review.

2542 Poster Session (Board #34), Mon, 8:00 AM-11:30 AM

Adherence to novel oral anticancer therapies in the phase I setting: The Royal Marsden experience. *First Author: Maxime Chenard-Poirier, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: The use of oral anticancer therapies has increased substantially in recent years. Nonadherence can impair the efficacy of such therapies as well as confound the interpretation of toxicity and pharmacokinetic data in phase I trials. However, there is a paucity of data regarding adherence patterns and barriers in this specific setting. **Methods:** We included patients treated in Phase I trials involving oral investigational medicinal products (IMPs) in the Drug Development Unit, Royal Marsden Hospital, UK, between 2012 and 2014. Patient, disease and treatment characteristics as well as compliance data from prospectively collected trial diary cards and drug accountability were recorded. Relationships between adherence rate and other variables were explored using logistic regression. **Results:** We collected data for 2819 patient-weeks, pertaining to 169 patients treated on 18 different phase I trials. Median age was 61 years (range 18-79), females predominated (60%), median number of previous systemic therapy was 3 (0-12) and median time on trial was 9 weeks (0.3-212.4). Hundred-percent adherence rate was 88% in the first cycle and 79% overall. Nonadherence occurred in 83 of 2819 patient-weeks (3.0%); including 75 (2.7 %) missed doses and 8 (0.3 %) overdoses. In univariate analysis, longer time on trial and a continuous treatment schedule were associated with poorer adherence, whereas fasting requirements pre- or post-dosing was associated with improved adherence. Known intracranial metastases, number of concomitant medications and opiates or anti-emetics use were not significantly associated to adherence. In multivariate analysis, fasting requirements (OR 5.347, 95%CI : 1.443-20.019, p = 0.012) and longer time on trial (OR 0.98, 95%IC : 0.961-0.996, p = 0.017) were statistically significant. **Conclusions:** This is the first report on adherence rates to oral anticancer IMPs in a large phase I trial population. Our observed adherence rates are at the higher end of published data in the general cancer population. Factors influencing adherence in phase I trials appear to be distinct, with fasting requirements being a unique finding. These findings may impact future early-phase trial design and conduct.

2543 Poster Session (Board #35), Mon, 8:00 AM-11:30 AM

Changes in numbers of randomized (RCT) versus non-randomized (NRCT) clinical trials from 2004-2016: Evidence of shifting cancer drug development pathway. *First Author: Laura Vidal Boixader, INC Research, Barcelona, Spain*

Background: Trials using randomized designs have been conducted for decades to demonstrate efficacy of novel anti-cancer drugs (NACD). Recently, several NACD have shown high antitumor activity in early phase studies, prompting suggestions that NRCT could expedite drug development. We sought to determine what changes have occurred in numbers of NACD RCT vs NRCT conducted from 2004-2016. **Methods:** We reviewed a database of NACD clinical trials conducted by INC (excluding phase I and I/II trials) and classified them by RCT vs NRCT, grouped by year ($\leq$ 2010 or $>$ 2010). We queried Citeline Trialtrove database for industry sponsored, phase 2 trials (P2T) initiated from 2006-2016 and examined numbers of RCT vs NRCT by year.A more detailed analysis of non-small cell lung cancer (NSCLC) clinical trials based on drug type category - Immunooncology (IO) vs. all other mechanims of action (NIO) was performed. **Results:** 190 INC-conducted trials were reviewed. 58 trials (31%) were performed $\leq$ 2010 and 132 trials (69%) $>$ 2010. Over this period, NRCT (n = 107, 56%) outnumbered RCT (n = 83, 44%). Whereas RCT outnumbered NRCT from 2004-2010 (74% vs 52%), after 2010, NRCT outnumbered RCT (58% vs 42%). Citeline Trialtrove search revealed 4776 industry sponsored P2T initiated from 2006-2016. The total number of P2T started annually was highest in 2007 (n = 621), decreasing to a low of 375 in 2016. The proportion of phase 2 RCT demonstrated an increase from 27% (n = 166) in 2006 to a peak plateau of 37-39% from 2011-2014, followed by a drop to 33% in 2015 and 29% in 2016. Among IO studies, RCT declined in 2015-6 vs. previous years, and a decreased for all NACD in 2016 vs. previous years also was noted. For studies in NSCLC, declines in RCT were evident from 2015-6 vs. previous years (45% in 2007-14 vs. 25% in 2015-6). **Conclusions:** Our data indicate a trend toward fewer trials of NACD using randomized designs and more studies using non-randomized designs, with overall fewer P2T initiated in the past year. This change reflects shifts in NACD development pathways, related to a better understanding of cancer biology, drive to develop personalized treatment and a more flexible regulatory drug approval process.

2544 Poster Session (Board #36), Mon, 8:00 AM-11:30 AM

FDA analysis of grade 3-4 safety events. *First Author: Marie-Anne Damiette Smit, U.S. Food and Drug Administration, Silver Spring, MD*

Background: In new drug/biologics applications, safety data provided to FDA include serious adverse events (SAEs), defined as adverse events (AEs) resulting in death, life-threatening AE, inpatient hospitalization or prolongation of hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or congenital anomaly/birth defect. One limitation of the SAE definition is that hospitalization practices differ across localities and among medical practitioners. Therefore, a safety signal may not be adequately reflected when analyzing SAEs. We hypothesize that evaluating CTCAE Grade 3 (severe) and Grade 4 (life-threatening) AEs, independent of whether or not these were classified as serious, provides a more complete assessment of patient safety. **Methods:** We reviewed SAEs from all nine registrational trials for new molecular entities approved for the treatment of cancer by the FDA in 2014. **Results:** A total of 25,548 AEs were reported in 1,781 patients treated with an investigational agent. There were 2,943 Grade 3-4 AEs and 912 Grade 3-4 SAEs. Information regarding hospitalization was available in 62% of Grade 3-4 AEs. Fifty-five percent of Grade 3-4 SAEs vs. 5.5% of Grade 3-4 non-serious AEs resulted in hospitalization. Several clinically serious Grade 3-4 AEs, including sepsis and respiratory failure, were not classified as SAE. **Conclusions:** There is significant overlap in most common Grade 3-4 AEs and most common Grade 3-4 SAEs. Most AEs that are clinically serious were appropriately classified as SAE. However, some clinically serious AEs and some AEs resulting in hospitalization were not classified as SAE. With the exception of information regarding hospitalization, characterization of the reason why certain AEs were classified as SAEs was not possible. In this pooled analysis, data from the analysis of AEs by severity was more informative than the analyses by SAEs.

Grade 3-4 AEs	% of patients	Grade 3-4 SAEs	% of patients
Anemia	6.6	Pneumonia	2.1
ALT increase	4.8	Anemia	1.5
Neutropenia	4	Febrile neutropenia	1.4
Fatigue	3.5	Abdominal pain	1.3
Febrile neutropenia	3.5	Dyspnea	1.2
Dyspnea	3.1	Sepsis	1
Pneumonia	2.6	Neutropenia	0.7
Abdominal pain	2.4	Pulmonary embolism	0.6
AST increase	2.3	Pneumonitis	0.6

2545 Poster Session (Board #37), Mon, 8:00 AM-11:30 AM

Effect of a novel IL-2 cytokine immune agonist (NKTR-214) on proliferating CD8+T cells and PD-1 expression on immune cells in the tumor microenvironment in patients with prior checkpoint therapy. *First Author: Chantale Bernatchez, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: NKTR-214 is a CD122-biased agonist designed to provide sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβγ) to preferentially activate and expand effector CD8+ T and NK cells over T regulatory cells in the tumor microenvironment. Immune changes in the tumor microenvironment after NKTR-214 treatment was assessed in patients with locally advanced or metastatic solid tumors. **Methods:** NKTR-214 was administered IV in an outpatient setting q2w or q3w. Serial blood and tumor tissue samples were collected to measure immune activation using immunophenotyping including flow cytometry, immunohistochemistry (IHC), T cell clonality and gene expression analyses. **Results:** 26 patients (pts) have been treated with NKTR-214 at q3w, 4@0.003, 9@0.006, 6@0.009 and 1@0.012 mg/kg. Six pts received 0.006 mg/kg q2w. 58% of pts had prior immunotherapy. The most common Gr1-2 TRAEs were fatigue (73%) and pruritus (65%), and decreased appetite (46%). One pt experienced Gr3 syncope and hypotension at the highest dose tested and continued treatment at a lower dose. No drug-related AEs led to study discontinuation. No immune-related AEs or capillary leak syndrome were observed. 6 pts (23%) experienced tumor shrinkage from 10-30%. Three immunotherapy naïve pts receiving sequential anti-PD1 therapy, after ending treatment with NKTR-214, experienced significant tumor regression at first scan. In all pts evaluated, blood samples showed increases in newly proliferating (Ki67+) T and NK cells 8 days post dose. Flow cytometry and/or IHC revealed an up to 10-fold increase from baseline in tumor CD8+T and NK cells in the tumor microenvironment, with minimal changes to Tregs. PD-1 expression increased 2-fold in TILs. Gene expression analysis of tumor tissue showed increases in several immune checkpoint genes, cytotoxic markers (IFNg, PRF1, and GZMB), as well as a dynamic change in T cell clonality. **Conclusions:** Based on a favorable safety profile and strong correlative biomarker data, a phase 1/2 trial combining NKTR-214 and nivolumab is currently enrolling. Clinical trial information: NCT02869295.

2546 Poster Session (Board #38), Mon, 8:00 AM-11:30 AM

First-in-human phase I study of an oral HSP90 inhibitor, TAS-116, in advanced solid tumors. *First Author: Noriko Yanagitani, Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: TAS-116 is an oral non-ansamycin, non-purine, and non-resorcinol highly selective inhibitor of HSP90α/β. The objective of this FIH study was to determine the MTD and investigate the safety, tolerability, PK, PD (HSP70 protein levels in PBMCs), and antitumor activity of TAS-116. **Methods:** The study is being conducted in Japan and the UK. Patients with advanced solid tumors received escalating doses of TAS-116 once daily (QD) with an accelerated titration design. After the MTD was determined, safety and tolerability of 5 days on / 2 days off per week administration (QDx5) at the MTD in QD was explored. In parallel, the MTD with every other day administration (QOD) was evaluated by using a 3 + 3 design. **Results:** As of 20 September 2016, 52 patients were enrolled. TAS-116 was evaluated at doses of 4.8 to 150.5 mg/m^2/day in the QD schedule and doses of 107.5 to 295.0 mg/m^2/day in the QOD schedule. The MTD was 107.5 mg/m^2/day with QD and 210.7 mg/m^2/day with QOD. QDx5 at the MTD in QD using a flat dose of 160 mg was evaluated. The most common adverse events in all regimens were gastrointestinal disorders and increased creatinine. DLTs were observed in 4 patients in QD (night blindness, visual disorder, AST/ ALT/ gamma-GTP elevations, and anorexia) and in 2 patients in QOD (platelet count decreased, febrile neutropenia, pneumonia, respiratory failure, and septic shock). Reversible eye disorders were observed in all schedules, but those observed in QDx5 were limited to grade 1. The PK level demonstrated dose proportionality without unexpected accumulation under repeated administration. Dose-related HSP70 induction of PBMCs was observed. As of 20 September 2016, three confirmed durable PRs by RECIST were observed (239 days in GIST and 173 days in NSCLC with QD; 293 + days in NSCLC with QOD). PR and SD ≥ 12 weeks were observed in 15 out of 47 patients. **Conclusions:** TAS-116 had an acceptable safety profile under all schedules, especially QDx5. Preliminary antitumor activity was demonstrated with evidence of target engagement. Dose expansion at the MTD in this phase 1 study and the phase 2 study in patients with GIST are ongoing. Parts of this study will be expanded to the US with an amended study protocol. Clinical trial information: NCT02965885.

2547 Poster Session (Board #39), Mon, 8:00 AM-11:30 AM

The Drug Rediscovery Protocol (DRUP). *First Author: Daphne Liselotte Van Der Velden, Netherlands Cancer Institute, Division of Molecular Oncology, Amsterdam, Netherlands*

Background: Bringing precision medicine to cancer patients remains a challenge. For many cancers, the relative contribution of tumor type, mutations or CNV to drug sensitivity remains unknown. In addition, drug access is generally limited to the labeled indication, bypassing rarer disease subgroups for which large trials are not feasible. An innovative trial that facilitates drug access, whilst systematically analyzing treatment outcomes and biomarkers, could help overcome these challenges. **Methods:** We designed a prospective, non randomized clinical trial in which patients with advanced cancer are treated with targeted or immunotherapy matched to their tumor profile, defined by genetic aberration, microsatellite instability (MSI) or high mutational load (HML). Upon a mandatory pre-treatment tumor biopsy for biomarker research, patients are enrolled in multiple parallel cohorts, each defined by study drug, histologic tumor type and molecular tumor profile. Efficacy is analyzed per cohort, enrolling 8 patients in stage I and 16 more in stage II if ≥1 response is observed in stage I. Study endpoints include objective tumor response (CR or PR), stable disease (SD) at 16 weeks and grade≥3 adverse events. The DRUP is registered at ClinicalTrials.gov (NCT02925234). **Results:** Since start of recruitment in Sep 2016, 76 patients have been submitted for review (mean per month 15, range 8-17) and 16 (21%) have started treatment in 10 different cohorts, directed at either ATM (n = 1; breast cancer), BRAF (n = 2; salivary duct carcinoma and ACUP), BRCA (n = 1; breast cancer), ERBB2 (n = 2; CRC), HML (n = 2; prostate and CRC), MSI (n = 5; CRC, GBM and urothelial carcinoma), RET (n = 1; NSCLC) or RAS-RAF$_{wt}$ (n = 2; SCC and sarcoma). Out of the 7 patients for whom response evaluation is available, PR (n = 2) or SD at 16 weeks (n = 1) was observed in 3 (43%). Thirteen study drugs (supplied by 6 pharmaceutical companies) are currently available, 6 more are expected soon. **Conclusions:** Execution of a nationwide multidrug precision oncology trial is feasible. It contributes to oncologists' education on molecularly targeted therapies and to identification of early signs of activity in rare cancer subsets. Data sharing with similar studies such as TAPUR and CAPTUR will help to enlarge cohorts and affirm conclusions. Clinical trial information: NCT02925234.

2548 Poster Session (Board #40), Mon, 8:00 AM-11:30 AM

A study of vistusertib in combination with selumetinib in patients with advanced cancers: TORCMEK phase Ib results. *First Author: Peter Schmid, Barts Health NHS Trust, London, United Kingdom*

Background: PI3K/mTOR and MAPK pathways are aberrantly activated in many tumours and interact to promote tumour growth and therapeutic resistance. Activity of single pathway inhibition is limited due to compensatory activation of alternative signalling pathways. Dual pathway inhibition has demonstrated synergistic activity in preclinical models, with broad activity across a range of molecular backgrounds. This study was designed to evaluate the optimal doses and schedule of vistusertib (dual mTOR1/2 inhibitor) and selumetinib (MEK1/2 inhibitor) when given in combination. **Methods:** Thisphase Ib/IIa trial with a dose escalation part (Ib) in treatment refractory advanced solid tumours and expansion cohorts in TNBC, squamous and non-squamous NSCLC (KRASmt & WT) (IIa). Both, continuous daily (CC) (25, 35, 50mg BD) and intermittent (IC) schedules (50, 100, 125mg BD 2ds on, 5 ds off) of vistusertib were investigated. Selumetinib dose was given at a dose of 75mg BD daily. Treatment was given until PD (RECIST 1.1) or intolerable toxicity. The primary endpoint was DLTs. Secondary endpoints included response, clinical benefit, PFS and PK. **Results:** 23 evaluable patients were enrolled in the PhaseIb part. For the intermittent schedule, no DLTs were reported at any of the dose levels IC1-3. For the continuous schedule, 2 out of 9 patients treated at dose level C2C developed DLTs (G3 mucositis, dizziness and rash). Dose level C3C was not tolerated with DLTs observed in 2 out of 3 patients (G3 mucositis and G3 LFTs). Separate MDTs were determined for intermittent (I3C) and continuous schedules (C2C). Adverse events were in keeping with established single agent safety profiles. Anti-tumour efficacy was demonstrated at various dose levels and across tumour types including uveal melanoma, breast, cervical, uterine, skin or colorectal cancers. There were no objective responses but confirmed stable disease for $>$ 16 weeks were observed in 7 patients with a duration of response ranging up to 55+ weeks. **Conclusions:** Based on DLTs, dose intensity and cumulative toxicity, the intermittent schedule I3C was selected as RP2D for expansion cohorts. Preliminary anti-tumour activity was observed. Clinical trial information: NCT02583542.

2549 Poster Session (Board #41), Mon, 8:00 AM-11:30 AM

Pharmacokinetics (PK) and pharmacodynamics (PD) of a novel carcinoembryonic antigen (CEA) T-cell bispecific antibody (CEA CD3 TCB) for the treatment of CEA-expressing solid tumors. *First Author: Ignacio Melero, CIMA, CUN, University Navarra, Centro de Investigación Biomédica en Red de Oncología (CIBERONC), Pamplona, Spain*

Background: CEA CD3 TCB (RO6958688) targets CEA on tumor cells and is agonistic for CD3e on T cells. In mouse models, CEA CD3 TCB displays potent anti-tumor activity, leads to increased intra-tumoral T cell infiltration and activation and up-regulates the PD-1/PD-L1 pathway. **Methods:** Biodistribution was assessed in mice using SPECT/CT. Patient (pts) samples correspond to 2 dose-escalation studies in CEA+ solid tumors. Study 1 (S1): single agent weekly (qW) (0.052 to 600 mg, iv, n = 80), and Study 2 (S2): combination of RO6958688 qW (5 to 160 mg, iv) with 1200mg atezolizumab q3W (n = 38). Analytical methods: PK - population modeling approach; anti-drug antibodies (ADA) - ELISA; immunophenotyping in peripheral blood (PB) by flow cytometry (FCM), in pre- (BSL) and on-treatment (OT) biopsies by immunohistochemistry (IHC) and FCM; plasma cytokines - multiplex assays; PD-L1 - SP142 assay. **Results:** In mice, RO6958688 preferentially accumulated in CEA+ tumors. In pts with no ADAs tested thus far in both studies (S1 29; S2 21), RO6958688 showed near linear PK and exposure. In S1, OT biopsies demonstrated a statistically significant increase in density and activation profile of T cells (CD3: 2.6-fold, n = 21; CD3/CD8: 3.7 fold, n = 17; CD3/Ki67: 4-fold, n = 20; CD8/PD1: 1.7-fold, n = 15) without dose-dependence. In S2, preliminary data of T cell density (5-80mg) were similar to S1 (2-fold). In S1, a significant correlation was observed between treatment-induced tumor lesion reduction and increases of OT CD8/CD25 fluorescence intensity from BSL (p = 0.028). PD-L1 expression increased in OT biopsies in both studies. In S1, from week 4, a moderate expansion of activated CD8 T cells (HLA-DR/Ki67) but not of CD4, was detected in PB at doses $>$ 60mg ($>$ 3.3 fold). Transient increases of several cytokines were seen in both studies with levels peaking within 24hrs. **Conclusions:** PK and PD results consistent with tumor inflammation and mechanism of action support that RO6958688 is the first tumor-targeted T cell bispecific to show intra-tumoral biological activity in pts with CEA+ solid tumors. Updated data will be presented. Clinical data are reported separately.

2550 Poster Session (Board #42), Mon, 8:00 AM-11:30 AM

Whole exome sequencing (WES) of multiple spatially distinct biopsies from single metastatic lesions to evaluate tumour heterogeneity and identify actionable truncal mutations (ATMs) in patients (pts) with advanced solid malignancies using a radiologically-guided single-pass percutaneous technique. *First Author: Valerie Heong, National University Hospital, Singapore, Singapore*

Background: Genomic profiling of single core biopsies (bx) are confounded intratumoral heterogeneity, resulting in sampling bias. We explored the use of a novel technique to obtain multiple bx from single metastatic lesion in pts to evaluate heterogeneity and identify therapeutic ATM. **Methods:** 15 pts (5 NSCLC; 3 ovarian; 2 colon, 2 uterine and 1 breast, cervix and HCC) with biopsiable lesions were identified. Using a single pass radiologically guided percutaneous bx technique, we obtained multiple spatially distinct core bx samples from a single metastatic lesion. Each bx underwent DNA extraction and WES using the NextSeq500. **Results:** Median of 4 core bx were obtained from each lesion. Complication rate utilizing this technique was 0%. 2 pts were omitted from analysis due to poor quality DNA with 13 pts successfully sequenced. In 1 pt, only 2 of 4 cores were successfully sequenced. The median amounts of total and non-synonymous variants were 137 (27-1286) and 66 (10-649) respectively. The median (range) filtered variants detected in 1/4, 2/4, 3/4, and 4/4 bx cores was 63(16-91)%, 5(1-65)%, 4(0-30)% and 26(0-63)% respectively, suggesting significant subclonal diversity within a single lesion. ATMs were identitified in 8/13 pts. 4/13 pts (31%) had no ATM across all 4 cores. 3 pts received therapy with inhibitors targeting ATMs. A pt with AKT1_E17K ATM received an AKT inhibitor with 21% tumour shrinkage and PFS 6.1 mths. 2 NSCLC pts harbouring an EGFR_T790M ATM were treated with an EGFRT790M specific TKI. 1 withdrew due to toxicity after 2mths and another had PFS $>$ 16.5 mths. Tumour mutational burden (TMB) was consistent across multiple bx from each lesion. A NSCLC pt with the highest TMB received a checkpoint inhibitor with ongoing $>$ 4 mths stable disease. **Conclusions:** Utilizing a single pass radiologically guided techniqueto obtainmultiple bx is feasible, safe and informative. This allows reconstruction of a tumour's subclonal genomic architecture, providing insights into mutational heterogeneity and help guide therapy.

2551 Poster Session (Board #43), Mon, 8:00 AM-11:30 AM

Axitinib plus crizotinib in patients with advanced solid tumors and metastatic renal cell carcinoma (mRCC): Preliminary phase 1b results. *First Author: M Dror Michaelson, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Axitinib (AX) is a tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR) and a standard treatment for mRCC. Upregulation of mesenchymal-epithelial transition factor (c-MET) is implicated in resistance to VEGFR-directed therapy. An ongoing ph Ib study (NCT01999972) evaluated the safety and efficacy of AX + crizotinib (CZ), a TKI of c-MET, anaplastic lymphoma kinase (ALK), and *ROS1*. **Methods:** mRCC patients (pts) with advanced solid tumors were treated with AX + CZ in a dose escalation phase (DESC). After determining maximum tolerated dose (MTD) (modified toxicity probability interval), mRCC pts were enrolled into 2 cohorts in a dose expansion phase (DEXP). Cohort 1 (C1) was treatment-naïve and C2 had 1–2 prior therapies. The primary objectives were to assess the tolerability of AX + CZ, to obtain the MTD, and to select the recommended phase II dose. **Results:** As of Aug 5, 2016, 24 pts were screened and 22 pts treated in the DESC. Pts received AX 3 mg twice daily (BID) + CZ 200 mg BID (n = 5); AX 3 mg BID + CZ 250 mg BID (n = 3); AX 5 mg BID + CZ 200 mg BID (n = 4); or AX 5 mg BID + CZ 250 mg BID (n = 10) in a median 4 (range 1–23) cycles. There were no cycle 1 dose-limiting toxicities. One pt discontinued due to an AX-related alanine aminotransferase increase. Fifteen (68.2%) pts experienced Grade 3–4 adverse events (AEs), none in $\geq$2 pts; 1 pt had a Grade 5 AE (disease progression). AX 5 mg BID + CZ 250 mg BID was established as the MTD. Most frequent AEs in the MTD group were fatigue (70.0%), nausea (70.0%) and diarrhea (60.0%). In the ongoing DEXP, 15 pts have been treated at the MTD (n = 11 in C1, and 4 C2). Response evaluation (RECIST) is ongoing, with 1 complete response (CR), 3 partial responses (PR) and 4 stable disease (SD) in 10 pts in C1, and 1 PR and 2 SD in 4 pts in C2. Overall, 10 (66.7%) pts experienced Grade 3–4 AEs and 1 pt had a Grade 5 AE (disease progression). Most frequent AEs ($\geq$60% pts) were nausea and diarrhea. **Conclusions:** We have identified AX 5 mg BID + CZ 250 mg BID as the MTD for combination therapy. This regimen has manageable toxicities and exhibits antitumor activity in treatment-naïve and pretreated mRCC. Further studies in VEGFR, c-MET, ALK and *ROS1* tumor types are warranted. Clinical trial information: NCT01999972.

2552 Poster Session (Board #44), Mon, 8:00 AM-11:30 AM

Safety and pharmacokinetics of crizotinib in patients (pts) with hepatic impairment (HI) and advanced cancer. *First Author: Anthony B. El-Khoueiry, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Crizotinib is a kinase inhibitor approved for treating ALK+ and ROS1+ advanced non-small cell lung cancer. Since crizotinib undergoes hepatic metabolism, this phase 1 study evaluated the pharmacokinetics (PK) and safety of crizotinib in pts with liver dysfunction. **Methods:** Crizotinib-naïve pts with different types of advanced cancer (ALK and ROS1 status unknown), ≥ 18 yr old, and ECOG PS 0–2 were enrolled. Pts were assigned to groups A1 – D based on liver function: normal (A1/A2) = both AST and TB ≤ the upper limit of normal (ULN); mild impairment (B) = AST > ULN and TB ≤ ULN, or TB > 1.0 – 1.5 × ULN; moderate (C1/C2) = TB > 1.5 – 3 × ULN; severe (D) = TB > 3 × ULN. Starting dose was based on HI. Pts in A1 and A2 were matched for weight, age, gender, race and ECOG PS to pts in B and C2, respectively. Study objectives included PK, safety and antitumor activity. **Results:** 88 pts were enrolled in A1 (n=11), A2 (n=15), B (n=20), C1 (n=10), C2 (n=16) and D (n=16). The geometric means of PK parameters at steady-state (Cycle 2 Day 1) are shown below. 75% of pts experienced treatment-related AEs (TRAEs), 9 (81.8%), 14 (93.3%), 15 (75.0%), 6 (60.0%), 11 (68.8%) and 11 (68.8%) in groups A1, A2, B, C1, C2 and D, respectively. 25% of pts experienced Grade 3/4 TRAEs, 3 (27.3%), 3 (20.0%), 3 (15.0%), 1 (10%), 7 (43.8%), 5 (31.3%) in groups A1, A2, B, C1, C2 and D, respectively. Three (3.4%) pts, all in A2, experienced treatment-related SAEs. Two pts (10%) in B and 1 (6.3%) in C2 required dose reductions for TRAEs. TRAEs associated with permanent discontinuation of treatment occurred in 1 pt in A1, A2, C2 and D. Overall, 3 pts had partial responses with durations of 96, 17 and 17 wks; 25 pts had stable disease. **Conclusions:** Systemic exposures of crizotinib in pts with mild HI receiving 250 BID and in pts with moderate HI receiving 200 mg BID are comparable with that of pts with normal hepatic function at 250 mg BID. All TRAEs were manageable across the various levels of hepatic function. Clinical trial information: NCT01576406.

Group	A1 (n=8)	A2 (n=9)	B (n=10)	C1 (n=7)	C2 (n=8)	D (n=6)
Dosing Regimen	250 mg BID	200 mg BID	250 mg BID	250 mg QD	200 mg BID	250 mg QD
AUC_{daily}, ng·h/mL	7107	5422	6476	2305	8108	4596
C_{max}, ng/mL	375.1	283.9	342.1	152.9	408.3	272.4

2553 Poster Session (Board #45), Mon, 8:00 AM-11:30 AM

Phase I study combining MLN8237 with nab-paclitaxel in patients with advanced solid malignancies. *First Author: Kian-Huat Lim, Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO*

Background: MLN8237 is a potent Aurora A kinase inhibitor which synergizes with paclitaxel in preclinical studies for various solid malignancies. **Methods:** We conducted a two-part, phase 1 study combining MLN8237 with nab-paclitaxel in patient with advanced, refractory solid malignancies (NCT01677559). The part 1, dose-escalation phase utilizes a standard a 3+3 design for determination of maximum tolerated dose (MTD) and dose limiting toxicities (DLTs), starting from nab-Paclitaxel 100mg/m2/week 3 out of a 4-week cycle, and MLN8237 20mg BID D1-3/week (denoted nP/M 100/20). In the part 2, dose-expansion cohort, patients with advanced pancreatic ductal adenocarcinoma (PDAC) or high grade neuroendocrine tumor (pNET) who progressed on standard chemotherapy were enrolled. **Results:** Totally 33 patients (17 in part 1 and 16 in part 2) with a median age of 61 were enrolled. In part 1, the most frequent treatment-related toxicities (all Grade/Grade 3-4) were: nausea (65%/6%), neutropenia (61%/18%), fatigue (47%/6%), anorexia (47%/0%), oral mucositis (53%/6%) and anemia (35%/18%). Two of 3 patients experienced a DLT at dose nP/M 100/50 (Grade 4 neutropenia; febrile neutropenia). No treatment-related mortality occurred. MTD was set at nP/M 100/40 for part 2. At data cutoff, totally 20 patients from the entire study were evaluable for treatment response. One patient with small cell lung cancer achieved partial response and is in cycle 29. Nine other patients (9/20, 45%) with the following tumor histology achieved stable disease after two cycles: 1 small cell lung cancer, 1 lung neuroendocrine carcinoma, 1 lung squamous cell carcinoma, 1 PDAC and 5 high grade pNET (range: 3 and ongoing ~ 18 cycles). **Conclusions:** MLN8237 plus nab-paclitaxel has manageable side effect profile with very promising activity in tumors with high grade neuroendocrine features, warranting further testing. Exploratory studies on pharmacodynamic markers are ongoing. Clinical trial information: NCT01677559.

2554 Poster Session (Board #46), Mon, 8:00 AM-11:30 AM

Final report of a phase I study of 2-hydroxyoleic acid (2OHOA) a novel sphingomyelin synthase activator in patients (pt) with advanced solid tumors (AST) including recurrent high grade gliomas (rHGG). *First Author: Analia Azaro, Medical Oncology Department Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain*

Background: 2OHOA is an orally bioavailable, first-in-class synthetic hydroxylated fatty acid, that activates SGMS1 and modulates the lipid content of cancer cell membranes. This regulates the localization of key signaling proteins, including Ras and PKC at the plasma membrane, leading to inactivation of Ras/MAPK, PI3K/Akt and PKC/cyclin/CDK signaling pathways. A dose escalation (DE) and partial expansion cohorts (EC) results of the phase 1 study have previously been reported. We now present the final results of the study. **Methods:** 2OHOA was evaluated in a 3+3 DE design (7 cohorts from 500mg/d to 16000mg/d) and 2 EC at 4000mg TID in 21 days cycles. PK profiles were determined after single dose (fasted [D-7] or fed [D1]) and multiple doses (fed [D21]) during DE phase and only on D1 throughout EC.Safety assessments were based on CTCAEv4.Tumor response was measured by RECIST and RANO every 6 weeks. **Results:** Overall 54 pt (DE: 32 pt; 21AST/11rHGG; EC: 22 pt; 12 AST/10 rHGG) were treated (median age 60, range 19-78 years). During the EC the most common treatment related G1-G2 toxicities were diarrhea (n = 13;11pt),nausea (n = 7;6pt), ALT increase (n = 6;4pt), pruritus in throat (4pt), fatigue (4pt) and vomiting (3pt). No G3-G4 toxicities or DLTs were reported confirming the MTD from the DE at 4g TID. Food intake did not alter oral 2OHOA bioavailability. Steady state was already achieved at D8. Power model showed dose proportionality in terms of AUC and Cmax, after single and multiple BID dosing. Average t1/2 ranged from1-2h to 8-12h with delayed Tmax and longer half-lives at higher doses. One glioblastoma (GBM) pt had sustained partial response (> 2,5 years) and 4rHGG pt (3 GBM) achieved stable disease for at least 6 months. They had previously received 2 lines of treatment without bevacizumab. Tumor markers were measured and will be presented. **Conclusions:** 2OHOA is well tolerated at the P2RD of 4000mg TID PO daily. The preliminary antitumor activity including a sustained PR in heavy pretreated rHGG pt warrants further investigation in a Ph2 study Clinical trial information: NCT01792310.

2555 Poster Session (Board #47), Mon, 8:00 AM-11:30 AM

Phase I study of the combination of balixafortide (CXCR4 inhibitor) and eribulin in HER2-negative metastatic breast cancer (MBC) patients (pts). *First Author: Marta Gil-Martin, Institut Català D'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain*

Background: Balixafortide (POL6326) is a cyclic peptide and a potent, selective antagonist of the chemokine receptor CXCR4. Evidence suggests that CXCR4 inhibition interferes with the tumor-protective microenvironment and sensitizes tumor cells to chemotherapy. The combination of balixafortide (B) and eribulin (E) was safe with early signs of efficacy in the dose escalation part of this study. **Methods:** The expanded cohort of thisopen label phase I study was designed to assess the anti-tumor activity, safety and pharmacokinetics of the addition of the recommended phase 2 dose (RP2D) of B to E in pts with MBC and with any CXCR4 expression level at the tumor site. Patients received E (1.4 mg/m^2) on days 2 and 9, flanked by B (5.5 mg/kg) on days 1-3, and 8-10 of 21-day cycles. **Results:** 24 pts with relapsed MBC (median age 59 [33-82]) were enrolled in the expanded cohort. Median number of prior chemotherapies for MBC was 2 (range 1-3). 20/24 (83%) pts were ER and/or PR positive; 3/24 (13%) pts had TNBC. Objective response rate (ORR) was 33%. 8/24 (33%) pts achieved a partial response and 4/24 (17%) pts had meaningful (≥ 6 months) stable disease for a Clinical Benefit Ratio of 50%. Median duration of treatment was 15.3 weeks (range 5-40) with 11 pts still on treatment. The most common Gr 3-4 adverse events were neutropenia (9/24, 38%) and leucopenia (3/24, 13%); 2 pts had febrile neutropenia and 1 patient died from sepsis. 15/24 (63%) pts experienced histamine-like infusion reactions related to B that were manageable with anti-histamines. **Conclusions:** The therapeutic activity of this treatment regimen appears promising with an ORR of 33% in patients with advanced MBC. B (5.5 mg/kg) can be combined safely with E (1.4 mg/m^2) and the safety profile resembles E monotherapy as previously reported. This is the first study of the treatment combination of E with B in relapsed MBC pts. Further confirmatory studies are being considered. Clinical trial information: NCT01837095.

2556 Poster Session (Board #48), Mon, 8:00 AM-11:30 AM

A multicenter phase I trial of the DNA-dependent protein kinase (DNA-PK) inhibitor M3814 in patients with solid tumors. *First Author: Mark van Bussel, The Netherlands Cancer Institute (NKI), Amsterdam, Netherlands*

Background: Agents that generate breaks in DNA are frequently used as cancer therapeutics. These agents induce different forms of DNA damage including double-strand breaks (DSBs), which are the most lethal if left unrepaired. M3814 targets tumor cell growth and survival by inhibiting DNA-PK, which is part of a critical DSB DNA damage repair mechanism. The purpose of the phase I, first in man trial was to evaluate the dose-limiting toxicity (DLT), establish a recommended phase II dose (RP2D), and assess the pharmacokinetic (PK) profile and single-agent clinical activity of M3814. **Methods:** Patients (pts) with potential aberrations in the DNA-damage and repair systemwere included. A standard 3+3 design was implemented with a starting dose of M3814 of 100 mg once daily, determined based on non-clinical safety. M3814 was given continuously and DLT was evaluated after 3 weeks. Throughout the trial rich PK sampling was taken. Tumor evaluation was performed every second cycle and treatment continued until progression, unacceptable toxicity, pt wish, or physician decision. **Results:** A total of 25 pts were enrolled at 6 dose levels (DL). Three pts were enrolled per DL, except at 300 and 400 mg BID where 9 and 4 pts were enrolled, respectively. At 300 mg BID one DLT (several low grade adverse events [AEs] lasting $>$ 1 week) was seen. No DLTs were observed at 400 mg BID, which was declared as the RP2D; further dose escalation was not possible due to an impurity in the drug. An additional 6 pts were included at the RP2D. The most frequent AEs were nausea, vomiting, decreased appetite, constipation, diarrhea, pyrexia, fatigue, and rash, all seen in $>$ 20% of pts. No pts discontinued due to AE and no grade 4 AEs were reported. Six pts (20%) had stable disease for at least 18 weeks; no pt had a partial remission. PK analysis demonstrated high variability of exposure with a tendency for skin rash in pts with the highest exposure. **Conclusions:** M3814 was found to be safe and tolerable at doses up to 400 mg BID, with limited single-agent activity in the studied population. Clinical evaluation of M3814 is ongoing in combination with radiotherapy as well as chemo-radiotherapy and planned in combination with chemotherapy. Clinical trial information: NCT02316197.

2557 Poster Session (Board #49), Mon, 8:00 AM-11:30 AM

A phase II study of copper-depletion using tetrathiomolybdate (TM) in patients (pts) with breast cancer (BC) at high risk for recurrence: Updated results. *First Author: Sheena Sahota, New York Presbyterian Hospital, Weill Cornell Medical College, New York, NY*

Background: The tumor microenvironment (TME) plays a critical role in the spread of tumors. Bone marrow derived VEGFR2$^+$endothelial progenitor cells (EPCs) and copper-dependent lysyl oxidase (LOX) are key in tumor progression. We hypothesized TM-associated copper depletion inhibits tumor metastases by reducing the number of EPCs and other copper dependent (CD) processes in the pre-metastatic niche. These results are an update with longer follow-up. **Methods:** Phase II study of BC pts at high risk for recurrence, defined as node+ triple negative (TNBC), stage 3 and 4 with no evidence of disease (NED) were enrolled on a trial of CD with TM. Ceruloplasmin (Cp) levels were maintained between 8-16 mg/dl for two years with an extension phase or until relapse. The primary endpoint was change in EPCs measured by flow cytometry before and during treatment. Secondary endpoints included tolerability, safety, PFS and LOXL-2 levels. **Results:** 75 pts received 2650 cycles of TM on primary and extension study. The median age is 51 years (range 29-66). Forty-five pts have stage 2/3 BC and 30 with stage 4 NED. TNBC pts were 48% and 40% of pts are stage 4 NED. Median Cp level decreased from 28 to 16 ($p < 0.0001$) after one cycle. Copper depletion was most efficient in TNBC where Cp levels dropped from 23.5 to 13 after one cycle. TM was well tolerated with grade 3/4 toxicities including: reversible neutropenia (2.3%), febrile neutropenia (0.04%), fatigue (0.2%). Five-year analysis showed a decrease in EPC's ($p = 0.004$) and LOXL-2 ($p < 0.001$). At a median follow-up of 6.9 years, the EFS for 75 pts is 75.6%. PFS for 36 pts with TNBC is 79.2%. EFS for stage 2/3 TNBC is 90% and for stage IV TNBC is 66.7%. **Conclusions:** TM is safe, well tolerated and appears to affect multiple components of the TME creating an inhospitable environment for tumor progression especially in high risk patients such as TNBC. Randomized trials are warranted, especially in patients at high risk for relapse. Clinical trial information: UL1TR000457.

2558 Poster Session (Board #50), Mon, 8:00 AM-11:30 AM

Phase I study of indenoisoquinolines LMP776 in adults with relapsed solid tumors and lymphomas. *First Author: Geraldine Helen O'Sullivan Coyne, Early Clinical Trials Development Program, DCTD, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Indenoisoquinolines (ID) are non-camptothecin inhibitors of topoisomerase (TOP1) identified following a COMPARE analysis of the National Cancer Institute's (NCI) in vitro anticancer drug discovery screen. IDs have improved characteristics over camptothecin top1 inhibitors, with better chemical stability (lacking the labile hydroxylactone E-ring) producing stable DNA breaks that are resistant to reversal of the trapped DNA-TOP1 cleavage complex and at different DNA sequence sites to camptothecins (Kohlhagen *et al*. Mol Pharmacol. 2005). IDs have shown more activity against camptothecin-resistant cell lines and mouse models, as well as in cells overexpressing the ATP-binding cassette (ABC) transporters, and multidrug resistance (MDR-1/ABCB1) genes. A parallel first-in-human Phase I study conducted at the NCI of LMP400 in patients with refractory solid tumors and lymphomas showed this molecule to be well tolerated (Kummar *et al*, Cancer Chemother Pharmacol. 2016). A trial of LMP776 (NSC725776), has completed accrual. Primary Objectives: define the maximum tolerated dose (MTD) of LMP776 and the dose-limiting toxicities (DLTs). **Methods:** Phase I trial using Design 4 of the Simon accelerated titration designs (Simon et al. JNCI, 1997), with doses escalated based on toxicity during cycle 1. LMP776 was administered via central line QD over 1 hour on days 1–5 q 28-days. Response is defined by RECIST 1.1 on CT. **Results:** 32 of 34 patients (pts) were evaluable for toxicity and response. Enrollment was expanded at dose level (DL) 2 to 6 pts due to a hypocalcemia DLT, with subsequent enrollment on a 3+3 design. MTD was established at DL7 (12mg/m^2, DLT myelosuppression). Common Grade 3/4 adverse events by CTCAE v.4 included anemia (5 pts, 15%), thrombocytopenia (5), lymphopenia (5) and neutropenia (3 pts, 9%). 12 (37%) pts experienced stable disease (SD), with a median of 4 cycles of treatment (range 2-9). 10 (30%) pts with SD remained on study for $\geq$4 months, with 4 pts on study $\geq$6 months. **Conclusions:** LMP776 is overall well tolerated. Explorative correlatives and additional trials are being considered. Clinical trial information: NCT01051635.

2559 Poster Session (Board #51), Mon, 8:00 AM-11:30 AM

An open-label expanded-access study to evaluate the safety, tolerability, and pharmacokinetics of trifluridine/tipiracil in patients with advanced solid tumors and hepatic impairment. *First Author: Wasif M. Saif, Tufts University School of Medicine, Tufts Cancer Center, Boston, MA*

Background: The Phase 3 RECOURSE study showed that trifluridine/tipiracil (FTD/TPI) was effective in the treatment of refractory metastatic colorectal cancer (Mayer et al. N Engl J Med 2015;372:1909-19). A Phase 1 open-label study evaluated the safety and pharmacokinetics of FTD/TPI in patients with advanced solid tumors and varying degrees of hepatic impairment to inform dosing recommendations for these patients. **Methods:** Patients aged $\geq$18 years with advanced solid tumors, an Eastern Cooperative Oncology Group performance status $\leq$2, normal hepatic function, and mild, moderate, or severe impaired hepatic function according to the National Cancer Institute criteria were enrolled. Patients received FTD/TPI 35 mg/m^2 orally twice daily on days 1-5 and days 8-12 of each 28-day cycle, except for those with severe impaired hepatic function (dose was to be determined). **Results:** 24 patients were enrolled to normal (n=8), mild (n=10), and moderate (n=6) groups. Study enrollment was stopped as 5/6 patients in the moderate group experienced elevated bilirubin levels (grade $\geq$3). The other baseline characteristics were similar across groups. Overall, 12 patients (50%) had at least 1 adverse event leading to study discontinuation: 2 in normal, 5 in mild, and 5 in the moderate hepatic impairment groups. Pharmacokinetic results are summarized in the table. **Conclusions:** The exposure to FTD or TPI was not increased by hepatic impairment and the patients who experienced grade 3 and 4 increased total bilirubin were not overexposed to FTD or TPI. Clinical trial information: NCT02301104.

FTD/TPI pharmacokinetic parameters (mean ± SD)		FTD			TPI		
		Normal	Mild	Moderate	Normal	Mild	Moderate
Day 1	$AUC_{0\text{-}inf}$, ng·hr/mL	6873 ± 2407	6324 ± 2208	4594 ± 1586	421 ± 208	272 ± 120	591 ± 419
Day 12	AUC_{tau}, ng·hr/mL	20392 ± 5609	17489 ± 7379	15406 ± 1244	335 ± 230	305 ± 112	495 ± 288

$AUC_{0\text{-}inf}$, area under the plasma concentration–time curve from time 0 to infinity; AUC_{tau}, area under the plasma concentration–time curve from time 0 to the end of dosing interval for Day 12 only; SD, standard deviation.

Sponsorship: Taiho Oncology, Inc. **Editorial Assistance:** Complete HealthVizion.

2560 Poster Session (Board #52), Mon, 8:00 AM-11:30 AM

GMI-1271, a novel E-selectin antagonist, combined with induction chemotherapy in elderly patients with untreated AML. *First Author: Daniel J. DeAngelo, Dana-Farber Cancer Institute, Boston, MA*

Background: The outcomes for elderly patients (pts) with acute myeloid leukemia (AML) remain poor, therefore newer and less toxic therapies are urgently needed. The binding of E-selectin (E-sel), an adhesion molecule expressed in the bone marrow, to the leukemic cell surface activates survival pathways and promotes chemotherapy resistance. GMI-1271, a novel E-sel antagonist, enhances chemotherapy responses and protects from common toxicities in preclinical models (Becker ASH 2013; Winkler ASH 2013 and 2014). We report interim Phase 2 data for GMI-1271 plus chemotherapy in elderly untreated pts with AML. **Methods:** Pts ≥ 60 yrs with untreated AML, ECOG 0-2, and adequate renal and hepatic function were eligible. Prior treatment of MDS was allowed. GMI-1271 (10 mg/kg) was given 24 hrs prior, during and 48 hrs post induction with infusional cytarabine and idarubicin (7 +3). Safety, tolerability, and anti-leukemia activity were assessed. Two cycles of induction were allowed and responders could receive consolidation with GMI-1271 plus intermediate dose cytarabine. Dose-limiting toxicity (DLT), defined as myelosuppression in the absence of disease or related Grade 3 (Gr) non-hematologic toxicity beyond day 42, was assessed in the first 3 pts. **Results:** 24 pts have been enrolled to date and 17 are evaluable for response. The median age was 68 years (range, 60-79) with 58% male pts, 50% secondary AML (sAML) pts and 25% with high-risk cytogenetics (by SWOG). The first 3 pts had no DLT, allowing enrollment to proceed. Common Gr 3/4 AEs included febrile neutropenia (47%), pneumonia (20%), pulmonary edema (13%) and non-fatal respiratory failure (13%). 2 pts died of sepsis within 60 days. The remission rate (CR/CRi) was 12/17 (71%). CR/CRi rate was 75% for pts with *de novo*disease and 67% for pts with sAML. E-sel ligand was expressed at high levels on blasts in the majority of pts. **Conclusions:** The addition of GMI-1271 to anthracycline-based induction chemotherapy in untreated elderly pts with AML demonstrates a high remission rate with acceptable side effect profile and low induction mortality. This study compares favorably to previous studies (Lancet, ASCO 2016). A randomized trial is being planned. Clinical trial information: NCT02306291.

2561 Poster Session (Board #53), Mon, 8:00 AM-11:30 AM

A phase Ib/II clinical trial of a novel oxygen therapeutic in chemoradiation of glioblastoma. *First Author: Evan C. Unger, NuvOx Pharma, Tucson, AZ*

Background: Tumor hypoxia limits the response of glioblastoma multiforme (GBM) to radiotherapy (RT) and chemotherapy (temozolomide[TMZ]). Additionally, patient biomarkers are strong predictors of responsiveness to TMZ. The purpose of this study is to evaluate the use of a novel oxygen therapeutic, dodecafluoropentane emulsion (DDFPe), in chemoradiation treatment of GBM and stratify the results based on predicted TMZ response. **Methods:** 11 adult GBM patients have been enrolled. Patients were administered DDFPe via IV infusion (2% w/vol at doses of 0.05, 0.1 or 0.17 mL/kg) an hour prior to each 2 Gy fraction of RT (30 fractions over 6-weeks) with supplemental oxygen. Patients also received standard concurrent and adjuvant TMZ. To confirm tumor re-oxygenation, patients underwent TOLD MRI before and after DDFPe administration. Archived tumor specimens were studied with GliomaSTRAT assay for methylated genes predictive of response. Patients were also studied with serial MRI scans per standard of care and followed for survival. **Results:** There were minimal acute adverse events related to DDFPe administration. One patient at each of dose levels 0.1 and 0.17 mL/kg developed symptomatic radiation necrosis, which was judged to be related to DDFPe. Enrollment has continued at the 0.1 mL/kg dose without additional significant DDFPe-related toxicity. TOLD MRI showed significant decrease in $T_1$of tumor tissue consistent with tumor re-oxygenation (p=0.015) with no significant change in oxygenation of normal brain tissue. Historically, the average overall survival for GBM patients, for both TMZ responders and non-responders, is about 14.6 months. The progress chart for patient overall survival is listed below, 4 patients have died. All other patients are alive. **Conclusions:** DDFPe is a promising oxygen therapeutic for reversing tumor hypoxia. A Phase II study is being planned to assess its effectiveness. Clinical trial information: NCT02189109.

Progress chart: Phase Ib GBM trial.

Patient Number	Age/Sex	DDFPe (mL/kg)	TMZ responder	Overall Survival (months)
1	48-M	0.05	no	21*
2	65-F	0.1	no	19*
3	48-F	0.17	yes	21.5
4	68-M	0.1	yes	15
5	47-M	0.1	no	14
6	30-M	0.1	no	12
7	58-F	0.1	no	8.5*
8	60-M	0.1	no	5*#
9	39-M	0.1	no	9
10	47-F	0.1	yes	8
11	60-M	0.1	no	6.5

*patient deceased, # cause of death: pneumonia

2562 Poster Session (Board #54), Mon, 8:00 AM-11:30 AM

Patterns of failure on Ga PSMA (GaPSMA) and F18 FDG (FDG) PET CT in a prospective phase 2 trial of ^{177}Lu DKFZ PSMA 617 (LuPSMA) in men with castrate resistant metastatic prostate cancer (mCRPC). *First Author: Anthony M. Joshua, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: LuPSMA is emerging as an effective therapy in mCRPC, with retrospective series reporting high PSA response rates in men undergoing treatment (tx). However, not all men have prolonged tx responses. We report the prospective imaging (GaPSMA/FDG) and PSA response of men who progress biochemically during LuPSMA tx to gain information on characteristics of failure patterns, to determine optimal future tx strategies. **Methods:** Men with mCRPC, who had failed androgen blockade, failed/ineligible/refused chemotherapy, with GaPSMA positive disease were enrolled in a prospective phase 2 trial. All men underwent LuPSMA therapy 6-8Gbq, 4 doses at 6 weekly intervals. Imaging with FDG, GaPSMA, bone scan and CT scans was at screening, at subsequent PSA rise, or 3 months post completion of 4 cycles of therapy. **Results:** 14 men met eligibility criteria and enrolled. 4/14 (28%) men had progressive disease (no PSA response). 10/14 (72%) PSA reduced by a mean 56% .Overall 9/14 (64%) men had >30% decline in PSA, and 5/15(36%) >50% reduction in PSA. 7/15 men were reimaged with GaPSMA, FDG at biochemical failure or 3/12 post tx completion. Imaging revealed 4 distinct patterns (P) of progression. **Conclusions:** PSMA acts as both target for radionuclide therapy and biomarker for effective tx response. PSMA and FDG imaging at PSA failure following or during LU PSMA therapy identifies phenotypic patterns of failure that have implications for determining next best tx options in men with mCRPC.

	Finding	Significance for management
P 1	Progression with diffuse, widespread low PSMA avid disease (SUV max 2-7 all sites)	Progressive non PSMA avid phenotype. change tx
P 2	Marked tx response at all initial sites. Solitary PSMA -/FDG+ lesion	Treat solitary site of PSMA – disease with focal tx. Continue treating with Lu PSMA
P 3	Marked reduction in PSMA + sites, but persistent PSMA activity (SUV max >10)	Disease amenable to tx with LuPSMA. Consider continuing beyond 4 doses of Lu PSMA.
P4	Marked reduction in PSMA /FDG at all sites (>75%). Low volume residual activity only	Cease tx with Lu PSMA until PSA rise / repeat PSMA shows progression, then retreat with Lu PSMA.

2563 Poster Session (Board #55), Mon, 8:00 AM-11:30 AM

Pharmaco-kinetics/dynamics (PK/PD) evaluation and individual patient cross-over studies with growth trajectory assessment to adaptively develop ilorasertib. *First Author: Michael L. Maitland, Inova Schar Cancer Institute, Falls Church, VA*

Background: We evaluated PK/PD of the AURK B/VEGFR2 inhibitor ilorasertib. To detect activity in CDKN2A-deficient tumors, we measured changes-in-tumor-burden by CT-volume before, during, and after discontinuation of therapy. **Methods:** Study 1: open-label, dose-escalation, phase 1 in 58 patients (pts) with advanced solid tumors. Arms I, II, and III assigned: 23 pts (10–180 mg oral QD), 28 pts (40–340 mg oral BID), and 7 pts (8–32 mg i.v. QD), to ilorasertib monotherapy Days 1, 8, and 15 every 28 days. We evaluated PK/PD for validated biomarkers: change-in-diastolic blood pressure (ΔDBP), change-in-plasma [PlGF] (ΔPlGF), and change-in phosphorylated histone H3 (Δ%pHH3) in skin biopsies. Study 2: open-label trial, of 10 solid tumor pts with CLIA-lab-detected *CDKN2A* disruption. Pts received ilorasertib 250 mg oral BID on same schedule. On CT images collected prior to screening, and ~ study days -7, 49, and 98 individual lesion volumes were determined by central lab semi-automated segmentation algorithms on DICOM files. Pts who tolerated ilorasertib with RECIST-stable disease at day 98 discontinued ilorasertib for 42 days and underwent re-imaging before restarting ilorasertib. **Results:** Study 1: the DLTs and frequent adverse events reflected VEGFR2 inhibition. PK/PD analysis showed peak VEGFR2 inhibition on ΔDBP and ΔPlGF at lower systemic concentrations than for peak AURKB-inhibition detected with Δ%pHH3. Two pts in Arm II had partial response; one had homozygous deletion of *CDKN2A*by FISH. Pre-clinically the CDKN2A-deficient cell lines (OVCAR5, MDA MB 231, A549) were among the most ilorasertib-sensitive. At time of submission, Study II enrolled 10 pts, with 5 evaluable for longitudinal tumor burden assessments. Three pts had sustained negative growth trajectories after ilorasertib therapy; one of these had positive growth after cessation of treatment but restabilization of disease after restarting ilorasertib. **Conclusions:** The development plan adapted to the in-human PK/PD assessment. We prospectively conducted individual change-in-tumor burden cross-over studies to assess clinically the sensitivity of CDKN2A-deficient tumors. Clinical trial information: NCT02540876 and NCT01110486.

2564 Poster Session (Board #56), Mon, 8:00 AM-11:30 AM

The utility of genomics and functional imaging to predict irinotecan pharmacokinetics and pharmacodynamics: The PREDICT IR study. *First Author: Michael Michael, Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: BSA-based dosing of Irinotecan (IR), does not account for its pharmacokinetic (PK) and pharmacodynamic (PD) variability. Given IR's unique metabolism, functional hepatic nuclear imaging (HNI) with probes for hepatic transporters correlated with its PK. This study further evaluated the utility of HNI combined with extensive excretory/metabolic/PD pharmacogenomics (PG) to predict IR PK and PD in patients (pts) treated with FOLFIRI to enable dose individualization. **Methods:** Eligible pts had advanced colorectal cancer, suitable for $1^{st}/2^{nd}$-line FOLFIRI± Bevacizumab. Pts had blood analyzed by Affymetrix DMET™ Plus Array and additional SNPs were genotyped. For HNI, pts were given IV 250MBq ^{99m}Tc-IDA and imaging data analyzed for hepatic extraction/excretion parameters (clearance [CL], 1hour retention [1hRET], deconvulutional CL [DeCL], hepatic extraction fraction [HEF]). Pts treated with chemotherapy, q2-weekly, and restaged after 4 cycles. Blood taken for IR and metabolite (SN38, SN38G) analysis on day 1 cycle 1, PK parameters derived by non-compartmental analysis. Statistical correlations were evaluated between (i) IDA HNI and (2) PGs, with IR PK, toxicity, objective response (ORR) and progression-free survival (PFS). **Results:** 32 pts analysed, 31 pts completed 4 cycles. (1) PK correlates: (a) HNI CL and 1hRET with SN38 Metabolic CL, ($P = 0.04$) and (b) HNI DeCL with IR $AUC_{(0-\infty)}$ ($P = 0.04$). (2) Grade 3+ diarrhea ($N = 4$, 13%) predicted by SN38 $AUC_{(0-\infty)}$ and Metabolic CL ($P = 0.04$), and gene variants for SCL22A2 and -28A3, ABCC2, UGT2B17, CYP2C18 and DPYD ($P < 0.05$). (3) Grade 3+ neutropenia ($N = 9$, 28%) predicted by SN38 PK exposure ($P < 0.02$), HNI CL and 1hRET ($P < 0.0001$) and variants for SLC7A7-, SLC22A2-, CHST1-, UGT1A1-, -2B7, ABCB1. (4) ORR ($N = 6$, 20%) predicted by Methylene tetrahydrofolate reductase (MTHFR) 677C > T ($P = 0.002$), SN38 exposure ($P < 0.003$), and variants in metabolic/transporter genes ($P < 0.05$). (5) PFS by SN38 PK exposure, MTHFR 677C > T, HNI CL, HNI HEF and variants in PK genes ($P < 0.05$). **Conclusions:** Hepatic functional imaging with extensive pharmacogenomics correlate with Irinotecan PK and PD enabling the development of nomograms to individualize dosing. Clinical trial information: ACTRN12610000898055.

2565 Poster Session (Board #57), Mon, 8:00 AM-11:30 AM

A phase I study of the tolerability, safety, pharmacokinetics and preliminary antitumor effects of KBP-5209, a novel pan-HER inhibitor, in patients with advanced solid tumors. *First Author: Sarina Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: KBP-5209 is a novel potent and irreversible inhibitor of tyrosine kinases of the human epidermal growth factor receptor (EGFR) family that preclinically has demonstrated potent antitumor activities in esophageal and gastric cancers and NSCLC. **Methods:** This first-in-human study (NCT02442414) was conducted to determine tolerability, safety, pharmacokinetics and antitumor activity of KBP-5209 administered QD or BID in patients (pts) with advanced solid tumors. Dose escalation (DE) initially was based on a modified accelerated titration plan and then shifted to a standard 3+3 design. The starting dose was 20 mg QD. Eligible patients were adults with advanced, refractory solid tumors with ECOG PS < 1. A cycle was 28 days. DLTs were evaluated for during the first cycle. DE enriched for patients with tumors having molecular alterations in EGFR or HER2/3. Dose escalation continues so dose expansion has not initiated. **Results:** As of 26 Nov, 2016, 23 pts (15 females, 8 males) are a part of the evaluable population with a median age 57 (37-79) treated at doses of 20mg (1), 40mg (3), 60mg (7), 70mg (4), 80mg (6) QD and 20mg BID (2).Tumor types included breast (6), CRC (4), ovarian (3), H&N (2), sarcoma (2), and NSCLC, sinus, gastric, gallbladder, pancreas, CUP tumor (1 each). Tumor genetic profiles were available for 20 pts. DLTs were G3 diarrhea, nausea, and vomiting, which occurred in 1 pt at 80mg QD and G3 Diarrhea, occurring in 1pt at 80mg QD. The most common adverse events related to study drug were diarrhea (60.9%), nausea (47.8%), vomiting (43.5%), fatigue (21.7%), decreased appetite (17.4%) and lipase increased (17.4%). Serious adverse events (SAEs**)** related to study drug were reported in 4pts: diarrhea (1 pt, 70mg QD; 1pt, 80mg QD), nausea and vomiting (1pt, 70mg QD), and diarrhea, nausea and vomiting (1 pt, 80mg QD). Stable disease has been observed in 7pts up to 24 weeks, in which 2/28 pts (7%) achieved tumor shrinkage. **Conclusions:** Based on the present data, KBP-5209 has been well tolerated with a safety profile similar to other pan-HER inhibitors. For QD dosing, maximum tolerated dose has been identified as 70mg QD. The BID dose escalation continues. Clinical trial information: NCT02442414.

2566 Poster Session (Board #58), Mon, 8:00 AM-11:30 AM

Population pharmacokinetics of durvalumab and fixed dosing regimens in patients with advanced solid tumors. *First Author: Paul Baverel, MedImmune, Cambridge, United Kingdom*

Background: Durvalumab is a human monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 and CD80. The objectives of this analysis were to develop a population pharmacokinetics (PK) model of durvalumab, to quantitate the effect of patient/disease characteristics on PK, and to compare weight (WT)-based versus fixed dosing regimens. **Methods:** Data were pooled from two studies: Study 1108 (Phase 1/2; various tumor types) and ATLANTIC (Phase 2; NSCLC). A total of 1324 patients provided data following 0.1 to 20 mg/kg IV durvalumab. The population PK was performed using a non-linear mixed effects modeling approach in NONMEM software. The impact of demographics, clinical indices, and biomarkers on PK was explored. **Results:** Durvalumab PK was best described using a 2-compartment model with both linear and non-linear clearances. The mean (between-patient variability) linear clearance (CL) and central volume of distribution (V_1) were 226 mL/day (~29%) and 3.51 L (~21%), respectively. Although population PK analysis identified a few statistically significant covariates (WT, sex, CrCL, post-baseline ADA, ECOG performance status, LDH, sPDL1 levels, tumor type, and albumin), none were found to be clinically relevant (effect on PK parameters < 30%), indicating no need for dose adjustment. Simulations indicated similar overall PK exposures following WT-based (10 mg/kg Q2W) and fixed dosing regimens (1500 mg Q4W or 750 mg Q2W); with all regimens expected to maintain target trough exposure of ~50 μg/mL in ≥95% patients. In a post-hoc analysis, durvalumab clearance was found to decrease slightly over time, with a mean maximal reduction from baseline value of 15.5%. The decrease in CL was associated with tumor shrinkage, decreased LDH, increased albumin and decreased neutrophil to lymphocyte ratio. The small decrease in CL was not considered relevant to PK exposure or dosing. **Conclusions:** A population PK model of durvalumab was developed and validated. No dose adjustments were needed based on any patient or disease characteristics. The analysis demonstrated the feasibility of switching to a fixed dose regimen. Clinical trial information: NCT02087423 and NCT01693562.

2567 Poster Session (Board #59), Mon, 8:00 AM-11:30 AM

The potential clinical impact of pre-emptive screening of multiple polymorphisms in gene-encoding DPD on patients candidate for fluoropyrimidine based-chemotherapy: An experience of the Northern Italy Cancer Centre. *First Author: Francesco Iachetta, Medical Oncology Unit, Clinical Cancer Centre, Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia, Italy*

Background: Dihydropyrimidine dehydrogenase (DPD) is a key enzyme in the metabolism of fluorouracil. Deleterious polymorphisms in gene-encoding DPD (*DPYD*) results in a DPD deficiency that causes life-threatening toxicities when the standard dose of fluorouracil is used. DPYD*2A (IVS14+1G > A) is the most common single-nucleotide polymorphism (SNP) associated with critical DPD deficiency. At present, most of the evidence supports screening for at least 3 SNPs (DPYD*2A, c.2846 A > T, c.1679T > G). The aim of this study is to confirm that the detection of additional polymorphisms of DPYD could enhance prevention of fluoropyrimidine toxicity. **Methods:** In 2011, we began to screen DPYD*2A in patients candidate for fluoropyrimidine based-chemotherapy. As the first step of the evaluation, we selected all cases of DPYD*2A wild type, from 2011 to 2012, who developed CTC-NCI-V.3 toxicity ≥ G3. In these patients, we researched the other 3 SNPs (c.2846 A > T, c.1679T > G, c.2194C > A). Mutational status was analyzed with real Time PCR. **Results:** From 2011 to 2016 we pre-emptively screened DPD deficiency in 1,863 patients and 32 subjects (1.6%), with results mutated for DPYD*2A. As the first step of the evaluation, 548 subjects were assessed from 2011 to 2012. We found 7 patients who were carriers of the DPYD*2A mutation (1.27%). Of the 541 wild type cases, 114 presented toxicities ≥ G3. In this subgroup, 22 patients (19%) proved to be mutated for the other SNPs of DPYP, as reported in the table below. **Conclusions:** Preliminary data show that in 22 (19%) of 114 patients who presented severe toxicity which was not correlated with DPYD*2A, we found other polymorphisms of gene encoding DPD. Out of the 3 SNPs evaluated, c.2194 C > A proved to be the most frequent, although it is the polymorphism that is least known and least studied. Such results suggest that the evaluation of additional polymorphisms could enhance the prevention of fluoropyrimidine toxicity. The results are expected to be clarified further in the second step, which is ongoing.

SNPs	No. of pts	%
c.2846 A > T	1	0.88
c.1679T > G	2	1.75
c.2194C > A	19	16.6
Total	22	19.3

2568 Poster Session (Board #60), Mon, 8:00 AM-11:30 AM

Exposure-efficacy and safety analysis of durvalumab in patients with urothelial carcinoma (UC) and other solid tumors. *First Author: Chaoyu Jin, MedImmune, Mountain View, CA*

Background: Durvalumab is a human monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 and CD-80. The objective of this analysis was to evaluate the relationship between durvalumab PK exposure with efficacy and safety following 10 mg/kg Q2W durvalumab. **Methods:** Data from Study 1108 (Phase 1/2; all tumor types) and ATLANTIC (Phase 2; NSCLC) were used for exposure-safety analysis for Study 1108 UC cohort, Study 1108 all patients and ATLANTIC patients, respectively, whereas the exposure-efficacy analysis was performed using data from Study 1108 UC cohort. The observed PK exposure metrics included PK concentrations after the first, second or steady state doses. Efficacy endpoints used were objective response rate (ORR) and best percentage change in target lesion from baseline per BICR assessment. Safety endpoints included Grade 3+ AE (any AE, drug-related AE, AESI, and drug-related AESI) and AE leading to treatment discontinuation. **Results:** Overall, no association of PK exposure with efficacy or safety was observed. Distribution of PK metrics were similar between responders and non-responders. The probability of objective response was similar in all quartiles of exposure (p-value ranged from 0.37 to 0.67; n = 96) with no obvious trends between PK exposures and change in tumor size. For Grade 3+ AE (all types) and AE leading to treatment discontinuation, higher PK exposure was not associated with an increased risk of AE (p-value ranged from < 0.00005 to 0.88; n = 158, 929 and 434 for 1108 UC cohort, 1108 all patients and ATLANTIC all patients, respectively). A few inverse trends were observed, likely due to confounding effect of ECOG or albumin since covariate analysis demonstrated that both variables correlated with PK and AEs. In addition, the association of ECOG and albumin versus PK exposure were also observed in the population PK modeling. **Conclusions:** The exposure-efficacy and exposure-safety analyses suggested that 10 mg/kg IV Q2W regimen was an appropriate dose for durvalumab as single agent in UC patients. Overall, no relationship of PK exposure with either the efficacy or safety was observed following 10 mg/kg IV Q2W regimen. Clinical trial information: NCT02087423 and NCT01693562.

2569 Poster Session (Board #61), Mon, 8:00 AM-11:30 AM

Vitamin K epoxide reductase complex subunit 1 (VKORC1): A pharmacogenomic predictor of response and survival in patients (pts) on triplet hepatic artery infusion (HAI) and intravenous cetuximab (IV-Cet) for initially unresectable liver metastases from colorectal cancer (uLM-CRC) (EU trial OPTILIV). *First Author: Francis Levi, Cancer Chronotherapy Unit, Warwick Medical School, Coventry, United Kingdom*

Background: The HAI of Irinotecan-Oxaliplatin-5-Fluorouracil (IFO) with IV-Cet achieved 29.7% complete uLM-CRC resections (R0+R1) and an overall median survival (OS) of 25.7 months in previously treated pts *(Lévi, Ann Oncol 2016)*. **Methods:** To identify pharmacogenomic predictors of outcomes, 207 single nucleotide polymorphisms (SNPs) from 34 pharmacology genes were analysed in blood mononuclear cells (ADME PGx, MassArray platform, Sequenom, USA). Relations between SNPs and tumor response, R0+R1, survival, and toxicities were tested using adjusted Mann Whitney, Fisher Exact, Log Rank tests and Hardy-Weinberg Equilibrium. **Results:** Pts (16F;36M; 33-76 yo; WHO performance status 0-1) received protocol treatment as 2nd (21 pts) or 3-4thline (31 pts). VKORC1 SNPs in promoter (rs9923231) and intron (rs9934438) were consistently associated with early and objective responses, and overall survival. For rs9923231, T/T (N = 8) as compared to C/T (N = 21) had greatest chance of achieving early response (50% vs 5%, p = 0.029) or 4-y survival (46% vs 0%, p = 0.006). VKORC1 SNPs also related to HA thrombosis (rs992331, T/T, 77% vs C/C, 30%, p = 0.04). In contrast, NAT2 SNPs (rs1041983 and rs1801280) were associated with up to 5-fold differences in R0-R1 resection rate. Statistically significant associations ($p < 0.05$) of SNPs with clinical outcomes were found for oxydo-reduction (CYP2E1 and HA thrombosis; CYP2C9 and diarrhea; CYP2C19 and diarrhea, fatigue, and early response), conjugation (UGT1A1 and diarrhea; NAT2 and fatigue); and transport (ABCB1 or SLCOB3 and neutropenia; SLC22A1 and diarrhea; SLC 15A2 and early response). **Conclusions:** VKORC1 was highlighted for the first time, as a pharmacogenomic predictor of HAI efficacy for LM-CRC. Conversion-to-resection was associated with NAT2 polymorphism. VKORC1 γ-carboxylates vitamin K-dependent proteins. Its polymorphism guides personalized warfarin dosing. VKORC1 SNPs determination could help identify the uLM-CRC pts who best benefit from intensive HAI therapy. Clinical trial information: NCT00852228.

2570 Poster Session (Board #62), Mon, 8:00 AM-11:30 AM

A first in human phase I study of AZD8186, a potent and selective inhibitor of PI3K in patients with advanced solid tumours as monotherapy and in combination with the dual mTORC1/2 inhibitor vistusertib (AZD2014) or abiraterone acetate. *First Author: Aaron Richard Hansen, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Loss of PTEN function leads to increased PI3Kβ signalling. AZD8186 (AZD) exhibits significant anti-tumour activity in PTEN-deficient preclinical models, particularly when combined with anti-androgens or the dual mTORC1/2 inhibitor vistusertib (AZD2014). Here we report on the dose-finding part of this Phase 1 study. **Methods:** AZD single agent was administered twice daily (BD) in 3 different schedules (5 days on/ 2 days off, 2 days on/ 5 days off and continuous). Escalating doses of AZD were evaluated in cohorts of 3-6 patients treated until progression, unacceptable toxicity, or consent withdrawal. Accrual is ongoing in the combination arms with vistusertib or abiraterone acetate. **Results:** As of 16 Jan 2017, 87 patients have received AZD at doses of 30–360 mg BD, with 28 confirmed as PTEN deficient (IHC). The selected RP2D for the 5 days on/2 days off monotherapy schedule is 60 mg BD. PK parameters show that systemic exposures to AZD and its major active metabolite increase in a dose proportional manner. 69 serious adverse events (SAEs) were reported in 31 patients on AZD monotherapy with 23 SAEs considered possibly related to AZD. In the 5/2 schedule: 5 dose limiting toxicities (G3 rash with ≥G2 fever and/or chills) were observed in 5 patients at doses of 120-360mg. Adverse events ≥G1 in $>$ 20% included diarrhoea, nausea, fatigue, LFT elevations and decreased appetite. 20 patients remained on study for $>$ 100 days. Dose-dependent target inhibition has been demonstrated in surrogate tissue (platelets). Evaluation of direct tumour target engagement in paired biopsies is currently ongoing. Preliminary efficacy: Confirmed PRs seen in a CRPC patient (BRCA2 and androgen receptor mutant) treated in combination with vistusertib (on study for 411 days) and in one ongoing monotherapy PTEN-deficient colorectal cancer patient (on study $>$ 329 days). Updated data will be presented. **Conclusions:** AZD has potential for treatment of PTEN-deficient tumours. Investigation of the safety/tolerability and preliminary efficacy in combination with vistusertib or abiraterone acetate is continuing. Clinical trial information: NCT01884285.

2571 Poster Session (Board #63), Mon, 8:00 AM-11:30 AM

TAX-TORC: A phase I trial of vistusertib (AZD2014) in combination with weekly paclitaxel with integrated pharmacodynamic (PD) and molecular characterization (MC) studies. *First Author: Raghav Sundar, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: In ovarian cells isolated from ascites, p-S6K levels were found to correlate with resistance to chemotherapy. We hypothesised that inhibiting p-S6K signalling with dual m-TORC1/2 inhibitor vistusertib (V) in addition to paclitaxel (P) would improve outcomes of patients with high-grade serous ovarian cancer (HGSOC). **Methods:** In the dose escalation part, weekly P 80mg/m^{2}IV (6/7 weeks) was evaluated in combination with two schedules of V; Schedule A: V (25, 50 or 75mg) BID PO on day(D) 1-3/week and Schedule B: V (75 or 100mg) BID PO D1-2/week. This was followed by an expansion cohort in 25 HGSOC patients. **Results:** Dose limiting toxicities in Schedule A were fatigue and mucositis and in Schedule B were diarrhoea, rash and fatigue. The AUC, Cmax and half-life of V in the 50mg-cohort were 2821ng.hr/ml, 926ng/ml and 3hrs, comparable to single agent studies. PD analysis (from six 50mg-cohort patients) in platelet-rich plasma showed increased phosphorylation of Ser473 AKT following P induction (1.4 fold, p = 0.1378). Following addition of V to P, phosphorylation levels 4hrs post-treatment with V fell significantly to 53% of pre-dose levels (p = 0.0495). This was 61% lower than the corresponding time point following P alone. Based on toxicity, pharmacokinetic and PD evaluation, recommended phase 2 dose was established as P 80mg/m^2 D1 and V 50mg BID D1-3 for 6/7 weeks. In the HGSOC expansion, 96% of patients had relapsed within 12 months of last platinum therapy and 100% had received previous paclitaxel, with a median of 3 previous lines of treatments. RECIST and GCIG CA125 response rates were 13/25 (52%) and 15/25 (60%) respectively, with median progression free survival of 5.5 months. MC was performed on archival tumor tissue of 24/25 HGSOC expansion cohort patients, with the most common mutations occurring in *p53* (100%), *BRCA* (17%), and *MUC16* (17%). *ATM* mutations occurred in 17% (n = 4), 3 of whom had a response. **Conclusions:** We report a highly active combination of paclitaxel with an intermittent schedule of vistusertib in patients with HGSOC. This combination is now being evaluated in a randomised controlled trial for this indication. Clinical trial information: NCT02193633.

2572 Poster Session (Board #64), Mon, 8:00 AM-11:30 AM

Investigating novel resistance mechanisms to third generation EGFR TKI osimertinib in non-small cell lung cancer patients using next generation sequencing. *First Author: Qiuxiang Ou, Geneseeq Technology Inc., Toronto, ON, Canada*

Background: Third generation epithelial growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) osimertinib (AZD9291) has proven effective in Non-small cell lung cancer (NSCLC) patients who have developed *EGFR* T790M-mediated resistance to other EGFR TKIs. Unfortunately, a majority of patients still undergo progressed disease after receiving osimertinib treatment. Acquired *EGFR* C797S mutation has been identified as one major mechanism; however, resistance mechanisms of remaining cases are still largely unknown. **Methods:** Using next generation sequencing (NGS) targeting 416 cancer-relevant genes, we analyzed the mutation profiles of 99 NSCLC patients that were clinically resistant to osimertinib. **Results:** In addition to the notable *EGFR* C797 variants (22%), L792 mutations were identified in 10% of patients, and a further 7% cases carry L718 mutations. Further analysis of 14 patients with paired pre-treatment samples confirmed that these *EGFR* mutations were acquired during treatment. Interestingly, all L792 mutations are *in cis* with T790M and *in trans* with C797 mutations (when present in the same patient). 2 out of 10 L792-positive patients and 6 out of 7 L718-positive patients did not have co-existing C797 mutations, suggesting C797-, L792- and L718-mutated cells may represent different resistant clones. *In vitro* experiments demonstrated that L792 and L718 mutants also increase osimertinib IC50, and therefore confer their resistance. Besides secondary *EGFR* mutations, alterations in other key genes such as *MET*, *KRAS*, *ERBB2 and PIK3CA* may also contribute to osimertinib resistance. Notably, *MET* and *KRAS* amplifications are present only in patients without above *EGFR* secondary mutations. **Conclusions:** In this study, we identified secondary mutations on C797, L792 or L718 residues of *EGFR* in 29% of osimertinib-resistant patients. Combined with *in vitro* study, our data strongly suggest that L792 and L718 mutations are likely to alternatively cause osimertinib resistance. Furthermore, *MET* and *KRAS* amplification may serve as bypass resistance mechanisms in patients who are EGFR C797-, L792- and L718-wild type.

2573 Poster Session (Board #65), Mon, 8:00 AM-11:30 AM

A phase I trial of selective PI3K inhibitor taselisib (tas) plus palbociclib (palb) with and without endocrine therapy incorporating pharmacodynamic (PD) studies in patients (pts) with advanced cancers. *First Author: Joline Si Jing Lim, Royal Marsden Hospital, Sutton, United Kingdom*

Background: The phosphatidylinositol 3-kinase (PI3K) pathway is commonly mutated in cancer. Tas is a selective β-isoform-sparing PI3K inhibitor with improved therapeutic index compared to pan-PI3K inhibitors. Palb is a CDK4/6 inhibitor now standard of care in combination with endocrine therapy (ET) in hormone receptor positive breast cancer. Combination of Tas, Palb and ET is synergistic in preclinical models. **Methods:** This investigator-initiated study investigated safety and tolerability, pharmacokinetics (PK), PD and antitumor activity of Tas+Palb, with addition of ET in dose expansion. Pts were enrolled in 3+3 dose escalation design. Tas was given continuously or 3-weeks-on, 1-week-off (3/1), Palb was given on 3/1 schedule. PD studies included analyses of platelet-rich plasma (PRP) (n = 20) and paired tumor biopsies (n = 5). Serial circulating tumor DNA was monitored in pts with *PIK3CA* mutations. **Results:** 24 pts were treated, 22 with Tas+Palb, 2 with Tas+Palb+fulvestrant(ful); M/F 11/13, median lines prior therapy 4. Treatment was well tolerated with mainly G1-2 toxicities. Most frequent G3 toxicities were neutropenia (5/24), thrombocytopenia (5/24) and rash (5/24), with no G4/5 toxicities. Two pts had dose-limiting toxicities (DLT) at DL2. No DLTs were observed at DL4, although pts experienced delayed neutrophil recovery. PK was linear and comparable with monotherapy. At 125mg Palb, significant decreases in pAKT and pGSK3β in PRP confirmed PI3K target inhibition. Two pts with *PI3KCA* H1047R mutant breast cancers have ongoing RECIST partial response; 1 pt with *PIK3CA* E542K colorectal cancer had stable disease for 20 weeks. **Conclusions:** Tas+Palb is well tolerated with evidence of PD and antitumor activity. Dose expansion including recruitment to triplet Tas+Palb+ful and Tas+Palb+letrozole is ongoing with continuous Tas 2mg QD, and Palb 100mg QD on 3/1 schedule, increasing to 125mg after cycle 1 in absence of myelosuppression. Clinical trial information: NCT02389842.

Dose level (DL)	Palb dose (mg)	Tas dose (mg)	Tas schedule	N	DLT
1	100	2	3/1	4	-
2	100	4	3/1	3	G3 mucositis G3 hyperglycemia G3 fatigue
3	125	2	3/1	7	-
4	125	2	continuous	6	-

2574 Poster Session (Board #66), Mon, 8:00 AM-11:30 AM

Phase 1 results of PTC596, a novel small molecule targeting cancer stem cells (CSCs) by reducing levels of BMI1 protein. *First Author: Jeffrey R. Infante, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: PTC596 is an oral investigational new drug that reduces levels of BMI1, a protein required for CSC survival. PTC596 reduced the number of CSCs in preclinical models and slowed growth rates of tumor xenografts in rodent models. The primary objectives of this first-in-human trial of PTC596 were to determine safety, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and pharmacokinetics (PK). Secondary objectives included exploratory assessments of biological efficacy, pharmacodynamic changes and anti-tumor activity. **Methods:** A Phase I multi-center, open-label study was conducted in patients with advanced solid tumors using a modified 3+3 design, followed by a dose-confirmatory 10-patient expansion. PTC596 was administered using bodyweight-adjusted twice-per-week (biw) oral dosing in 4 week cycles. Dose escalation and MTD were based on observed cycle 1 DLTs. Anti-tumor activity was assessed by RECIST 1.1. **Results:** A total of 31 patients with a broad range of tumor types were enrolled at dose levels of 0.65 (N = 3), 1.3 (N = 3), 2.6 (N = 3), 5.2 (N = 11), 7 (N = 8) and 10 mg/kg (N = 3). Nausea, vomiting, and diarrhea were the most common all grade adverse events, though usually mild and manageable. At 10 mg/kg one patient experienced DLTs of neutropenia, mucositis, and thrombocytopenia. The other two patients at this dose level also experienced poor tolerability with Grade 2 nausea, vomiting, and diarrhea that may be partially due to the overall pill burden and excipients. The recommended dose for the expansion and further study was 7 mg/kg. Over the dosing range, plasma concentrations of PTC596 increased in an approximately dose-proportional manner and at doses of 2.6 mg/kg and above exceeded those associated with activity in vitro and in vivo models. Best response was stable disease in 5 patients including two with minor radiographic reductions in tumor volume. **Conclusions:** PTC596 is tolerable with manageable gastrointestinal side effects. At 7 mg/kg biw exposures exceeded those associated with preclinical activity and future clinical studies are planned for this first-in class molecule that targets CSCs. Clinical trial information: NCT02404480.

2575 Poster Session (Board #67), Mon, 8:00 AM-11:30 AM

Phase 1 study of the p53-MDM2 inhibitor AMG 232 combined with trametinib plus dabrafenib or trametinib in patients (Pts) with *TP53* wild type (TP53WT) metastatic cutaneous melanoma (MCM). *First Author: Stergios J. Moschos, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: Large sequencing studies in MCM have shown a TP53WT incidence of approximately 80%. In preclinical TP53WT melanoma models, the oral p53-MDM2 inhibitor AMG 232 exhibited synergistic, cytotoxic-type antitumor activity when combined with MAPK inhibitors. This phase 1 study assessed the toxicity (CTCAE 4.03), maximum tolerated dose (MTD), pharmacokinetics (PK), and preliminary antitumor activity (RECIST 1.1) of AMG 232 plus trametinib (T) and dabrafenib (D) ($BRAF^{V600\text{-}mutant}$) or T ($BRAF^{V600\text{-}WT}$) in pts with TP53WT MCM. **Methods:** Using 3+3 dose escalation design, pts with advanced TP53WT (using a CLIA-approved assay) MCM received AMG 232 PO QD for seven days of each 3-week cycle (7/21) at 120, 240, or 480 mg plus either T 2 mg PO QD and D 150 mg PO BID (Arm 1; $BRAF^{V600\text{-}mutant}$) or T 2 mg QD (Arm 2; $BRAF^{nonV600\text{-}mutant}$). **Results:** At the time of this analysis, 21 pts (median age, 58 y [range 24–76]; male, n = 11; at least 2 systemic treatments, n = 15) were treated. Arm 2 enrolled first: AMG 232 120 mg (n = 6), then 240 mg (n = 6). Due to chronic grade (G) 2 gastrointestinal toxicity, an intermediate dose (180 mg; n = 3) was determined as the preliminary MTD. Arm 1 enrolled at AMG 232 120 mg (n = 4), then 180 mg (n = 2). The most common reasons for AMG 232 withdrawal were disease progression (n = 8) and AEs (n = 4); 6 pts remain on AMG 232. All 21 pts had treatment-related AEs (TRAEs); the most common TRAEs were nausea (n = 18), fatigue (n = 17), diarrhea (n = 14), and vomiting (n = 13). The only DLT (Arm 2; 240 mg) was G 3 pulmonary embolism. Preliminary PK analysis suggests that AMG 232 exposure (area under the curve) is similar to that as monotherapy at the same dose, with no apparent drug-drug interaction between AMG 232 and T; analysis of D and T PK is ongoing. Of 21 pts, 6 had partial response (Arm 1/2, n = 4 [67%]/2 [13%]), 13 had stable disease (Arm 1/2, n = 2 [33%]/11 [73%]), and 2 progressed (Arm 1/2, n = 0/2 [13%]) as best response; 17 had tumor reduction (Arm 1/2, n = 6 [100%]/11 [73%]). **Conclusions:** In this population of pts with MCM, AMG 232 combined with D and/or T during DE was tolerable up to 180 mg QD 7/21 days, showing an acceptable PK profile and early antitumor activity. Clinical trial information: NCT02110355.

2576 Poster Session (Board #68), Mon, 8:00 AM-11:30 AM

Phase 1 dose escalation study of the folate receptor-targeted small molecule drug conjugate EC1456. *First Author: Wael A. Harb, Horizon Oncology Center, Lafayette, IN*

Background: The folate receptor (FR) is highly expressed in a variety of cancers including adenocarcinoma of the lung, but is expressed at low levels in most normal tissues, making it a potential target for therapeutic intervention. EC1456 is an FR-targeted small molecule drug conjugate (SMDC) consisting of folic acid chemically attached through a bio-releasable linker system to a potent microtubule inhibitor, tubulysin B hydrazide (TubBH). EC1456 binds to, and is endocytosed by the FR-expressing cancer cell to deliver TubBH. Following endocytosis, the FR recycles back to the membrane surface every 18-24 hours. Therefore alternative EC1456 schedules will be evaluated for safety, pharmacokinetics, and therapeutic benefit. **Methods:** Part A (dose escalation) is being evaluated in unselected patients (pts) with advanced solid tumors. 4 schedules (3-week cycle) are being evaluated: BIW (twice weekly); QW (once weekly); CWD (continuously weekly); QIW (four times a week). The primary objective of Part A is to determine the RP2 dose and schedule of EC1456. Part B (expansion) will confirm the MTD and RP2 dose and evaluate efficacy of EC1456 in ^{99m}Tc-etarfolatide-selected NSCLC patients in up to three schedules. **Results:** 74 Part A pts are evaluable for toxicity. Median age is 68 (range: 26-88); 53 pts are female. Toxicities are primarily Grade (Gr) 1 and 2. Common treatment-related adverse events (TRAE) are gastrointestinal, fatigue, metabolic changes, alopecia, and headache. 5 Gr 3 DLTs have been observed: infusion reaction (4.5 mg/m^2 QW), headache (10.0 mg/m^2 QW), and abdominal pain (7.5 mg/m^2 BIW, 12.5 mg/m^2 QW and 10.0 mg/m^{2}CWD). TRAEs are summarized in the table for each schedule. Durable stable disease of 12 wks or longer has been observed in 12 pts (6 BIW and 6 QW). **Conclusions:** All Part A EC1456 schedules have been well tolerated. RP2 dose for BIW is 6.0 mg/m^2 and QW is 12.5 mg/m^2; dose escalation is ongoing for CWD and QIW. Early signs of efficacy in an unselected pt population may be suggested by durable stable disease. Safety and efficacy evaluation in the ^{99m}Tc-etarfolatide-selected NSCLC population (Part B) is ongoing. Clinical trial information: NCT01999738.

	BIW n=33	QW n=35	CWD n=5	QIW n=1
AE	26	29	1	0
SAE	2	9	1	0
Gr 3/4 AE	7	9	1	0
dose reduction	1	2	0	0
discontinuation	0	4	0	0

2577 Poster Session (Board #69), Mon, 8:00 AM-11:30 AM

A phase Ia study of CC-90003, a selective extracellular signal-regulated kinase (ERK) inhibitor, in patients with relapsed or refractory BRAF or RAS-mutant tumors. *First Author: Monica M. Mita, Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA*

Background: CC-90003 is an irreversible inhibitor of ERK 1/2 with potent anti-proliferative activity in *KRAS* and *BRAF* mutant tumor models. We conducted a first-in-human study of CC-90003 in patients with *RAS* or *BRAF* mutant tumors. **Methods:** Patients received escalating doses of oral CC-90003 on a 21/28 day cycle. Standard safety (adverse events, chemistry/hematology, physical findings, ECGs and cardiac ECHO/MUGA scans) and PK parameters were assessed. Response was assessed per RECIST 1.1. A proprietary ELISA-based assay measured ERK levels unbound to CC-90003 in peripheral blood mononuclear cells. **Results:** Nineteen patients (median age: 60 yrs) harboring *KRAS* (n = 15), *NRAS* (n = 1), or *BRAF* (n = 3) mutant tumors received CC-90003 doses from 20 to 160 mg /day. The MTD was 120 mg based on the occurrence of Grade 3 transaminase elevations (n = 2) and hypertension (n = 1) observed at 160 mg (the NTD). Patients completed a median of 2 cycles (range: 1 to 5). AEs (mostly Grade 1 or 2) reported in ≥ 3 patients included constitutional (asthenia, fatigue), gastrointestinal (anorexia, nausea/vomiting, diarrhea), hepatic (transaminase elevations) and neurologic (dizziness, gait disturbance, paresthesias) toxicities. Grade 1-3 neurotoxicity was observed primarily at doses from 80 to 160 mg/day and resolved with dose reduction/interruption. PK parameters were highly variable, with AUC and C_{max} increasing overall, with increasing dose. CC-90003 accumulation was observed after multiple doses. There were no objective responses. Levels of free ERK were reduced by ≥80% compared to baseline by C1D8 at doses ≥ 80 mg/day. **Conclusions:** ERK inhibition may be an attractive target for the management of mutant *RAS* or *BRAF*-driven tumors, however proof-of-concept demonstration for CC-90003 was limited by a lack of objective responses, an unfavorable PK profile and unanticipated neurotoxicity. Clinical trial information: NCT02313012.

2578 Poster Session (Board #70), Mon, 8:00 AM-11:30 AM

SWOG S1221: A phase 1 dose escalation study co-targeting MAPK-dependent and MAPK-independent BRAF inhibitor resistance in BRAF mutant advanced solid tumors with dabrafenib, trametinib, and GSK2141795 (ClinicalTrials.gov NCT01902173). *First Author: Alain Patrick Algazi, University of California, San Francisco Medical Center-Mt. Zion, San Francisco, CA*

Background: Aberrant PI3K/AKT signaling in BRAF mutant cancers contributes to resistance to MAPK pathway blockade. We conducted parallel phase 1 dose escalation studies of the doublet of the BRAFi dabrafenib with the AKT inhibitor GSK2141795 and of the triplet of dabrafenib, the MEKi trametinib, and GSK2141795. **Methods:** Patients (pts) with BRAF-V600E/K mutant advanced solid tumors with adequate end-organ function were eligible regardless of prior BRAFi and MEKi exposure. All pts received dabrafenib at 150 mg twice daily (bid), in the doublet cohorts together with dose escalation (3 + 3 scheme) of GSK2141795 started at 50 mg daily (qd), and in the triplet cohorts with dose escalation of both trametinib starting at 1.5 mg qd and GSK2141795 starting at 25 mg qd. DLTs included significant grade 3 and 4 adverse events (CTCAE v4) within the first 56 days of treatment. Radiographic responses were assessed at 8-week intervals. **Results:** No DLTs were observed in the doublet cohorts (N = 8) up to dabrafenib 150 mg bid and GSK2141795 75 mg qd. In the triplet cohorts (N = 11), no DLTs were observed at doses of up to trametinib 1.5 mg daily with GSK2141795 75 mg daily. At the highest triplet dose with dabrafenib 150 mg bid, trametinib 2 mg qd with GSK2141795 75 mg qd, 1 of 2 evaluable pts had a DLT of grade 3 febrile neutropenia and grade 3 maculopapular rash. 2/2 treatment-naïve in the doublet cohorts had PRs (1 melanoma and 1 thyroid) the latter lasting over 1 year. 1/6 BRAF inhibitor-refractory (melanoma) pts also had an objective response. In the triplet cohorts, 3 of 6 treatment-naïve pts had a PR (1 melanoma, 2 lung). One lung pt remains in PR at 2 months and the otherhas an uPR at 1.2 months. **Conclusions:** Inhibition of both MAPK and PI3K/AKT pathways was well tolerated, leading to durable objective responses in pts with metastatic melanoma, thyroid cancer, and lung cancer. Further study of dual pathway inhibition is warranted. Funding: Supported in part by NIH/NCI grants CA180888, CA180819; and in part by Novartis Pharmaceuticals Corporation and GlaxoSmithKline, LLC. Clinical trial information: NCT01902173.

2579 Poster Session (Board #71), Mon, 8:00 AM-11:30 AM

A phase 1 dose escalation study of eFT508, an inhibitor of mitogen-activated protein kinase-interacting serine/threonine kinase-1 (MNK-1) and MNK-2 in patients with advanced solid tumors. *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO*

Background: Dysregulated translation of messenger RNA (mRNA) plays a role in the pathogenesis of multiple solid tumors. eFT508, a potent and highly selective small molecule inhibitor of MNK-1 and 2 blocks activation of eIF4E, a key regulator of mRNA translation, and thereby selectively regulates translation of a small set of mRNAs. In addition to direct antitumor activity, eFT508 triggers an anti- tumor immune response and enhances responses to checkpoint inhibitors in preclinical models. **Methods:** Using a 3+3 dose escalation schema, cohorts of solid tumor patients (pts) were treated with eFT508 administered orally once daily at doses ranging from 50 mg to 600 mg. **Results:** 28 pts were treated, and the most common tumor types were colorectal cancer (8), prostate cancer (3), and soft tissue sarcoma (3). Median number of prior therapies was 4. The most common observed adverse events (AEs) included nausea (47%), vomiting (47%), dyspepsia (23%), fatigue (20%), and constipation (20%). Two pts treated at 600 mg experienced Gr 3 related AEs, including one pt with Gr3 nausea and vomiting (met criteria for dose limiting toxicity) and one pt with reversible Gr3 AST/ALT elevation. 6 pts achieved stable disease with duration ranging from 82 to 196 days. Pharmacokinetic analysis revealed that eFT508 is bioavailable and rapidly absorbed, with median T_{max} of 2 hours and a mean $T_{1/2}$ of 12 hours. Minimal accumulation was observed between Days 1 and 14/15, with mean accumulation factor of 1.2-fold. Analysis of eIF4E phosphorylation in peripheral blood cells suggested that doses ≥ 300 mg achieved engagement sufficient for maximal efficacy as predicted by preclinical models. **Conclusions:** Preliminary results suggest that eFT508 is well tolerated, and dose escalation continues with a cohort of pts providing pretreatment and on treatment biopsies for evaluation of target engagement and immunomodulatory effects. After determination of the recommended phase 2 dose, further evaluation will include monotherapy cohorts in specific tumor types as well as cohorts to evaluate efficacy and tolerability in combination with checkpoint inhibitors. Clinical trial information: NCT02605083.

2580 Poster Session (Board #72), Mon, 8:00 AM-11:30 AM

Phase I dose escalation study of CVM-1118, a novel anti-vascular mimicry agent, in patients with advanced cancers. *First Author: Anthony W. Tolcher, START, San Antonio, TX*

Background: CVM-1118 is an oral NCE that demonstrated potent anti-tumor effects in several tumor xenograft models, via multiple MOAs including induction of cancer cell cycle arrest and apoptosis, and reducing vasculogenic mimicry (VM) network formation in cancer cells, providing a promising therapeutic means in the treatment of malignant tumors that have metastatic potential. **Methods:** Patients with advanced tumors are being enrolled into 2 ongoing open-label Phase I dose escalation studies in both US (CVM-001) and Taiwan (CVM-002) to evaluate ethnic differences in drug responses. CVM-1118 capsules are administrated orally QD/BID in a 28-day cycle for 4 cycles. The primary objectives are to evaluate the safety, tolerability and pharmacokinetics (PK) and establish the Recommended Phase 2 Dose (RP2D). The secondary objective is to evaluate the therapeutic response after receiving treatment. Beyond 4 cycles, patients showing clinical benefit with CVM-1118 may enter extension cohort to continue the treatment. **Results:** To date, 28 pts (16 M/12 F)received CVM-1118 across 6 dose levels (50 to 800 mg daily). Median number of days was 52 (range 2 to 135). For CVM-001, 2 DLTs (grade 5 dehydration and grade 3 fatigue) were reported at cohort 6 (800 mg/daily) and the MTD is currently under evaluation. For CVM-002, 3 cohorts (100 to 400 mg/daily) have been completed without DLT. Enrolment to cohort 5 (600 mg/daily) is in progress. From both studies, the most common drug-related AEs included manageable diarrhea, nausea, and vomiting. Rapid oral absorption was observed with Tmax $<$ 2 hr. Bioconversion to active metabolite, CVM-1125, occurred rapidly and the drug exposure increased with increasing dose levels. However, patients in US study showed higher drug exposure than those in Taiwan study. Two patients at 200 mg/daily cohort in Taiwan completing 4-cycle treatment and showing stable disease continued into extension cohort with higher dose. **Conclusions:** In this ongoing study, Asian patients in Taiwan appear to have better tolerance for CVM-1118 than those in US, likely due to lower drug exposure at same dose level, and some patients have experienced clinical benefit. Clinical trial information: NCT02507544; NCT02703298.

2581 Poster Session (Board #73), Mon, 8:00 AM-11:30 AM

Molecular markers to predict response to selective fibroblast growth factor receptor inhibitors (FGFRinh) in patients (pts) with FGFR-amplified (amp) or mutated (mut) tumors. *First Author: Cinta Hierro, Medical Oncology Department, Vall d'Hebron University Hospital, Molecular Therapeutics Research Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Several FGFR and ligand (11q) alterations have been described in cancer. While FGFR fusions are recognized biomarkers of response to FGFRinh, it is still unclear to what extent FGFRamp, FGFR mRNA high expression (mRNAh) or FGFRmut predict sensitivity in the clinic. **Methods:** Retrospective analysis of pts with molecularly-selected FGFRamp/mRNAh/mut tumors treated with FGFRinh in phase 1 trials at our institution. Mut were detected with IlluminaÒ or Foundation OneÒ. FGFR1-2amp were analyzed by in situ hybridization and mRNA levels by qRT-PCR or nCounterÒ. Clinical benefit (ClinBen) was defined as any tumor shrinkage plus disease control for ³ 4 months (m). Time to progression (TTP) was defined as time between start of FGFRinh and end for any cause. **Results:** From 2011 to 2016, 36 pts with FGFRamp(25)/mRNAh(5)/mut(6) received an FGFRinh (irreversible- [11 cases (c)] or reversible-FGFR1-4inh [23 c], isoform-specific FGFRinh [3 c] or combo with PI3Kinh [1 c]). Median age 55 yrs (34-76); median prior palliative lines was 3 (0-8); tumor types: breast (17), colorectal (3), esophagus (3), liver (3), lung (3), others (7). Median TTP was 1.67 m (CI 95%; 1.40-2.87). In the FGFRamp/mRNAh population (30), 7 pts achieved ClinBen (23%). 4 out of these seven pts had mRNAh (1 FGFR2amp breast with FGFR2 mRNAh, 1 bladder FGFR3 mRNAh and 2 liver FGFR4 mRNAh without known amp), and 2 pts harboured 11q co-amplification (1 FGFR2amp breast, 1 FGFR2amp head and neck). There was no correlation between ClinBen and level of FGFRamp in the overall population ($p = 0.51$) or in the breast cancer group ($p = 0.29$). Of 6 FGFRmut pts, one with bladder cancer had ClinBen (clonal oncogenic FGFR3 S249C). The remaining 5 unresponsive FGFRmut pts had subclonal events, some of these FGFRmut were of unknown functional significance, and had coexisting oncogene mut in MAPK or PI3K pathways. **Conclusions:** Our results suggest that ClinBen with FGFRinh in the FGFRamp setting is enriched in pts with high mRNA expression and/or ligand co-amplification, and in the FGFRmut population may be dependent on clonality and functionality of the event and co-existence of driver mut.

2582 Poster Session (Board #74), Mon, 8:00 AM-11:30 AM

Clinical next generation sequencing for precision oncology in rare cancers. *First Author: Roman Groisberg, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Rare tumors receive little financial support or interest from major drug developers or clinical investigators. They are by nature difficult to study even in a large academic medical center. As such, no standard of care exists for many of these cancers and treatment is often extrapolated. ESMO defines rare tumors as 5/100,000 persons per year. We examined patients with rare tumors for potentially targetable genomic alterations using next generation exome sequencing (NGS). **Methods:** We reviewed charts of patients with rare tumors per the ESMO definition. Sarcomas were excluded. Patients were referred to investigational therapeutics department and underwent CLIA certified comprehensive genomic profiling (Foundation Medicine). Actionable alterations were defined as targeted by a drug available on-label, off-label, or in clinical trials. **Results:** Among the 95 patients analyzed median age was 51 years (range 2-75). M:F ratio 46:49. Overall, there were 47 different subtypes in our dataset with the most common being adenoid cystic (13%), cholangiocarcinoma (7%), metaplastic breast (6%), gallbladder (5%), and carcinoid (4%). Eighty-seven out of 96 patients (92%) had at least one genomic alteration identified with mean of 2.6 mutations per patient. Of the patients with identifiable mutations, the most common were *TP53* (23%), *KRAS* (10%), *PIK3CA* (9%), *CDKN2A/B* (8%), *BRAF* (7%), *MLL* (7%), and *ARID1A* (6%). Thirty-six patients (38%) had at least one potentially actionable alteration in 21 different tumors (eg: PI3K in metaplastic breast and adenoid cystic carcinomas and $BRAF^{V600E}$in Erdheim-Chester disease). Nine patients received targeted therapy. Of these 9 patients, 3 had PR, 4 had SD, and 2 had PD as best response (table). **Conclusions:** The addition of CGP to management of rare tumors adds a potential line of therapy especially in RAF pathway altered ultra-rare cancers that have no standard of care.

Disease	Aberration	Therapy	Best Response
Cholangiocarcinoma	$BRAF^{V600E}$	BRAFi	PR
Erdheim-Chester	$BRAF^{V600E}$	BRAFi	PR
Glioblastoma Multiforme	$BRAF^{V600E}$	BRAFi	PR
Adenoid Cystic	PIK3R1 E515fs*1	Akt i	SD x 24 cycles
Salivary gland adenocarcinoma	$BRAF^{V600E}$	BRAFi	PR
Erdheim-Chester	$BRAF^{V600E}$	BRAFi	SD x 3 years

2583 Poster Session (Board #75), Mon, 8:00 AM-11:30 AM

Proof-of concept phase I study of everolimus, letrozole and trastuzumab in hormone receptor-positive, HER2-positive/amplified or mutant metastatic breast cancer or other solid tumors: Evaluating synergy and overcoming resistance. *First Author: Shubham Pant, Oklahoma University Health Sciences Center, Edmond, OK*

Background: Preclinical models suggested synergistic antineoplastic activity of anti-estrogen therapy with HER2 and mTOR inhibitors. **Methods:** We designed a 3+3 dose escalation phase I study of the aromatase inhibitor letrozole 2.5mg PO daily, mTOR inhibitor everolimus 2.5-10mg PO daily and HER2 antibody trastuzumab 4-8mg loading dose followed by 2-4mg maintenance dose IV on day 1 of 21-day cycle in patients with hormone-receptor positive, HER2-positive/amplified or mutant advanced cancers (confirmed by immunohistochemistry and/or FISH and/or next-generation sequencing). The primary objectives were to determine maximum tolerated dose (MTD), dose limiting toxicities (DLT), overall safety and response. **Results:** A total of 18 patients (men, 1; women, 17; HER2 amplification, 14; HER2 mutation, 4; breast cancer, 15; ovarian cancer, 1; cervical cancer, 1; gastroesophageal junction cancer, 1), median age 56 years, median of 6 prior therapies (including letrozole [9] or other aromatase inhibitor [8]; everolimus [3]; trastuzumab [14] or other HER2 targeted therapy [1]) were enrolled in the planned 6 dose levels. The MTD has not been reached and grade 3 (G3) mucositis at the dose level 4 was the only DLT. Other G3 or G4 drug-related toxicities included G4 hyperglycemia in 1 patient, G3 hyperglycemia in 3 patients, G3 thrombocytopenia in 1 patient, G3 anemia in 1 patient and G3 headache in 1 patient. Of 18 patients, 3 (17%) had a partial response (all with heavily-pretreated breast cancer with HER2 amplification [2] or $HER2^{A775\_G776insYVMA}$ mutation [1]), 11 (61%) stable disease (SD) including 7 (39%) patients with SD $>$ 6 months (all with heavily-pretreated breast cancer), 3 (17%) progressed and 1 had pending evaluation. The median change in size of target lesions per RECIST 1.1. was -11% (-68% to +47%). Median progression-free survival was 9 months (95% CI 5.8-12.2). **Conclusions:** The combination of letrozole, everolimus and trastuzumab is well tolerated with encouraging activity in heavily-pretreated patients with HER2-amplified or mutant advanced breast cancer. Clinical trial information: NCT02152943.

2584 Poster Session (Board #76), Mon, 8:00 AM-11:30 AM

First-in-human phase 1 study of ETC-159 an oral PORCN inhbitor in patients with advanced solid tumours. *First Author: Matthew Ng, Division of Medical Oncology, National Cancer Centre, Singapore, Singapore*

Background: The Wnt signalling pathway is involved in cellular proliferation, differentiation, migration and implicated in stem cell function in several cancers. ETC-159 is a selective small molecule inhibitor of porcupine, an enzyme required for palmitoylation and secretion of all Wnt ligands. In preclinical studies, ETC-159 induced tumour regression in patient-derived xenograft models. **Methods:** Open-label, multi-centre study to determine safety, maximum tolerated dose, pharmacokinetics, pharmacodynamics (PD) of ETC-159 given orally, once every other day in a 28d cycle. PD was evaluated by AXIN2 mRNA levels in whole blood and hair follicles and bone turnover by radiological and serum markers. Dose escalation was by ordinal continual reassessment method with a dose-limiting toxicity (DLT) period of 28d. **Results:** As of 18 Jan 2017, 16 patients (pts) were treated in 6 cohorts at 1 mg (2pts), 2 mg (2pts), 4 mg (3pts), 8 mg (4pts); 16 mg (3pts), and 30 mg (2pts). 80% were male, median age (range) was 55yr (19-68). One DLT was seen at 16 mg due to hyperbilirubinaemia. Adverse events ($\geq$ 20%) were vomiting (32%); anorexia and fatigue (31%); dysgeusia and constipation (25%). ETC-159 C_{max} increased with dose with a mean $t_{1/2}$ of 14 hr. Plasma levels of ETC-159 that inhibited colony formation in vitro were attained from 4 mg onwards. Reduction of whole blood and hair follicle AXIN2 mRNA levels and doubling of serum β-CTX levels was first observed at 4 mg and at C1D15 in some patients. PD modulation increased with dose, consistent with on-target modulation of Wnt signalling. Two pts had β-CTX rise $>$ 1000 pg/mL (reference limit) and a $\geq$ 5% reduction in bone density by C3D1. Both took vitamin D and calcium supplements and were given i.v. bisphosphonates. No responses were seen but 2 pts (2 mg: colorectal and 4 mg: peritoneal carcinoma) had stable disease for 6 and 8 cycles respectively. Dose-escalation is ongoing at 30 mg. **Conclusions:** ETC-159 inhibits Wnt signalling at doses that are well tolerated. β-CTX levels increased early on, and in two pts were associated with reduced bone mineral density. Early and regular monitoring of bone turnover is indicated. This study was sponsored by D3 which is funded by NMRC, NRF and BMRC Singapore. Clinical trial information: NCT02521844.

2585 Poster Session (Board #77), Mon, 8:00 AM-11:30 AM

A phase I dose expansion cohort study of dasatinib in combination with bevacizumab in advanced solid tumors (NCT01445509). *First Author: Akosua Osei-Tutu, National Cancer Institute, Bethesda, MD*

Background: Dasatinib is a known inhibitor of the SRC family kinases and is approved for use in chronic myelogenous leukemia. Bevacizumab inhibits angiogenesis, binding to human vascular endothelial growth factor (VEGF, or VEGF-A) with high affinity. VEGF receptor signals intracellularly via a cascade regulated by SRC. Given the presence of this signaling pathway in both tumor cells and endothelial cells, we hypothesized that attenuation of both SRC and VEGF simultaneously would have synergistic antitumor activity. We previously reported the maximum tolerated dose (MTD) of dasatinib 100mg daily with bevacizumab 10mg/kg q2wk in patients with advanced solid tumors. We now report clinical activity of the combination, and translational endpoints of an expansion cohort. **Methods:** This is a phase 1 dose escalation with non-randomized expansion cohort. We monitored safety, and response was assessed every 8 weeks using RECIST criteria. Correlative endpoints include blood flow by dynamic MR imaging, endothelial cell density by CD31 immunohistochemistry, functional angiogenic potential by plasma cytokines and rat aortic ring assay, and tumor cell activation state by phosphoprotein analysis. **Results:** We enrolled 39 patients at the MTD for a total of 50 patients on study, including both the dose escalation and dose expansion phases. No patient experienced dose limiting toxicities during dose escalation. The most common adverse events were grade 2 hypertension and proteinuria. By RECIST, 5 (10%) patients had a partial response, and stable disease was seen in 29 (58%) of patients with a range from 12-145+ weeks on study. We had two exceptional responders with endometrial carcinoma who continue on study to date (112 weeks and 145 weeks). Translational endpoints were correlated with clinical outcome. **Conclusions:** Bevacizumab and dasatinib are safe in combination, with potential clinical activity. This combination warrants further investigation in solid tumors. Ongoing translational research using specimens from exceptional responders will suggest potential biomarkers of clinical benefit, to be tested in future prospective clinical trials. Clinical trial information: NCT01445509.

2586 Poster Session (Board #78), Mon, 8:00 AM-11:30 AM

Anticancer and immunostimulatory activity of the imipridone ONC201, a selective DRD2 antagonist, in advanced cancer patients. *First Author: Mark N. Stein, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: ONC201 is an orally active, small molecule selective antagonist of the G protein-coupled receptor DRD2 that has established a new class of compounds referred to as imipridones. A first-in-human trial of ONC201 defined its recommended phase II dose (RP2D) as 625mg using once every three week administration that was very well tolerated at doses that yielded antitumor effects. ONC201 also showed stimulatory effects on immune cells in preclinical studies, including increased intratumoral NK cell infiltration in xenografts. Based on the exceptional safety profile of ONC201, weekly dosing has been evaluated. **Methods:** This open-label, 3+3 dose-escalation study used a starting dose of 375mg and escalated to 625mg using a weekly administration schedule. The primary endpoint was to determine the RP2D of ONC201 and secondary endpoints included PD, PK, toxicity, and anti-tumor efficacy. Based on signs of clinical activity and preclinical tumor type sensitivity studies of ONC201, the patient population was enriched for advanced glioblastoma, prostate cancer, and endometrial cancer. Six additional patients were treated at the weekly RP2D. **Results:** The RP2D for the weekly regimen was defined as 625 mg. Twelve evaluable patients were treated at this dose level and no drug-related AEs $>$ grade 1 occurred. Five patients had stable disease by RECIST criteria for 21-29 weeks. A metastatic prostate cancer who received 375mg ONC201 weekly had significantly diminished intensity in bone scans after 6 doses. PK was consistent with previous reports: Cmax consistently reaches therapeutic micromolar plasma concentrations, ~11 hour half-life, evidence of sustained and delayed activity, no systemic accumulation. In agreement with preclinical observations of ONC201-induced NK cell populations, a 2-10 fold increase in circulating activated NK cells was observed in 5 prostate cancer patients. **Conclusions:** ONC201 is well tolerated at an oral dose of 625mg weekly, exhibits sustained and late anti-cancer activity, and increases circulating NK cells. Observation in this study, and other clinical studies, warrant further evaluation of the immune oncology effects of ONC201. Clinical trial information: NCT02250781.

2587 Poster Session (Board #79), Mon, 8:00 AM-11:30 AM

A phase IB study of the combination of selumetinib (AZD6244, ARRY-142886) and cyclosporin A (CsA) in patients with advanced solid tumors with an expansion cohort in metastatic colorectal cancer (mCRC). *First Author: Anuradha Krishnamurthy, University of Colorado-Denver, Aurora, CO*

Background: MEK inhibition is of interest in cancer drug development. However, better strategies are needed to overcome acquired resistance to MEK inhibitors. Preclinical studies have shown Wnt pathway overexpression in KRAS mutant cell lines resistant to the MEK inhibitor, selumetinib. The combination of selumetinib and cyclosporin A (CsA), a non-canonical Wnt pathway modulator, demonstrated antitumor activity in patient-derived xenograft (PDX) models. We conducted an NCI CTEP-approved Phase I/IB trial (NCI # 9571/COMIRB # 13-2628/NCT02188264) of selumetinib and CsA combination. Biomarkers of response are being co-developed. **Methods:** Patients with advanced solid tumors were treated with the combination of selumetinib and CsA in dose escalation followed by an expansion cohort in patients with irinotecan and oxaliplatin-refractory mCRC (n = 20). The expansion cohort utilized a selumetinib "run-in" to evaluate efficacy in RAS-WT and RAS-MT mCRC to identify those patients most likely to respond to the combination. **Results:** As of January 2017, 18 patients were enrolled in the dose escalation phase and 20 patients were enrolled in the dose expansion phase. The most common adverse events and grade 3/4 toxicities were rash, hypertension, and edema. Three DLTs - Grade 3 hypertension, rash and increased creatinine were reported. The maximum tolerated dose was identified as selumetinib 75 mg BID and CsA 2 mg/kg BID on a 28-day cycle. The selumetinib "run-in" did not favor a specific RAS type. Two partial responses were noted. Sixteen patients had stable disease, and 6 patients had progression of disease as their best response to therapy. **Conclusions:** Selumetinib in combination with cyclosporin A appears to be well tolerated with evidence of activity in mCRC. Tumor response data are currently being updated. FZD will be evaluated as a potential biomarker of response. Clinical trial information: NCT02188264.

2588 Poster Session (Board #80), Mon, 8:00 AM-11:30 AM

SWI/SNF complex subunit aberrations in diverse cancers: Next-generation sequencing of 539 patients. *First Author: Roman Groisberg, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The SWI/SNF complex is an ATP-dependent chromatin remodeler that is enriched at promoters and enhancers of active genes. It has been implicated as both an oncogene and tumor suppressor. Specific subunit mutations have even been associated with specific cancers with increased PRC2 component EZH2 activity. EZH2/ EED inhibitors are in early stage development to target SWI/SNF complex. **Methods:** We analyzed 539 consecutive patients with diverse malignancies who were referred for Phase 1 clinical trials and had CLIA certified targeted next-generation sequencing (Foundation one) for presence of aberrations in SWI/SNF complex genes *(ARID1A, ARID2, PBRM1, SMARCA4, SMARCB1)*. Patient charts were reviewed for general demographics (sex, age at diagnosis and death, performance status), tumor histology, stage, metastatic sites, treatment history, outcomes and co-occurring alterations. **Results:** Fifty patients had mutations in SWI/SNF subunits. Median age at diagnosis was 56 (14-79 years) and M:F ratio 21:29. Kidney, colorectal, ovary and breast were the most common among 15 different cancers. Most were stage IV at diagnosis (68%), had a strong family history of cancer (80%) & were smokers (42%). The most common mutated subunit was *ARID1A* (50%) followed by *PBRM1* (16%), *ARID2* (12%), *SMARCA4* (12%), and *SMARCB1* (10%). All mutations were predicted to be inactivating. Actionable co-occurring pathway alterations were found in 58% of patients, most commonly PI3K (26%), FGFR(16%), and NOTCH1/2 (10%). The majority of patients (62%) were enrolled on a clinical trial. Best responses on other targeted agents included 1 CR ($BRAF^{V600E}$ colon), 4 PR (transformed teratoma, skin SCC, ovarian, NSCLC), 12 SD. Exceptional responders included $BRAF^{V600E}$ colon cancer on BRAFi based therapy for 66 cycles, NSCLC on Nivolumab for 34 cycles, and MSI-H colon cancer on regorafenib/cetuximab for 27 cycles. **Conclusions:** The role of SWI/SNF in patients with extended clinical benefit from other targeted agents should be explored. Co-occurring genetic alterations are observed in PI3K, FGFR, and NOTCH pathways. Future pre-clinical and/or clinical studies could target these pathways in combination with EZH2/EED inhibitors.

2589 Poster Session (Board #81), Mon, 8:00 AM-11:30 AM

Phase 1 study of the bone-targeting cytotoxic conjugate, etidronate-cytosine arabinoside (MBC-11), in cancer patients with bone metastases. *First Author: Shawn Zinnen, MBC Pharma Inc, Aurora, CO*

Background: MBC-11 is a first-in-class therapeutic conjugate of the bone targeting bisphosphonate etidronate covalently linked to the antimetabolite cytosine arabinoside (Ara-C). In preclinical studies, MBC-11 localizes at the site of cancer-induced bone disease (CIBD) where it demonstrates both antiresorptive and antitumor activities following local release of Ara-C. Robust efficacy was observed in several rodent models of CIBD, as well as in spontaneous osteosarcoma in dogs. Herein, the results of the first-in-human study of MBC-11 are reported. **Methods:** Patients with advanced solid cancers and CIBD were treated with escalating doses (0.5-10 mg/kg/day) of MBC-11 administered as an intravenous infusion daily for 5 days every 4 weeks for up to 4 cycles. Fifteen patients (prostate cancer [PC; 7], breast cancer [BC; 7], cervical cancer [1]) received 38 total cycles. The study sought to characterize the safety, pharmacokinetics, and the effects of MBC-11 on bone turnover, and tumor response by ^{18}F-FDG-PET/CT imaging and tumor biomarkers. **Results:** Myelosuppression was generally grade 1-2, involved all lineages, and was the principal toxicity of MBC-11. Two of three patients treated at the 10 mg/kg dose level had dose-limiting toxicity (DLT), each with both grade 4 neutropenia and thrombocytopenia, the maximum tolerated dose (MTD) was 5 mg/kg. Four of 5 patients with pretreatment elevations of the bone resorption marker Trap5b had persistent decrements. ^{18}F-FDG-PET/CT imaging demonstrated partial metabolic responses in 3 patients; one BC patient treated at the 0.5 mg/kg and two CRPC patients treated at 1.0 mg/kg dose levels. An additional 3 patients had stable metabolic responses according to PERSIST. SUV values were reduced by at least 25% in 111 (53.8%) of 206 measurable bone lesions; significant activity was noted at all doses. **Conclusions:** At doses that were well tolerated and even much lower than the MTD, MBC-11 treatment resulted in substantial reductions in metabolic activity in CIBD patients, providing a foundation for further disease-directed studies to further assess efficacy. Clinical trial information: NCT02673060.

2590 Poster Session (Board #82), Mon, 8:00 AM-11:30 AM

The effect of supplemental estrogen on the outcomes of NSCLC patients in the SEER-Medicare database. *First Author: Samuel P. Heilbroner, Columbia University Medical Center, New York, NY*

Background: Women with lung cancer have better survival regardless of treatment type. Estrogen has been shown to have cancer-specific and non-cancer effects. However, there is conflicting data on the effect of estrogen hormone therapy on lung cancer incidence and mortality in women. We used the SEER-Medicare database to examine the association of estrogen use with overall and cancer cause specific survival in elderly women with non-small cell lung cancer (NSCLC). **Methods:** Patients in our cohort were women 65+ years old; were diagnosed with Stage I-IV NSCLC between 2007 and 2012; had Part A and B coverage one year before to one year after diagnosis without supplemental coverage from a HMO; had Part D coverage during the 6 months prior to diagnosis; were not in a nursing home at diagnosis. Using an intention to treat analysis, drug use was defined as having at least one Part D claim for estrogen within six months prior to diagnosis. Event free survival was assessed using a multivariate Cox proportional hazard model accounting for the patient (age, socioeconomic status, race, Charlson score) and tumor (stage, site, histology) characteristics. **Results:** There were 10,562 patients in our cohort. 688 used estrogen and 9,874 did not. The median age was 75 years with median overall survival of 1.0 year. There was a significant difference in age, socioeconomic status, race, Charlson score, stage, site, and tumor histology between the two groups ($p < 0.05$ for all). Estrogen use was associated with a significant improvement in overall and cause specific survival on univariate and multivariate regression (see table). **Conclusions:** Estrogen was associated with a significant improvement in survival. Limitations of this study are inherent to a retrospective claims-based database without knowledge of actual drug use or intent.

	Univariate		Multivariate		
Event	**HR**	**P**	**HR**	**P**	**# Events**
Overall Survival	0.78	< 0.01	0.82	< 0.01	8139
Cause specific survival	0.81	< 0.01	0.84	< 0.01	6483

2591 Poster Session (Board #83), Mon, 8:00 AM-11:30 AM

A phase 1/2 study of intermittent, high dose sunitinib in patients with advanced solid tumors. *First Author: Maria Rovithi, Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: Despite widespread clinical integration, refinement of treatment with sunitinib is actively pursued. Sub-therapeutic blood levels rather than true resistance and tumor adaptation through drug accumulation have been accounted as reasons for treatment failure. Based on our preclinical data with high dose sunitinib and prospective analyses supporting the concept of intermittent dosing, we designed a phase 1 trial to investigate the feasibility and tolerability of high dose, once weekly (1w) or once every two weeks (2w) sunitinib (NCT02058901). **Methods:** Eligible were patients (pts) with advanced solid tumors, refractory to standard treatment, measurable disease, WHO ≤ 1. Sunitinib was administered orally 1w or 2w. Starting dose was 200 mg, with cohorts escalating in 100 mg steps until maximum tolerated dose (MTD). Response was evaluated by RECIST 1.1. Treatment continued until progression or unacceptable toxicity. Dedicated PK sampling was performed. Sunitinib plasma concentration was measured by LC-MS. **Results:** 34 (w) and 24 (2w) pts were included, predominantly with mCRC [56% (1w) and 55% (2w)]. MTD was set at 300 mg (1w) and 700 mg (2w). Most common adverse events were fatigue (79%, one pt with G3), nausea (71%, all G1-2), anorexia (29%, all G1-2). Median PFS of evaluable pts was 2.7 mo (1w) and 2.6 mo (2w), while 39% pts (1w) and 25% pts (2w) had PFS > 5 mo. CT scans in pts with treatment benefit showed extensive tumor necrosis. Mean sunitinib plasma Cmax was 190 [300 mg (1w), range: 185-295] and 476 ng/mL [(700 mg (2w), range: 323-580]. Accumulation was minimal. **Conclusions:** Once weekly or once every two weeks, high dose sunitinib is feasible and clinically efficacious in heavily pretreated pts with advanced solid tumors, while toxicity remains well manageable. Importantly, no accumulation was recorded and sunitinib exposure was significantly increased, compared to the universal, flat dose. Since increased sunitinib exposure has been correlated to improved outcome, we consider this alternative scheduling as promising strategy to produce enduring clinical benefit in a wider patient population. Expansion cohorts are ongoing. Clinical trial information: NCT02058901.

2592 Poster Session (Board #84), Mon, 8:00 AM-11:30 AM

A dose-escalation study of imipridone ONC201 administered every one (QW) or three weeks (Q3W) in advanced solid tumors and multiple myeloma. *First Author: Anthony J. Olszanski, Fox Chase Cancer Center, Philadelphia, PA*

Background: ONC201 is an orally active, first-in-class small molecule activator of the integrated stress response that selectively upregulates ATF4 to trigger tumor cell death. A phase I study of ONC201 exploring different dosing regimens and drug exposure was conducted to determine the maximum tolerated dose (MTD), and recommended phase II dose (RP2D). **Methods:** A modified accelerated-titration dose escalation design was employed to enroll patients onto 2 sequential dose-escalation arms: ONC201 Q3W and QW. Dose escalation proceeded with the following order: 125, 250, 500, and 625mg (Q3W) and 250, 375, 500 and 625 (QW). Dose exposure ranged from 125 mg/6 wks to 1875 mg/3 wks. Key eligibility: advance/refractory solid tumor or myeloma, ECOG 0/1, and no active CNS disease. Adverse events, SAEs, laboratory values, physical exam findings, EKGs and bio-samples (for PK/PD) are collected. Pre and post ONC201 dose biopsies are being obtained from the 500mg weekly cohort and above. **Results:** 17 pts (12F:5M) with treatment-refractory tumors have been enrolled to date. Dose/#pts Q3W: 125/6, 250/1, 500/1, and 625/1; QW: 250/4, 375/4. Two patients have been enrolled at 500mg QW after database lock and not included in this assessment. Median (range) age: 57 yrs (27-72). ECOG 0/1: 2/15. MTD has not been reached. No DLTs observed. Tumor types: 8 CRC, 3 pancreatic, 2 sarcoma and 1 each cervical, endometrial, NSCLC (adeno) and small bowel. Of 17 pts, 10 (59%) had ≥1 tx-related adverse events (TRAEs), possibly related. Most common TRAEs (≥15% pts): fatigue (9,53%), anorexia (5,29%), nausea (4,24%), vomiting (4,24%), abdominal pain (3,18%), and arthralgias (2,12%). Grade ≥ 3 TRAEs were observed in 3 pts (18%). Pharmacokinetic and pharmacodynamic analysis is ongoing. Fresh frozen and paraffin-embedded biopsies (baseline and week 2) are being assessed for tumor markers implicated in the mechanism of action. No objective responses by RECIST have been seen. Final cohort is enrolling. **Conclusions:** ONC201 was well tolerated throughout the Q3W dosing and weekly dosing has been well tolerated to date without an apparent increase in AEs. Final enrollment summary, AEs and PK/PD data will be presented. Clinical trial information: NCT02609230.

2593 Poster Session (Board #85), Mon, 8:00 AM-11:30 AM

Phase I study combining the aurora kinase A (AURKA) inhibitor alisertib (Ali) with mFOLFOX in gastrointestinal (GI) cancer. *First Author: Laura Williams Goff, Vanderbilt University Medical Center, Nashville, TN*

Background: Overexpression and cellular mis-localization of AURKA in GI cancers results in chromosomal instability, activation of several oncogenic pathways, and inhibition of pro-apoptotic signaling. Inhibition of AURKA causes mitotic delays, severe chromosome congression, and activation of p53/p73 causing cell death. Our preclinical data showed synergy of Ali and platinum agents in GI cells and xenografts, and suggested an optimal timing window of the combination. The purpose of this study was to assess safety of Ali + mFOLFOX, as this is a standard platinum-based therapy for GI cancers. **Methods:** This CTEP-sponsored, investigator-initiated, study (NCT02319018) used standard 3+3 dose escalation to determine the maximum tolerated dose (MTD) of Ali + mFOLFOX. Eligible patients (pts) had metastatic or unresectable GI cancer where standard therapies did not exist or were no longer effective, or for whom FOLFOX was appropriate. Pts received escalating doses of Ali starting at 10 mg twice daily (D1-3), with leucovorin + oxaliplatin (85 mg/m^2) on D2 followed by continuous 5FU (2400 mg/m^2) infusion on D2-4 in 14-day cycles. Dose-limiting toxicity (DLT) was any treatment-related non-hematologic ≥Gr3 toxicity (except diarrhea or nausea, vomiting, controllable with meds) or ≥Gr4 hematologic toxicity observed during the first 28 days. **Results:** 13 pts were enrolled and 2 dose levels explored; 2 pts were not evaluable for DLT and replaced. Zero DLTs observed in first 3 pts. Ali was escalated to 20 mg where 2/6 had a DLT [Gr3 fatigue (n = 2); Gr3 nausea, vomiting, dehydration with hospitalization (n = 1)]. Ali was de-escalated and 2 of 3 pts have been enrolled; 0 DLTs observed thus far. Most frequent toxicities (%) were nausea (54), fatigue (46), neuropathy (46), anorexia (38), and anemia (38), most ≤Gr2. One of 10 evaluable pts had a partial response, and 6 had stable disease for a 70% disease control rate. **Conclusions:** The MTD will be 10 mg Ali (D1-3) + oxaliplatin (D2, 85 mg/m^2) + continuous 5FU (D2-4, 2400 mg/m^2). The combination was tolerable, and preliminary clinical activity was seen in a majority of pts. Correlative biomarker studies to evaluate AURKA target inhibition are ongoing and will be reported. Clinical trial information: NCT02319018.

2594 Poster Session (Board #86), Mon, 8:00 AM-11:30 AM

A phase I trial of the oral hedgehog inhibitor taladegib (LY2940680) in combination with weekly paclitaxel in patients with advanced, solid tumours. *First Author: Rosalind Margaret Glasspool, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom*

Background: Aberrant Hedgehog (Hh) signaling is implicated in carcinogenesis and is associated with poor prognosis in multiple tumours types. Hh inhibitors increase sensitivity to paclitaxel in taxane-resistant cell lines. Taladegib is an orally bioavailable, potent inhibitor of Smoothened, a key Hh pathway component, with activity in basal cell carcinoma. The single agent recommended dose is 400mg od. We present the dose escalation phase of a phase I study of weekly paclitaxel with oral taladegib. **Methods:** Primary objective: determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of taladegib on a continuous oral daily dosing regimen in combination with paclitaxel (80mg/m^2, iv, day 1, 8 and 15 q 28) in patients with advanced solid cancers. Secondary objectives: assess the safety and tolerability, determine the recommended phase II dose (RP2D), and evaluate the pharmacokinetics of taladegib and paclitaxel. Exploratory objective: assess preliminary efficacy. A standard 3 + 3 dose escalation design was used. All patients received up to 6 cycles of paclitaxel. In addition, successive cohorts received continuous oral taladegib continued until progression or unacceptable toxicity as follows: dose level 1: 100mg od; 2: 200mg od; 3: 400mg od. **Results:** No DLTs were seen at dose level 1 or in the first 3 patients at dose level 2. 3 DLTs of grade 2 neuropathy were seen at dose level 3 (400mg taladegib); therefore, dose level 2 was expanded to 6 patients. No DLT was seen in the fourth patient and 2 additional patients have started treatment. After the DLT period 2 patients developed G2 and 4 developed G1 neuropathy. Other non DLT, drug-related G3 toxicities: uncomplicated neutropenia x2, muscle cramp x1 and fatigue x1. To date, 3 patients have had partial responses. **Conclusions:** The combination of daily oral taladegib and weekly paclitaxel is feasible. DLT of G2 neuropathy was seen at 400mg. Promising activity has been seen in solid tumours. A dose expansion cohort is due to commence in high grade ovarian carcinoma. ISRCTN No:ISRCTN15903698 Eudract Ref:2014-004695-37 Funded by Cancer Research UK C8361/A18775 and Ignyta. Sponsored by NHS Greater Glasgow and Clyde. Clinical trial information: ISRCTN15903698.

2595 Poster Session (Board #87), Mon, 8:00 AM-11:30 AM

A sensitive QPCR assay for EGFR mutation in plasma samples of NSCLC patients. *First Author: Qin Feng, Beijing Cancer Hospital, Beijing, China*

Background: Tyrosine kinase inhibitors (TKI) have improved the overall outlook and quality of life for most of EGFR mutation positive NSCLC patients. However, tumor tissues are often absent or insufficient for testing EGFR mutations to guide EGFR TKIs treatment of patients with nonsmall cell lung cancer (NSCLC). An assay that detects EGFR mutations in the plasma would provide a noninvasive technique to assess suitability for TK inhibitor therapy. The ACCB new EGFR Mutation Kit is a ARMS-PCR test for the qualitative detection of 45 mutations in exons 18, 19, 20, and 21 of the EGFR gene in DNA derived from human plasma from NSCLC patients. **Methods:** 10 mL tubes of blood were collected from patients who never had been treated by EGFR TKI, and plasma circulating tumor DNA were extracted from plasma by Biomark Circulating DNA Kit. Qubit 2.0 Fluorometer was used to make plasma circulating DNA tumor quantitation. The concentration of final DNA sample is ≦2ng/μl. Total, 272 plasma DNA samples from 246 lung adenocarcinoma, 23 lung squamous carcinoma and 3 lung adenosquamous carcinoma patients were collected. 104 paired tissue EGFR mutations were detected by the same kit. **Results:** EGFR mutation was detected in 88 from 272 plasma DNA samples, 86 lung adenocarcinoma, 1 lung squamous carcinoma, 1 lung adenosquamous carcinoma, with EGFR mutation rate were 35.0% (86/246), 4.3% (1/23), 33.3% (1/3) respectively. In 61 I~III and 211 IV stage NSCLC patients, EGFR mutation rate were 21.3% (13/61) and 35.5% (75/211) respectively. **Conclusions:** The ACCB new EGFR Mutation Kit is a sensitive, accurate, rapid, and reproducible assay capable of testing DNA extracted from human plasma from NSCLC patients.

TPS2596 **Poster Session (Board #88a), Mon, 8:00 AM-11:30 AM**

A phase 1, open-label, dose escalation study of enoblituzumab (MGA271) in pediatric patients with B7-H3-expressing relapsed or refractory solid tumors. *First Author: Kenneth Desantes, University of Wisconsin, Madison, WI*

Background: Enoblituzumab, is an Fc optimized humanized IgG1 monoclonal antibody that binds to B7-H3 (CD276), a member of the B7 family. It is Fc-engineered to enhance effector function including antibody dependent cellular cytotoxicity (ADCC). IHC analyses with the parental anti-B7H3 mAb specificity incorporated in enoblituzmab revealed limited B7-H3 expression in normal tissues but high expression in many cancers (Loo et al., 2012). Among pediatric solid tumors, high expression of B7-H3 has been reported in neuroblastoma, rhabdomyosarcoma, osteosarcoma, Wilms tumor, Ewing's sarcoma and desmoplastic small round cell tumor. B7-H3 overexpression correlates with poor prognosis in a broad range of cancers in adults suggesting a potential role in enabling tumor immune escape. ADCC and potential modulation of T cell function resulting in enhanced antitumor immune response are presumed mechanisms of action of enoblituzumab. **Methods:** This is an open-label, dose escalation / cohort expansion phase 1 study (NCT02982941) designed to characterize the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of enoblituzumab in children and young adults with B7-H3-expressing relapsed or refractory malignant solid tumors. A 3+3 design is used in escalating dose cohorts of weekly intravenous (IV) enoblituzumab starting at 10 mg/kg. Response is first determined at 8 weeks. irRECIST is used for response assessment for patient management. Enoblituzumab may continue up to 2 years based on response. Cohort expansion phase, to further define the safety and initial antitumor activity of enoblituzumab, will start after maximum tolerated dose is determined. The patients are assigned to 1 of 5 cohorts based on disease type as follows: 1) neuroblastoma - measurable disease, 2) neuroblastoma - non-measurable disease, 3) rhabdomyosarcoma, 4) osteosarcoma, and 5) Ewing's sarcoma, Wilms' tumor and desmoplastic small round cell tumors. Enrollment is ongoing. Ref : Development of an Fc-enhanced anti-B7-H3 monoclonal antibody with potent antitumor activity. Loo D, Alderson RF, Chen FZ, Huang L et al. Clin Cancer Res. 2012; 18:3834-45. Clinical trial information: NCT02982941.

TPS2597 **Poster Session (Board #88b), Mon, 8:00 AM-11:30 AM**

An open-label study of rovalpituzumab tesirine in patients with DLL3-expressing advanced solid tumors. *First Author: Edward Kavalerchik, AbbVie Stemcentrx, San Francisco, CA*

Background: Delta-like protein 3 (DLL3) is an inhibitory ligand of the Notch receptor family. It is highly expressed in high-grade neuroendocrine carcinoma (NEC), such as small cell lung cancer (SCLC) and large cell NEC (LCNEC), but is not expressed in normal tissue. DLL3 is expressed in melanoma, glioblastoma (GBM), neuroendocrine prostate, medullary thyroid carcinoma (MTC), and other solid cancers. Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate targeting DLL3, composed of a DLL3-specific IgG1 monoclonal antibody joined to a toxic DNA cross-linking agent by a cleavable linker. Rova-T binds to DLL3 on target-expressing cells, is internalized and cleaved, releasing the toxin to induce cell death. A Phase 1 study of Rova-T in SCLC showed encouraging antitumor activity in DLL3-high patients (pts), and was well-tolerated (Rudin et al., Lancet Oncol, 2016). As novel therapies are needed for multiple cancers that express DLL3, Rova-T may be effective in these tumors. **Methods:** This is a Phase 1/2, open-label, multicenter study (NCT02709889) with 8 cohorts of pts (up to ~318 total, 14 pts enrolled as of 20 January 2017) with melanoma, MTC, GBM, LCNEC, neuroendocrine prostate cancer, gastroenteropancreatic NEC, other NEC, or other solid tumor. In Part A, a 3+3 dose escalation will be used. Rova-T 0.2, 0.3, or 0.4 mg/kg will be given on Day 1 of each 42-day cycle. Dose-limiting toxicities (DLTs) will be assessed over a 21-day period. Dose escalation will proceed within cohort until a maximum tolerated dose is reached. Part B expansion, Stage 1, will explore the recommended dose in 7 pts in disease specific cohorts. Stage 2 will use an adaptive 2-stage design to determine sample size. Pt eligibility: $\geq$ 18 years; histologically confirmed, measurable, advanced solid tumor; relapsed/refractory to prior standard therapy; ECOG 0-1; no prior exposure to a pyrrolobenzodiazepine-based drug. Primary objective: assess safety and tolerability of Rova-T. Secondary objectives: explore Rova-T antitumor activity, pharmacokinetics, and incidence of anti-therapeutic antibodies. Exploratory objectives: explore the relationship between DLL3 and clinical outcome, and effects on biomarkers and pharmacodynamics. Clinical trial information: NCT02709889.

TPS2598 **Poster Session (Board #89a), Mon, 8:00 AM-11:30 AM**

A study of rovalpituzumab tesirine in frontline treatment of patients with DLL3 expressing extensive small cell lung cancer. *First Author: Christine L. Hann, Johns Hopkins University, Baltimore, MD*

Background: Treatment and survival of SCLC patients (pts) has remained mostly unchanged over past decades with high response rates to initial therapy (cisplatin/carboplatin + etoposide), but relapse is near universal with median survival $<$ 1 year in extensive disease. Delta-like protein 3 (DLL3) is an inhibitory ligand of the Notch receptor family identified as a novel target in high-grade neuroendocrine tumors, and is highly expressed in SCLC but not in normal tissue. Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate targeting DLL3. A Phase I study of Rova-T monotherapy in 2nd and 3rd line SCLC pts demonstrated encouraging antitumor activity with an ORR of 18% in all pts, and an ORR of 38% in DLL3-high pts (Rudin et al., *Lancet Oncol*, 2016.). **Methods:** This is a Phase I, open-label, multicenter study (NCT02819999; no pts enrolled as of 7 February 2017).In Phase Ia (escalation), 15-34 previously untreated DLL3-high pts will be enrolled and randomized to 1 of 4 cohorts. The primary objective of the Phase Ia portion is assessment of safety and dose-limiting toxicities (DLTs). Phase Ib (expansion) will enroll up to 2 cohorts of 30 pts each, and its primary objective is to characterize antitumor activity of the selected cohort(s). Secondary objectives (Phase Ia/b) include assessment of pharmacokinetics and anti-therapeutic antibodies against Rova-T, and characterization of antitumor activity (Phase Ia). Eligible pts: adults with histologically or cytologically confirmed extensive DLL3-high SCLC based on immunohistochemistry; ECOG 0-1; and life expectancy $\geq$ 12 weeks. Clinical trial information: NCT02819999.

Cohort	Component	Rovalpituzumab tesirine cycle is 6 weeks Cisplatin/etoposide cycle is 3 weeks							
1		C1		C2					
	Rovalpituzumab tesirine	0.3 mg/kg		0.3 mg/kg					
2		C1		C2		C3	C4	C5	C6
	Rovalpituzumab tesirine	0.3 mg/kg		0.3 mg/kg					
	Cisplatin					80 mg/m^2	80 mg/m^2	80 mg/m^2	80 mg/m^2
	Etoposide					100 mg/m^2	100 mg/m^2	100 mg/m^2	100 mg/m^2
3		C1	C2	C3	C4				
	Rovalpituzumab tesirine	0.1 mg/kg		0.1 mg/kg					
	Cisplatin	80 mg/m^2	80 mg/m^2	80 mg/m^2	80 mg/m^2				
	Etoposide	100 mg/m^2	100 mg/m^2	100 mg/m^2	100 mg/m^2				
4		C1	C2	C3	C4	C5		C6	
	Rovalpituzumab tesirine					0.3 mg/kg		0.3 mg/kg	
	Cisplatin	80 mg/m^2	80 mg/m^2	80 mg/m^2	80 mg/m^2				
	Etoposide	100 mg/m^2	100 mg/m^2	100 mg/m^2	10 0mg/m^2				

TPS2599 **Poster Session (Board #89b), Mon, 8:00 AM-11:30 AM**

A phase 1, open-label, dose-escalation study of olaratumab as a single agent and in combination with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients with relapsed or refractory solid tumors. *First Author: Leo Mascarenhas, Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA*

Background: Olaratumab (LY3012207, IMC-3G3), a PDGFRα antagonist, is a targeted human IgG1 monoclonal antibody that specifically binds PDGFRα, blocking PDGF-AA, -BB, and -CC binding and receptor activation. Preclinical studies of olaratumab with or without chemotherapy have demonstrated antitumor activity in human sarcoma xenograft models. Positive survival outcomes were observed in adult patients with advanced soft tissue sarcoma when they were treated with olaratumab + doxorubicin vs doxorubicin alone in a randomized phase 2 trial. **Methods:** This multicenter clinical trial (NCT02677116) includes patients $<$ 18 years of age with a diagnosis of relapsed or refractory solid tumors not amenable to curative treatment, for whom chemotherapy with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide is deemed appropriate. The primary objective is to determine a recommended dose of olaratumab + $\geq$1 chemotherapy regimen (s) in pediatric patients based on any dose-limiting toxicity, and olaratumab serum exposure-matching between adult and pediatric patients. Secondary objectives include assessment of antitumor activity of each combination, immunogenicity, and pharmacokinetics. At least 12 pediatric patients will be treated with 1 cycle (21 days) of olaratumab monotherapy (dose level 1 [Part A] and dose level 2 [Part B]) on Days 1 and 8. If the patient does not experience a dose-limiting toxicity in the first cycle of monotherapy, the patient will then receive olaratumab plus either doxorubicin, vincristine/irinotecan, or high-dose ifosfamide per investigator discretion. Dose-limiting toxicity criteria will also be evaluated for the respective combinations in cycle 2. Treatment will continue until disease progression or other discontinuation criteria are met. Dose level 2 will be initiated after acceptable safety results from dose level 1 monotherapy (a minimum of 6 evaluable patients, and the pharmacokinetic profile). As of December 2016, enrollment is currently occurring in dose level 1. Clinical trial information: NCT02677116.

TPS2600 Poster Session (Board #90a), Mon, 8:00 AM-11:30 AM

A phase I study to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of oral COH29, a novel ribonucleotide reductase (RNR) inhibitor in adult patients (pts) with advanced solid tumors. *First Author: Joseph Chao, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Human RNR catalyzes the rate-limiting step in the formation of deoxyribonucleotide triphosphates (dNTPs) necessary for DNA repair and replication. Rapidly dividing tumor cells are especially sensitive to RNR inhibition due to elevated dNTP requirements. Overexpression of the RNR RRM2 subunit is also associated with neoplasia, metastasis, and poor prognosis. COH29 is an aromatically substituted thiazole compound that is a novel small molecule inhibitor of RNR activity, and exhibits unique mechanisms and target specificity that overcomes the weaknesses of other small molecule RNR inhibitors. Preclinically, it is more potent than hydroxyurea and gemcitabine, and is not associated with iron chelating-related toxicities such as hypoxia. Cell lines deficient in BRCA1 also exhibit greater sensitivity to COH29 than BRCA1 wildtype cell lines, implicating inhibition of DNA repair mechanisms in line with PARP inhibitors. **Methods:** In this Phase I, single site, dose escalation, safety study pts will receive oral COH29 twice a day for 21 days of a 28-day cycle. Eligible pts are age $\geq$ 18 years, ECOG $\leq$ 2, able to take oral medication, have adequate organ and marrow function, and diagnosed with any solid tumor refractory to standard therapies. Dose escalation will be pursued utilizing a Simon's accelerated titration design, which allows skipping of dose levels (dose doubling) during the accelerated dose-finding phase. Primary objectives are to determine the maximum tolerated dose of COH29, toxicities per CTCAEv4, and PKs. Secondary objectives include assessment of objective response per RECIST 1.1 every 2 cycles. PD assessment includes measurement of plasma CK18 levels to determine degree of cellular apoptosis, evaluation of dNTP pool levels in peripheral blood mononuclear cells (PBMCs) to evaluate RNR inhibition, as well as measurement of PAR expression in PBMCs to assess PARP inhibition. Quantitation of tumor RRM2 expression using dual-color immunohistochemistry will be explored as a predictive biomarker of anti-tumor response to COH29. Clinical trial information: NCT02112565.

TPS2601 Poster Session (Board #90b), Mon, 8:00 AM-11:30 AM

A phase I study to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activities of daily oral BAL101553, a novel tumor checkpoint controller (TCC) in adult patients with progressive or recurrent glioblastoma (GBM) or high-grade glioma. *First Author: Alvaro Henrique Ingles Garces, The Royal Marsden Hospital and The Institute of Cancer Research, London, United Kingdom*

Background: BAL101553 (prodrug of BAL27862) is a novel TCC that promotes tumor cell death by modulating the spindle assembly checkpoint. BAL27862 is a lipophilic, small molecule (MW 387) shown in rats to penetrate the brain (1:1 plasma ratio) and has shown promising antitumor activity in orthotopic preclinical models of GBM as monotherapy or in combination with radiotherapy (RT) with/without chemotherapy. In a completed Phase 1 study with 2-h IV infusions (Days 1, 8, 15, q28d, NCT01397929, CDI-CS-001, Lopez et al. J Clin Oncol 34, 2016 suppl; 2525), dose-limiting vascular effects were observed and appeared C_{max} related. Preclinical data suggest that antiproliferative effects of BAL101553/27862 are driven by exposure (AUC); thus vascular toxicity and antitumor activity are mediated by different PK drivers. In this ongoing study (NCT02490800, CDI-CS-002), daily oral BAL101553 was initially examined in solid-tumor patients; no vascular toxicities were observed at doses up to the MAD of 30 mg QD. Given this absence, the study was amended to enroll separate cohorts of patients with progressive or recurrent GBM or high-grade glioma. **Methods:** This is an ongoing multicenter, open-label, Phase 1 dose-escalation study using a 3+3 design to determine the MTD, characterize dose-limiting toxicities and assess the PK, PD and antitumor activities of daily oral administration of BAL101553 in consecutive 28-day cycles at a starting dose of 8 mg QD. Patients with histologically-confirmed GBM or high-grade glioma, with progressive or recurrent disease after prior RT with/without chemotherapy, are eligible for enrollment. This includes patients with histologically-confirmed low-grade glioma with unequivocal evidence by imaging of transformation to high-grade glioma. Adverse events are assessed using CTCAEv4; tumor response by RANO (every 2 cycles). The dose escalation allows for doubling of dose levels depending on observed toxicities. PD assessments include circulating tumor cells. PK profiles are assessed throughout the first two treatment cycles. Clinical trial information: NCT02490800.

TPS2602 Poster Session (Board #91a), Mon, 8:00 AM-11:30 AM

A phase I study to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activities of BAL101553, a novel tumor checkpoint controller (TCC), administered as 48-hour infusion in adult patients with advanced solid tumors. *First Author: Markus Joerger, Cantonal Hospital St. Gallen, St. Gallen, Switzerland*

Background: BAL101553 (prodrug of BAL27862), is a novel TCC that promotes tumor cell death by modulating the spindle assembly checkpoint. BAL27862 has shown potent antitumor activity in diverse preclinical tumor models, including models refractory to standard therapies. In a completed Phase 1 study using 2-h IV infusions (Days 1, 8, 15, q28d, NCT01397929, CDI-CS-001, Lopez et al. JCO 34, 2016 suppl; 2525) dose-limiting vascular effects were observed and appeared C_{max} related. The recommended Phase 2 dose for 2-h IV BAL101553 is 30 mg/m^2. Vascular toxicity was not observed in an ongoing study with oral BAL101553 (NCT02490800, CDI-CS-002) at daily doses up to 30 mg (QD). Preclinical data suggest that antiproliferative effects of BAL101553/27862 are driven by exposure (AUC); thus vascular toxicity and antitumor activity are mediated by different PK drivers. BAL27862 has a half-life of ~15 h. Based on PK-modeling, extending the infusion from 2 h to 48 h was expected to result in ~4-fold higher AUC at a given C_{max}level and thereby improve the therapeutic window. **Methods:** This is an ongoing multicenter, open-label, Phase 1 dose-escalation study (NCT02895360, CDI-CS-003/SAKK67/15) using a 3+3 design to determine the MTD, characterize dose-limiting toxicities and assess the PK, PD and antitumor activities of 48-h infusions of BAL101553 in consecutive 28-day cycles at a starting dose of 30 mg/m^2 administered on Day 1, 8 and 15 (q28d). The dose escalation scheme foresees up to ~ 50% dose increments depending on observed toxicities. During cycle 2, patients receive 7 days oral (QD) BAL101553 (Day 15–21) instead of the weekly IV infusion to assess absolute oral bioavailability. Patients with histologically-confirmed advanced or recurrent solid tumors are eligible for enrollment. Adverse events are assessed using CTCAEv4; tumor response by RECIST 1.1 (every 2 cycles). PD assessments include optional tumor biopsies and circulating tumor cells. PK profiles are assessed during the first 2 cycles. Two dose cohorts (30 and 45 mg/m^2) have completed without DLTs or signs of vascular toxicity. Clinical trial information: NCT02895360.

TPS2603 Poster Session (Board #91b), Mon, 8:00 AM-11:30 AM

Phase IB study to evaluate the safety of selinexor in combination with multiple standard chemotherapy agents in patients with advanced malignancies. *First Author: Aung Naing, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Selinexor is a first-in-class, slowly reversible, Selective Inhibitor of Nuclear Export (SINE) compound that specifically blocks XPO1. Inhibition of XPO1 results in nuclear localization, accumulation, and reactivation of tumor suppressor proteins, therefore selectively inducing apoptosis in cancer cells, while largely sparing normal cells. This unique property of XPO1 inhibition has been deployed as a novel therapeutic strategy with success in several solid tumors and hematologic malignancy clinical trials. Preclinical studies have shown that SINE compounds behave synergistically to enhance cancer cell death with combined with different therapeutic agents. This Phase I trial is based on such preclinical evidence. The primary objective of the study is to establish the safety and tolerability of selinexor when given in combination with thirteen standard chemotherapy regimens. The secondary objectives are to determine disease control and progression-free survival of patients receiving selinexor administered with standard chemotherapy treatments in specific tumor subsets. **Methods:** Adult patients $\geq$ 18 years of age are eligible if they have histologically confirmed neoplasms (excluding hematological malignancies and brain tumors) that are refractory to established therapy known to provide clinical benefit for their condition. Patients are required to have either measurable disease (RECIST 1.1) or evaluable disease, and an ECOG performance status of 0-1. Enrollment is ongoing for dose escalation with the plan for dose expansion as follows: Clinical trial information: NCT02419495.

Treatment Arm	Dose Expansion (N)
Selinexor + Carboplatin	Any Histology (9)
Selinexor + Paclitaxel	Ovarian (25)
	Breast (25)
Selinexor + Eribulin	Any Histology (9)
Selinexor + Doxorubicin/ Cyclophosphamide	Any Histology (9)
Selinexor + Carboplatin / Paclitaxel	Ovarian (25)
	NSCLC (25)
Selinexor + Carboplatin / Pemetrexed	Any Histology (9)
Selinexor + Topotecan	Ovarian (25)
Selinexor + FOLFIRI	CRC (25)
Selinexor + Irinotecan	CRC (25)
Selinexor + XELOX	CRC (25)
Selinexor + Olaparib	Ovarian (25)
Selinexor + Pembrolizumab	Melanoma (25)
	NSCLC (25)
Selinexor + Nivolumab	Melanoma (25)
	NSCLC (25)
	RCC (25)

TPS2604 Poster Session (Board #92a), Mon, 8:00 AM-11:30 AM

EphA2 gene targeting using neutral liposomal small interfering RNA (EPHARNA) delivery: A phase I clinical trial. *First Author: Aung Naing, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: EphA2 is a member of the largest subfamily of receptor tyrosine kinases, with over 14 receptors and 8 ligands. EphA2 overexpression is common in many human cancers, including lung, breast, prostate, colorectal, pancreatic, melanoma, esophageal and endometrial cancers. EphA2 can function as an oncoprotein when introduced into cells with low expression. In addition, downregulation of constitutive expression reduces tumorigenicity in breast, endometrial, ovarian and pancreatic cancers *in vitro* and *in vivo* models. EphA2 is a desirable target because of its selective expression in cancer (vs. adult normal tissue), and its important role in promoting tumor growth and metastasis. It has kinase-dependent and independent functions, making it an ideal target for RNAi-based targeting. We have previously reported that EphA2 siRNA incorporated in DOPC nanoliposomes (EPHARNA) was highly effective in reducing EphA2 protein levels after a single dose. In addition, three weeks of treatment with EPHARNA (150 μg/kg twice weekly) in an orthotopic mouse model of ovarian cancer (HeyA8 or SKOV3ip1) significantly reduced tumor growth compared with non-silencing siRNA, and demonstrated synergistic anti-tumor activity when combined with conventional chemotherapy. EPHARNA underwent GLP development in 2 animal models (murine and primate) at M.D. Anderson to support the IND (#72924). The first-in-human trial (NCT01591356) is ongoing and recruiting study subjects. **Methods:** Adult Patients > 18 years of age with histologic proof of advanced recurrent solid tumors, who are not candidates for known regimens or protocol treatments of higher efficacy or priority. All patients (dose escalation and dose expansion phases) must be willing to undergo pre- and post-treatment biopsies. For dose expansion phase, patients must have EphA2 overexpression by IHC evaluation. Enrollment is ongoing for the dose escalation with the plan for dose expansion. A total of 16 patients have been enrolled and treated in the dose escalation phase. Clinical trial information: NCT01591356.

TPS2605 Poster Session (Board #92b), Mon, 8:00 AM-11:30 AM

GCT1021-01, a first-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (HuMax-Axl-ADC) in patients with solid tumors (NCT02988817). *First Author: Ulrik Niels Lassen, Rigshospitalet, Copenhagen, Denmark*

Background: HuMax-AXL-ADC is an antibody-drug conjugate (ADC) composed of an Axl-specific human monoclonal immunoglobulin G1 (IgG1κ) conjugated via a protease-cleavable valine-citrulline linker to the microtubule disrupting agent monomethyl auristatin E (MMAE). *In vivo*, HuMax-AXL-ADC demonstrated therapeutic anti-tumor efficacy in patient-derived xenograft models representing a variety of solid cancers, including pancreas, thyroid, lung, esophageal, cervical cancers and malignant melanoma. The non-clinical safety profile and pharmacokinetics (PK) of a once every 3 weeks (1Q3W) dosing schedule were established in cynomolgus monkeys. **Methods:** The primary objective of this trial is to determine the MTD and to establish the safety profile of HuMax-AXL-ADC in a mixed population of patients with specified solid tumors: ovarian, cervical, endometrial, thyroid cancer, NSCLC, and malignant melanoma. The trial consists of two parts, a phase I dose escalation part and a phase IIa expansion part. The dose escalation part explores two different dosing regimens: the first investigates doses from 0.3 up to 2.8 mg/kg to be administered 1Q3W. The second investigates doses in the range of 0.45 to 1.4 mg/kg to be administered weekly for 3 weeks followed by one treatment-free week (3Q4W dosing schedule). The second arm has a delayed start to inform a safe starting dose: when at least 8 patients have been evaluated for dose limiting toxicities, the 1.5 mg/kg cohort of the 1Q3W arm has been declared safe, and the predicted PK parameters of the starting dose in the 3Q4W arm are below pre-defined limits, the 3Q4W arm will be initiated. The 1Q3W arm follows a modified Bayesian Continuous Reassessment Method including escalation with overdose control in up to 41 patients on up to 7 main and 4 intermediate dose levels while the 3Q4W arm is run as a standard 3+3 trial design on up to 5-6 dose levels. In the phase IIa expansion part, further safety and biological activity data will be generated in selected indications using cohorts of 22 patients (11+11 patients in each cohort applying the Simon's two-stage design). Clinical trial information: NCT 02988817.

TPS2606 Poster Session (Board #93a), Mon, 8:00 AM-11:30 AM

A phase Ib, first-in-human, dose escalation and expansion study of XMT-1522, a novel antibody-drug conjugate (ADC) directed against HER2, in patients with advanced breast cancer and other advanced tumors expressing HER2. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Nashville, TN*

Background: XMT-1522 is an ADC consisting of a novel human IgG1 anti-HER2 monoclonal antibody conjugated to an auristatin-based cytotoxic payload (AF-HPA). An average of 12 AF-HPA molecules is conjugated to each antibody via a biodegradable polymer. In pre-clinical xenograft experiments XMT-1522 achieved complete, durable tumor regressions in models of HER2-positive and HER2 1+/2+ breast cancer, HER2 2+/3+ NSCLC, and HER2-positive and HER2 1+ gastric cancer. **Methods:** This study (NCT02952729) is comprised of two parts: a dose escalation segment (DES) and an expansion segment (EXP). The primary objectives of the DES are determination of the maximum tolerated dose and recommended Phase 2 dose (RP2D) and assessment of safety and tolerability. The DES will enroll patients with advanced or metastatic breast cancer who have progressed following standard therapies and have HER2 protein at least 1+ by IHC. XMT-1522 will be administered intravenously every 3 weeks. DES uses a 3+3 design. Post-dose assessments include LVEF measurement at the end of cycles 1, 3, then every 3 cycles, ophthalmologic exams at the end of cycles 1, 2, then every 2 cycles, and re-staging CT scans every 2 cycles. Pharmacokinetics of antibody, AF-HPA payload and an AF-HPA metabolite will be measured. Two patients have completed dose level 1 without DLT. The EXP segment will open at the RP2D and will further assess safety and tolerability of XMT-1522 and assess efficacy in selected patient populations. EXP will enroll 4 cohorts (N = 20 each).

- Cohort 1: HER2 1+/2+ advanced breast cancer with 2-3 prior chemotherapy regimens
- Cohort 2: HER2-positive advanced breast cancer with prior pertuzumab and ado-trastuzumab emtansine (T-DM1)
- Cohort 3: HER2-positive advanced gastric cancer with prior trastuzumab
- Cohort 4: HER2 2+/3+ NSCLC with at least 1 prior platinum regimen

The protocol requires archival tumor tissue for central confirmation of HER2 status, alternative HER2 measurements, and targeted gene expression and sequencing studies. Tumor biopsies will be requested at the time of progression from patients who responded to XMT-1522. Clinical trial information: NCT02952729.

TPS2607 Poster Session (Board #93b), Mon, 8:00 AM-11:30 AM

A phase I study of SRA737 (formerly known as CCT245737) administered orally in patients with advanced cancer. *First Author: Maxime Chenard-Poirier, CHU de Québec-Université Laval, Québec, QC, Canada*

Background: SRA737 is a highly selective, orally bioavailable small molecule inhibitor of Checkpoint kinase 1 (Chk1), a key cell cycle checkpoint and central regulator of the DNA Damage Response (DDR) network. In cancer cells, replication stress induced by genomic alterations in oncogenes (eg, *MYC* and *RAS*) combined with loss of function in tumor suppressors (eg, *TP53* and *ATM*) results in persistent DNA damage and genomic instability. Targeted inhibition of components of the DDR network such as Chk1 by SRA737 may be synthetically lethal to cancer cells and have utility as a monotherapy in a range of tumor indications. SRA737 is currently being investigated in two Phase 1 trials in patients with advanced cancer. We now describe the Phase 1 multicenter, dose-escalation, monotherapy study of SRA737 (NCT02797964). **Methods:** Up to 40 patients with advanced cancer will receive oral SRA737 administered daily on a 28-day schedule. For dose-escalation, an accelerated titration design with 100% dose escalation and single patient cohorts is allowed until Grade 2 related toxicity is observed, followed by a rolling-6 design. Dose expansion will include 6 patients with any solid tumor treated at the recommended Phase 2 dose (RP2D). Eligibility criteria include WHO performance status of 0-1 and ≤ 3 prior lines of cytotoxic chemotherapy for metastatic disease. Primary objectives are to assess the safety profile of monotherapy SRA737 and to establish a RP2D. The PK profile and PD biomarkers will be investigated. The study was opened to enrollment in mid-2016. An amendment, which includes the addition of indication specific expansion cohorts of subjects with genetically-defined tumors known to have Chk1-sensitizing aberrations such as gene mutations and amplifications/deletions, has been submitted and is pending regulatory review while enrollment continues. At the Annual Meeting, the amended design will be described. The dose and schedule identified in this trial will inform the design and conduct of Phase 2 studies of SRA737 as a single agent and in combination with other targeted or immunomodulatory agents. Clinical trial information: NCT02797964.

TPS2608 Poster Session (Board #94a), Mon, 8:00 AM-11:30 AM

A phase I, open-label, first-time-in-patient dose escalation and expansion study to assess the safety, tolerability, and pharmacokinetics of nanoparticle encapsulated Aurora B kinase inhibitor AZD2811 in patients with advanced solid tumours. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Nashville, TN*

Background: Aurora kinase B performs key roles in the regulation of the cell cycle and represents a potential target for anticancer therapy. AZD2811, formerly designated AZD1152 hydroxy-quinazoline pyrazole anilide (AZD1152 hQPA), is a potent and selective inhibitor of Aurora B kinase activity and has been incorporated into a polymer nanoparticle carrier for intravenous (IV) administration. The phosphate pro-drug of AZD2811, known as AZD1152 (barasertib), reached Phase II of clinical development as a continuous IV infusion. While promising efficacy was seen with barasertib in elderly acute myeloid leukaemia (AML) patients (Kantarjian HG et al., Cancer 2013;119:2611-19), continuous intravenous drug delivery precluded subsequent development in this disease setting and there were limited clinical responses in solid tumour patients due to dose-limiting myelotoxicity. AZD2811 nanoparticle has been designed to overcome these issues. **Methods:** Patients with relapsed advanced solid malignancies with no standard treatments are eligible for the part A dose escalation. Primary endpoint is to determine the maximum tolerated dose of AZD2811 nanoparticle using a 3+3 design. Patients with refractory/relapsed small cell lung cancer (SCLC) will be eligible for the part B expansion, where the safety, PK and anti-tumour activity of AZD2811 nanoparticle will be assessed as monotherapy and in combination with chemotherapy. Study enrolment is ongoing. Clinical trial information: NCT02579226.

TPS2609 Poster Session (Board #94b), Mon, 8:00 AM-11:30 AM

Phase I trial of the triplet veliparib + VX-970 + cisplatin in patients with advanced solid tumors. *First Author: Geraldine Helen O'Sullivan Coyne, Early Clinical Trials Development Program, DCTD, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: The DNA damage response (DDR) pathway is a key element of cellular integrity. Platinum compounds form covalent bonds with purine bases causing DNA cross-links that stall replication forks halting transcription. Poly (ADP-ribose)polymerase-1 (PARP-1) plays a pivotal role in DDR and base-excision repair. Ataxia-telangiectasia-related (ATR) protein kinase is also central to DDR and homologous recombination, activating a series of phosphorylation cascades culminating in cell cycle arrest to allow time for DNA repair. Veliparib (ABT-888) is a PARP 1/2 inhibitor (PARPi) with clinical evidence of antitumor activity in combination with cisplatin in BRCA mutation carriers (Rodler *et al*, Cancer Res. 2011). VX-970 is a potent ATR inhibitor, with antitumor activity across a range of cell lines in combination with DNA damaging agents, including cisplatin (Huntoon *et al*, Cancer Res. 2013). In this trial, we will evaluate whether the combination of veliparib + VX-970 impairs DNA repair, inducing a "BRCA null"-like phenotype leading to potentiation of the antitumor activity of cisplatin. **Methods:** Open label phase I trial of the veliparib+VX-970+cisplatin combination, following a 3+3 design, with dose limiting toxicities defined during cycle 1. Estimated enrollment: 24 patients (pts); Dana Farber and MD Anderson planned as additional sites. Drug administration over a 21-day cycle: VX- intravenously (IV) on Days 2 and 9; Veliparib orally twice daily (q12 hours $\pm$ 1 hour) Days 1-3 and 8-10; cisplatin 40 mg/m^2 IV Day 1 (with Day 8 added from DL3 onwards). Pts must be $\geq$ 18 years of age; have histologically confirmed solid tumors that have progressed on standard of care therapy known to prolong survival or without known standard, ECOG PS $\leq$2, and life expectancy $\geq$3 months. Pts with treated brain metastasis with stable disease $\geq$4 weeks without requiring steroids or anti-seizure medication are eligible. Exclusion criteria include a prolonged QTc interval, and sensory/motor neuropathy $\geq$grade 2 by CTCAE v.4. At this time, cohort 3 has enrolled 1 of 3 planned pts. Assessment of DDR and apoptosis biomarkers at the maximally tolerated dose using a validated and quantitative immunofluorescence assay is planned. Clinical trial information: NCT02723864.

TPS2610 Poster Session (Board #95a), Mon, 8:00 AM-11:30 AM

Combination immunotherapy with IDO vaccine and PD-1 inhibitors in advanced NSCLC. *First Author: Anders Mellemgaard, Herlev University Hospital, Herlev, Denmark*

Background: Multible checkpoints regulate host immune response, and development has focused on three of these: IDO, CTLA-4 and PD-1. Presently, several checkpoint inhibitors have been approved for advanced NSCLC including nivolumab, pembrolizumab, and atezolizumab all targeting PD-1 and PD-L1. Depending on level of PD-L1 tumor expression, response rates vary, and a substantial proportion of patients do not respond to treatment with immune checkpoint inhibitors. The combination of checkpoint inhibitors have been shown in malignant melanoma and other tumor types to clearly increase the effect. IO102 is a synthetic peptide under development as an immune-modulatory agent targeting cells expressing indoleamine 2,3-dioxygenase (IDO). IDO potently inhibits T-cell immunity in patients with cancer. Treatment with IO102 in NSCLC patients after first line palliative chemotherapy lead to long PFS in a number of patients in a small single arm study. **Methods:** IO102-001 is a randomized, double-blinded Phase 2 trial to evaluate the safety and efficacy of IO102 in combination with anti-PD-1 mAb in locally advanced and/or metastatic NSCLC stage III-IV patients eligible for anti-PD-1 mAb 2nd line treatment after first line of chemotherapy. Patients are randomized (2:1) to either a PD-1 inhibitor + IO201 vaccine or a PD-1 inhibitor (SOC). The PD-1 inhibitor will be administered according to label while IO102 will be given as s.c. injection every 2 weeks for the first 12 weeks, and subsequently every 4 weeks for 12 months or until progression, death or withdrawal from trial, whichever comes first. Treatment is continued to progression, unacceptable toxicity or withdrawal of consent. Main inclusion criteria is patients diagnosed with locally advanced and/or metastatic NSCLC Stage III-IV, measurable disease according to RECIST (1.1), patients eligible for anti PD-1 mAb treatment after 1st line of chemotherapy , ECOG performance status 0 or 1 and available tumor tissue for further analysis. A total of 90 patients will be included in the trial, and the trial will be active in countries in Europe and the US from Q2 2017.

TPS2611 Poster Session (Board #95b), Mon, 8:00 AM-11:30 AM

Phase Ib study of rebastinib plus antitubulin therapy with paclitaxel or eribulin in patients with metastatic breast cancer (MBC). *First Author: Jesus Del Santo Anampa Mesias, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY*

Background: TMEM (Tumor Microenvironment of Metastasis) are microanatomic structures formed by a Mena-expressing tumor cell, Tie2-expressing macrophage, and endothelial cell in direct content, which serve as the primary portal for tumor cell intravasation into the circulation and subsequent metastasis. Paclitaxel (P) induces the formation of TMEM in the primary tumors of patients treated with neoadjuvant chemotherapy (NAC), and in the primary tumor and distant metastases in the PyMT/PDX models. Tumor cell intravasation is mediated by release of VEGF at TMEM sites from TMEM-associated Tie2^{HI}/VEGF^{HI} macrophages upon binding of the Tie2 receptor to angiopoietin. The Tie2 inhibitor rebastinib (R) inhibits intravasation at TMEM sites, reduces circulating tumor cell (CTC) burden, prevents distant metastases, and improves survival in breast cancer animal models when added to either P or eribulin (E). We hypothesize that the addition of R to antitubulin therapy in patients with HER2-negative MBC will prevent hematogenous dissemination and distant metastasis by inhibiting TMEM function, reduce CTC burden; and improve clinical outcomes. **Methods:** Primary objective of this phase Ib study (NCT02824575) is to evaluate safety and tolerability of R in two dose levels (DL) (50mg or 100mg PO BID) combined with IV P 80mg/m2 (day 1, 8 and 15) or E 1.4mg/m2 (day1 and 8) for four 21-day cycles. Key eligibility includes histologically confirmed HER2 negative MBC, $\leq$ 2 non-taxane chemotherapy regimens for R plus P arm or $\geq$ 2 chemotherapy regimens (including a taxane) for E plus R arm, $\geq$2 endocrine therapies (including CDK4/6 inhibitor) for ER positive patients, ECOG PS 0 or 1; and normal organ and marrow function. Exclusion criteria include significant ocular or cardiac disease. Pharmacodynamic biomarkers to be measured during cycle 1-3 include CTCs, angiopoietin 1/2 levels and Tie-2 expressing monocytes. Tissue biopsy after two treatment cycles in 6 patients will be performed to evaluate TMEM score and function. With two DL of rebastinib, and 3-6 patients at each DL, it is anticipated that 6-12 patients will be required. This trial has enrolled two patients assigned to P arm combined with R 50mg BID. Clinical trial information: NCT02824575.

TPS2612 Poster Session (Board #96a), Mon, 8:00 AM-11:30 AM

First-in-human, first-in-class phase I study of MTL-CEBPA, a small activating RNA (saRNA) targeting the transcription factor C/EBP-α in patients with advanced liver cancer. *First Author: Debashis Sarker, King's College London, London, United Kingdom*

Background: saRNAs are small oligonucleotide drugs designed to selectively upregulate therapeutic proteins by recruiting endogenous transcriptional complexes to a target gene, leading to increased expression of naturally processed mRNA. Transcription factor C/EBP-α (CCAAT/enhancer-binding protein alpha) is a leucine zipper protein which acts as a master regulator of liver homeostasis and multiple oncogenic processes including cell cycle control, proliferation and angiogenesis. MTL-CEBPA comprises a double stranded RNA payload formulated inside a SMARTICLES liposomal nanoparticle to specifically target the CEBPA gene and has been shown to improve liver function and inhibit hepatocellular cancer (HCC) tumor growth in preclinical models (Reebye et al, Hepatology, 2014). MTL-CEBPA is the first saRNA and the first drug targeting C/EBP-α to enter clinical trials. **Methods:** Pts with advanced HCC (Child-Pugh A or B7 only) or secondary liver cancer refractory to or ineligible for standard treatment, ECOG PS 0-1, acceptable haematologic, liver and renal function, are currently being enrolled in a standard 3+3 dose escalation study. Once the RP2D is defined, 12-15 patients with advanced HCC will be evaluated further in a dose expansion cohort. MTL-CEBPA is administered as a 1-hr IV infusion on Day 1, 8 and 15 of a 28-day cycle. RECIST tumor response is assessed after every 2 cycles. The primary objective is to determine safety and tolerability; secondary objectives include PK, liver function improvement and anti-tumor activity. Correlative studies include C/EBP-α mRNA levels in PBMCs and optional tumor tissue, evaluation of C/EBP-α downstream target genes (e.g. TGFβ) and distal target engagement in white blood cells (e.g.IL-6, NF-κB, IFN-γ). Recruitment to cohort 2 is shortly to be completed, with no DLTs reported to date. Clinical trial information: NCT02716012.

TPS2613 Poster Session (Board #96b), Mon, 8:00 AM-11:30 AM

A phase I study of oral SRA737 (formerly CCT245737) given in combination with gemcitabine plus cisplatin or gemcitabine alone in patients with advanced cancer. *First Author: Alvaro Henrique Ingles Garces, Brazilian National Cancer Institute, Rio De Janeiro, Brazil*

Background: SRA737 is a highly selective, orally bioavailable small molecule inhibitor of Checkpoint kinase 1 (Chk1), a key cell cycle checkpoint and central regulator of the DNA Damage Response (DDR) network. In cancer cells, replication stress induced by genomic alterations in oncogenes (eg, *MYC* and *RAS*) combined with loss of function in tumor suppressors (eg, *TP53* and *ATM*) results in persistent DNA damage and genomic instability. Targeted inhibition of components of the DDR network such as Chk1 by SRA737 may be synthetically lethal to cancer cells. Chk1 is also believed to facilitate tumor cell resistance to chemotherapy or radiation-induced DNA damage and the combination of SRA737 with these standards-of-care may provide synergistic antitumor activity. SRA737 is being investigated in two Phase 1 trials in patients with advanced cancer. We now describe the Phase 1 multicenter, dose-escalation study of SRA737 in combination with gemcitabine/cisplatin (GC) or gemcitabine (G) alone (NCT02797977). **Methods:** Up to 70 patients will receive escalating doses of SRA737+GC in Stage 1 or SRA737+G in Stage 2 until a recommended Phase 2 dose (RP2D) is established, followed by expansion cohorts. Patients will receive a single SRA737 PK run-in dose followed by Gem on D1 and 8, Cis on D1, SRA737 on D2, 3, 9 and 10 of each 21-d cycle or Gem on D1, 8 and 15, SRA737 on D2, 3, 9, 10, 16, 17 of each 28-d cycle. Eligibility criteria include WHO performance status of 0-1 and ≤ 3 prior lines of cytotoxic chemotherapy for metastatic disease. Primary objectives are to assess the safety profile of SRA737 combination therapy and to establish a RP2D. The PK profile and PD biomarkers (eg, phosphorylation of Chk1 at Ser296, Ser345 and γH2AX foci in PBMCs and tumor tissue) will be explored. The study was opened to enrollment in mid-2016. An amendment, which includes the addition of an indication specific expansion cohort of subjects with genetically-defined tumors known to have Chk1-sensitizing aberrations (eg, gene mutations and amplifications/deletions), has been submitted and is pending regulatory review while enrollment continues. At the Annual Meeting, the amended design will be described. Clinical trial information: NCT02797977.

TPS2614 Poster Session (Board #97a), Mon, 8:00 AM-11:30 AM

A phase 1b, open label, single institution trial of nintedanib in combination with bevacizumab in patients with advanced solid tumors. *First Author: Ankit Madan, University of Alabama, Hoover, AL*

Background: Vascular endothelial growth factor (VEGF) is a potent factor in inducing angiogenesis. VEGF inhibitors have produced demonstrable but limited and transient clinical benefit for various cancers. One mechanism of resistance includes revascularization secondary to up-regulation of alternative pro-angiogenic signals such as platelet derived growth factor receptor (PDGF) and fibroblast growth factor receptor (FGFR) pathway. Nintedanib is an oral triple kinase inhibitor that blocks the VEGFR, PDGFR and FGFR pathways. Our study is using combination of Nintedanib (Nin) and Bevacizumab (Bev) which will block VEGF as well as salvage pathway of angiogenesis (PDGFR and FGFR). Phase I dose selection studies revealed that Nin is generally well tolerated (Clin Can Res 16:47, 2010). LUME-Lung 1 phase 3, international, double blind, placebo controlled trial using Nin and docetaxel in non-small cell lung cancer (NSCLC) showed significant improvement in progression free survival (PFS) regardless of histology and improvement in overall survival (OS) in lung adenocarcinoma (Lancet oncology 15:2, 2014). **Methods:** This is a phase 1b, open label, single institution trial with standard 3+3 design. Primary objective is to evaluate the safety and tolerability of combination of Nin and Bev. The secondary objective is to determine clinical efficacy (objective response), PFS, and evaluation of plasma levels of angiogenic and anti-angiogenic biomarkers like VEGF, PDGF, VEGF-R and FGF. Patients (pts) in cohort I will be treated with Bev 15 mg/kg day 1 intravenously every 3 weeks and Nin 150 mg orally (PO) twice daily (BID) from day 2-21. In the absence of dose limiting toxicities, Nintedanib dose will be increased to 200 mg PO BID in cohort II. Major inclusion criteria includes advanced solid tumors for which Bev has an indication (non-squamous, NSCLC, colon, ovarian, cervical and renal cancer), progression after at least 1 line of systemic treatment, and measurable disease. Pts with prior treatment with Bev can be enrolled. We will enroll 18 patients. Cohorts I has been completed without DLT (n = 3). Cohort II has enrolled 10 patients. Clinical trial information: NCT02835833.

TPS2615 Poster Session (Board #97b), Mon, 8:00 AM-11:30 AM

A phase Ib/II, open-label, dose escalation study to evaluate the safety, pharmacokinetics, and efficacy of SM88 in patients with prostate cancer. *First Author: Giuseppe Del Priore, Morehouse School of Medicine, Atlanta, GA*

Background: Non-hormonal treatments for biochemically recurrent non-metastatic prostate cancer (nmPC) are limited. SM88 is a novel combination of proprietary tyrosine isomer (TI) and other repurposed agents (CYP3a4 inducer, mTOR inhibitor and catalyst) designed to selectively increase metabolic oxidative stress in cancer cells. Early data reported SM88 activity in solid tumors without significant toxicity (Hoffman et al J Clin Oncol 2013; e22095, Hoffman et al Ann Onc 2016: vi551). **Methods:** This is an open-label multi-center, dose escalating, dose expansion study in nmPC who have failed or refused androgen deprivation. The study includes a dose escalation phase Ib and dose expansion phase 2. The primary objectives are to determine the effect of SM88 on circulating tumor cells (CTC), and progression-free survival. Secondary objectives are: LDH, bone-specific alkaline phosphatase, urinary N-telopeptide, neutrophyll/llymphocyte ratio, cutaneous hyper-pigmentation correlation, PSA doubling times, safety, and patient reported outcomes. As of Jan '17, Phase 1b cohorts 1 and 2, with TI and component PK evaluations, have completed enrollment with adequate numbers to establish the Phase 2 dose without DLT. Phase 2 has begun, with 33 patients planned for at least 6 cycles (@28d) to reach the desired power. This would be followed by a pivotal Phase 3 study in the same group of patients. We propose to conduct a pivotal randomized phase 3 of SM88 in rising PSA, nmPC versus patient's and clinician's choice, limited to 2 options i.e. observation or ADT therapy. Inclusion would include doubling time < 9 months, elevated CTCs and recurrent disease after localized curative intent therapy (the same population as our completed Phase I and ongoing phase II). Outcomes will include delay of radiographic PFS, and delay of time to subsequent toxic therapy i.e. cytotoxic systemic chemo and/or radiation therapy. We proposed this pivotal trial will lead to a successful NDA for an indication in this population of patients. Rapid accrual is expected at several institutions because of the urgent need for less toxic alternatives to androgen deprivation therapy.

TPS2616 Poster Session (Board #98a), Mon, 8:00 AM-11:30 AM

A phase 1, multicenter, dose-escalation study of PRN1371, an irreversible covalent FGFR1-4 kinase inhibitor, in patients with advanced solid tumors, followed by expansion cohorts in patients with FGFR genetic alterations. *First Author: Sarina Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: FGFR inhibition is a promising and clinically proven therapeutic approach in a number of solid tumors where genetic alterations of FGFR drive oncogenesis. PRN1371 is a highly selective oral, irreversible inhibitor of FGFR1-4 that exhibits high potency in cancer cell lines harboring FGFR alterations, including mutations and fusions. **Methods:** Part A of this phase 1 clinical trial explores ascending doses of PRN1371 in adult patients with advanced solid tumors in a "3 + 3" design, where cohorts of three patients are studied at each level until additional patients need to be added to better assess safety, establish the maximum tolerated dose and define the recommended phase 2 dose (RP2D). PRN1371 is dosed once or twice daily in continuous, 28-day cycles until disease progression. Part B studies include two or three expansion cohorts of different tumor types, 10 patients each with FGFR1-4 gene mutations, fusions, or amplification at the RP2D. The on-target effect of serum phosphorus and FGF23 increases are measured as potential pharmacodynamic biomarkers. Elevated serum phosphorus is managed with oral phosphate binding medications and a low phosphate diet, with dose interruptions and use of acetazolamide if certain thresholds are exceeded. Circulating tumor DNA from patients at baseline and during follow up is analyzed for FGFR genetic alterations. Pre and on-treatment tumor biopsies in Part B will be tested for a panel of pharmacodynamic biomarkers of FGFR inhibition. Clinical trial information: NCT02608125.

TPS2617 Poster Session (Board #98b), Mon, 8:00 AM-11:30 AM

Phase 1 study of onalespib, HSP90 inhibitor, and AT7519M, CDK9 inhibitor, in patients with advanced solid tumors. *First Author: Khanh Tu Do, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA*

Background: The 90kDa heat shock chaperone protein (HSP90) exerts housekeeping functions within cells. HSP90 participates in the folding, stabilization, activation, and proteolytic turnover of mutant or over-expressed "client proteins" that contribute to the growth and survival of cancer cells. HSP90 inhibition leads to degradation of these aberrant proteins through the ubiquitin-proteasome pathway, allowing for simultaneous targeting of multiple pathways. Inhibition of HSP90 alone stimulates a compensatory upregulation of HSP70, which is anti-apoptotic at the pre-mitochondrial, mitochondrial and post-mitochondrial levels. The transcriptional induction of HSP70 has been linked to the activity of CDK9. *In vitro* and *in vivo* studies show that disruption of HSP70 induction by CDK9 inhibition can augment HSP90 inhibitor responses. Combined inhibition of HSP90 and CDK9 may produce synergistic anti-tumor activity. **Methods:** We are conducting an a phase I trial of the combination of the HSP90 inhibitor onalespib, and the CDK9 inhibitor AT7519, utilizing a 3+3 trial design, with dose-limiting toxicities defined during cycle 1. Estimated enrollment: 37 patients. Onalespib and AT7519M are both administered on days 1, 4, 8, and 11 of a 21-day cycle following a 1-week lead-in of onalespib alone to facilitate PK/PD endpoints. Patients must have histologically confirmed solid tumors that have progressed on standard of care therapy or for which no standard treatment exists, with an ECOG 0-1. Exclusion criteria include a prolonged QTc interval (Fridericia formula), pre-existing retinal disease, or cardiac dysfunction with EF $<$ 50% at study entry. Current pharmacodynamic analyses include the analysis of HSP70 expression in plasma and peripheral blood mononuclear cells after treatment with onalespib, and after the combination, as proof-of-principle of target inhibition. At this time, DL1 has completed enrollment; accrual is ongoing with measurement of HSP90 client proteins and HSP70 levels in patient plasma and PBMC samples. This trial is open through the ETCTN. Clinical trial information: NCT02503709.

TPS2618 Poster Session (Board #99a), Mon, 8:00 AM-11:30 AM

An open-label, phase II study of tipifarnib for the treatment of HRAS mutant solid tumors, including squamous cell carcinomas of the head and neck. *First Author: Alan Loh Ho, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tipifarnib is a potent and highly selective inhibitor of farnesyltransferase (FT). FT catalyzes the post-translational attachment of farnesyl groups to signaling proteins that are requisite for localization to the inner cell membrane. While all RAS isoforms (KRAS/NRAS/HRAS) are FT substrates, only HRAS is exclusively dependent upon farnesylation for membrane localization and signaling activation, making HRAS mutant tumors uniquely susceptible to tipifarnib mediated inhibition of FT. Tipifarnib has demonstrated robust activity in HRAS mutant head and neck squamous cell carcinoma (HNSCC) and HRAS mutant squamous non-small cell lung cancer (NSCLC) patient derived xenograft (PDX) models resistant to standard therapies. **Methods:** This is a multi-institutional, open-label Phase II trial evaluating the efficacy and safety of tipifarnib for pts with HRAS mutant solid tumors. Pts must have either unresectable, locally advanced or metastatic non-hematological malignancies that harbor a missense HRAS mutation. The primary endpoint of the study is overall response rate. Secondary endpoints include safety and tolerability, PFS, duration of response. Two cohorts (N = 18 each) are enrolling, each being evaluated with a Simon two-stage design. Cohort 1 is for patients with malignant thyroid tumors of any histology. Cohort 2 was originally designated for pts with any other solid tumor. The prespecified activity goal for the first stage of accrual in Cohort 2 was met. Based on data observed in the first stage of this group, enrollment to the second stage of Cohort 2 has been limited to HRAS mutant HNSCC since August 2016. Enrolled patients are treated with tipifarnib 900 mg administered orally twice daily on days 1-7 and 15-21 of 28-day treatment cycles until progression of disease or unacceptable toxicity. Clinical trial information: NCT02383927.

TPS2619 Poster Session (Board #99b), Mon, 8:00 AM-11:30 AM

Phase I study of CFI-402257, an oral TTK inhibitor, in patients with advanced solid tumors. *First Author: David W. Cescon, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: TTK (MPS1), a dual-specificity serine-threonine kinase, is critical for the spindle assembly checkpoint (SAC), chromosome alignment and error correction in mitosis. Inhibition of TTK causes premature mitotic exit with unattached chromosomes, resulting in chromosomal mis-segregation, aneuploidy and cell death. TTK is overexpressed in several tumor types, which may contribute to survival and proliferation of aneuploid cells, and higher expression correlates with adverse outcomes. The Campbell Family Therapeutics Group at the University Health Network (UHN) has developed CFI-402257, a potent (Ki = 0.09 nM, IC50 = 1.2 nM), highly selective and orally active inhibitor of TTK, with negligible activity towards 265 other kinases. Robust suppression of tumor growth was achieved upon oral dosing of single agent CFI-402257 at tolerated doses in several cell line (breast, colorectal) and patient-derived (ovarian) xenograft models. Pharmacodynamic effects including reduction in phospho-histone H3 were observed. In syngeneic mouse colorectal cancer models, CFI-402257 + PD-1 immune checkpoint blockade demonstrated greater activity than either agent alone, and resulted in tumor regressions and immunity to rechallenge. **Methods:** This multi-center Phase I dose escalation study (3+3 design) will determine the safety, tolerability and maximum tolerated dose (MTD) of CFI-402257 administered as daily continuous oral treatment. Secondary and correlative endpoints include plasma PK, antitumor activity, and molecular features associated with response or clinical benefit. An expansion cohort (n = 12) will be enrolled at the MTD. Key inclusion criteria: adult patients with advanced solid tumors, measurable disease (RECIST 1.1), adequate organ function and performance status (ECOG 0-1). Exclusion criteria: uncontrolled medical illness, CNS metastases (unless stable x 3 months). CFI-402257 will be dosed once daily on a continuous schedule in 28-day cycles, beginning at 5 mg/day with planned escalation to 56 mg/day. DL1 completed enrolment 01/2017 and accrual is ongoing. Phase II studies are planned (Stand Up to Cancer Canada Breast Cancer Dream Team). Funding: UHN, CIRM. Clinical trial information: NCT02792465.

TPS2620 Poster Session (Board #100a), Mon, 8:00 AM-11:30 AM

Sorafenib administered using a high-dose, pulsatile regimen in patients with advanced solid malignancies: A phase I exposure escalation study. *First Author: Lemonitsa Hillegonda Mammatas, Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: Sorafenib is currently prescribed at a standard fixed dose of 400 mg twice daily in a continuous schedule. Increased exposure to sorafenib is associated with improved outcome. However, further increase in the dose of this continuous schedule is precluded due to toxicity. A high-dose, pulsatile schedule may result in increased sorafenib exposure while maintaining acceptable toxicity and has demonstrated promising preclinical antitumor activity.[1] Sorafenib plasma concentrations present with large interpatient variability. As drug effectivity is largely dependent on AUC exposure, personalized dose titration based on the sorafenib plasma $AUC_{0\text{-}12h}$ of an individual patient seems more suitable than a standard fixed dose. In this phase I trial, a high-dose, weekly schedule of sorafenib is being studied, using exposure escalation cohorts based on a target $AUC_{0\text{-}12h,}$ instead of conventional dose escalation cohorts. **Methods:** Adult patients are included with locally advanced or metastatic solid tumors for whom no standard therapy exists. High-dose sorafenib is administered once a week. Pharmacokinetic monitoring is performed during the first 3 weeks of treatment in each patient to evaluate if the target plasma sorafenib $AUC_{0\text{-}12h}$ of the cohort is reached and sorafenib dose is adjusted accordingly. Cohorts consist of 3-6 patients per exposure level, starting with target $AUC_{0\text{-}12h}$ 25-50 mg x h/L, analogous to the continuous schedule. The target $AUC_{0\text{-}12h}$ is increased in subsequent cohorts until exposure limiting toxicity occurs. Main objectives are to assess safety and establish the maximum tolerated plasma $AUC_{0\text{-}12h}$ of high-dose, pulsatile sorafenib. At this dose level 10 extra patients will be included. Tumor biopsies are required in all patients of this expansion cohort to study antitumor effects and for direct comparison of plasma and intratumor sorafenib concentrations. Furthermore, a simplified method will be developed for measurement of plasma sorafenib exposure using dried blood spot sampling at 1-2 time points. Nine patients have already been included. Reference: [1]Wang X. et al. J Transl Med 2011;9:220. Clinical trial information: NCT02636426.

TPS2621 Poster Session (Board #100b), Mon, 8:00 AM-11:30 AM

The Molecular Screening and Therapeutics (MoST) Program: A precision medicine framework for biomarker-driven signal-seeking clinical studies for rare cancers. *First Author: Dominique Hess, Garvan Institute of Medical Research, Darlinghurst, Australia*

Background: Precision medicine aims to link molecular targets in tumors to cognate therapies and has the potential to yield new treatments for cancer patients with unmet clinical need. With the accelerating pace of discovery and genomic capacity, innovative approaches are needed to translate molecular opportunities into clinical care. The MoST program tests a novel paradigm for evaluation of biomarker-driven treatment of patients with advanced cancer. The key elements of the design are a molecular screening platform to identify 'actionable' variants and an overarching protocol for multiple, parallel, signal-seeking clinical substudies. **Methods:** 1000 patients with advanced solid cancer of any histologic type, having failed all standard therapies will undergo tumor molecular profiling on archival tissue with a 393-gene panel and other molecular assays. Eligibility for biomarker-driven substudies of targeted treatments is based on tumor variants assessed by a Molecular Tumor Board. A novel framework design allows expedited addition of substudies, with ≥12 open-label, single-arm, signal-seeking substudies planned. The primary objective is to identify signals of clinical activity, as measured by objective tumor response or the ratio of time-to-progression on study treatment over the preceding period. Cohorts of 16 patients will be recruited to each substudy. Substudies with ≥3/16 responding patients will be considered sufficiently interesting to investigate further.As of Feb 2017, 65 patients have been screened, and 8 recruited to 2 open sub-studies: CDK4/6 inhibitor (palbociclib) for Rb pathway defects; CTLA-4 plus PD-L1 checkpoint inhibitors (durvalumab + tremelimumab) for patients with no actionable mutations. Additional substudies under development include: PARP plus PD-L1 inhibitors (olaparib + durvalumab) for HR DNA repair defects; SMO inhibitor (vismodegib) for Hh pathway defects. The modular signal-seeking trial design will be evaluated and is intended to expedite testing of biomarker-based therapies for rare cancers. Clinical trial information: ACTRN12616000908437; ACTRN12616000931471; ACTRN12616001019493.

3000 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Open label, non-randomized, multi-cohort pilot study of genetically engineered NY-ESO-1 specific NY-ESO-1^{c259}t in HLA-A2^{+} patients with synovial sarcoma (NCT01343043). *First Author: Crystal Mackall, Stanford University School of Medicine, Stanford, CA*

Background: NY-ESO-1 is expressed in ~70% of synovial sarcomas (SS). NY-ESO-1^{c259}T cells recognizing an NY-ESO-1 derived peptide complexed with HLA-A*02 are being studied in SS. **Methods:** Eligible patients (pt) are HLA-A*02:01, 02:05 or 02:06, with unresectable, metastatic or recurrent SS expressing NY-ESO-1. Primary endpoint of ORR (CR+PR) is evaluated in high (≥ 50% tumor cells express 2+/3+) and low (≥ 1+ in ≥ 1% cells, not exceeding 2+/3+ in ≥ 50% cells) NY-ESO-1 expressers with different lymphodepleting regimens. Secondary endpoints are safety, DOR, PFS, OS, and gene-marked cell persistence. Lymphocytes are obtained by leukapheresis, isolated, activated, transduced to express NY-ESO-1^{c259}T, and expanded. Target dose is $1–6 \times 10^9$cells. Disease is assessed at wk 4, 8 and 12 post-T-cell infusion, and then every 3 months. **Results:** 34 pt have been enrolled with 24 treated. 50% are male; median age is 30 yr (range 15 – 73). 12/15 pt in cohort 1 were treated. ORR was 50% (1 CR; 5 PR). Time to response was 6 wk (range 4-9) and median DOR 31 wk (range 13-72). Cohort 3 was closed due to only 1 PR out of 5 pt. Evaluation is ongoing in cohorts 2 (6 enrolled; 5 treated) and 4 (8 enrolled; 2 treated) as of 1/9/17. The most common AE are leukopenia (96%), nausea and pyrexia (88%), neutropenia (88%), lymphopenia (83%), anemia (79%), and thrombocytopenia (79%). 11 events of CRS were reported (3 G3; 1 G4), with no events of seizure, cerebral edema or fatal neurotoxicity; all resolved with supportive therapy. One fatal SAE (bone marrow failure) occurred in cohort 2; investigations have not identified a mechanism by which NY-ESO-1^{c259}T may have caused this event. **Conclusions:** NY-ESO-1^{c259}T has promising efficacy and acceptable safety. CRS is not associated with severe neurotoxicity and appears manageable with appropriate supportive care. Cohort 3 data indicate that Flu may be important for efficacy. Efficacy and safety data will be further evaluated and presented. Clinical trial information: NCT01343043.

Cohort	NY-ESO-1 expression	Lymphodepletion
1*	high	Fludarabine (Flu) 30 mg/m^2/day × 4
2	low	cyclophosphamide (Cy) 1800 mg/m^2/day × 2
3*	high	Cy 1800 mg/m^2/day × 2
4	high	Flu 30 mg/m^2/day × 3, Cy 600 mg/m^2/day ×3

*Closed

LBA3001 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma. *First Author: Frank (Xiaohu) Fan, Nanjing Legend Biotech, Nanjing, China*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 5, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

3002 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Phase Ia and Ib studies of the novel carcinoembryonic antigen (CEA) T-cell bispecific (CEA CD3 TCB) antibody as a single agent and in combination with atezolizumab: Preliminary efficacy and safety in patients with metastatic colorectal cancer (mCRC). *First Author: Josep Tabernero, Vall d'Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain*

Background: CEA CD3 TCB (RG7802, RO6958688) is a novel T-cell bispecific antibody targeting CEA on tumor cells and CD3 on T cells. In preclinical models, CEA CD3 TCB displays potent anti-tumor activity, leads to increased intratumoral T cell infiltration and activation and upregulates PD-1/PD-L1. **Methods:** Intwo ongoing dose-escalation phase I studies, RO6958688 is given as monotherapy (S1) i.v. QW or in combination (QW) with atezolizumab 1200 mg Q3W (S2) in adult patients (pts) with advanced CEA+ solid tumors. In S1, 80 pts (mCRC: 68) were treated at dose levels from 0.05 mg to 600 mg; in S2, 38 pts (mCRC: 28) from 5 mg to 160 mg. In S1, a Bayesian logistic regression model with overdose control guided dose escalation. Data cutoff 25.01.17. **Results:** At doses ≥60mg (36 pts in S1; 10 in S2), CT scans revealed tumor inflammation within days of first dose, consistent with the mode of action of RO6958688. 2 (5%) pts in S1 (both microsatellite stable (MSS) and 2 (20%; 1 MSS) in S2 had a partial response (RECIST v1.1). Preliminary tumor size reduction (> -10% and < -30% [stable disease]) was observed in 4 (11%) additional pts in S1 and 5 (50%) in S2. At week 4-6 FDG PET scan assessment, 10 (28%) pts with mCRC in S1 and 6 (60%) in S2 had a metabolic partial response (EORTC criteria). At all doses in S1, the most common related AEs were pyrexia (56.3%), infusion related reaction (IRR, 50%) and diarrhea (40%). The most common grade ≥ 3 (G3) related AEs were IRR (16.3%) and diarrhea (5%). 5 patients experienced DLTs: G3 dyspnea, G3 diarrhea, G3 hypoxia, G4 colitis and G5 respiratory failure (G4-5 at 600mg). DLT events were likely associated with tumor lesion inflammation. In S2, there was no evidence of new or additive toxicities, with 1 DLT at 160 mg (G3 transient increase of ALT in a patient with liver metastases). PK/PD data are reported separately. **Conclusions:** Evidence of antitumor activity was observed with RO6958688 monotherapy in ongoing dose escalation. Activity appeared to be enhanced with doses in combination with atezolizumab, with a manageable safety profile. Updated data will be presented. Clinical trial information: NCT02324257 and NCT02650713.

3003 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Epacadostat plus nivolumab in patients with advanced solid tumors: Preliminary phase I/II results of ECHO-204. *First Author: Raymond P. Perez, University of Kansas Clinical Research Center, Fairway, KS*

Background: ECHO-204 is an ongoing, open-label, phase 1/2 (P1/2) study of epacadostat (E; potent and selective oral inhibitor of the immunosuppressive enzyme indoleamine 2,3-dioxygenase 1) plus PD-1 inhibitor nivolumab (N) in patients (pts) with advanced cancers (NSCLC, MEL, OVC, CRC, SCCHN, B-cell NHL [including DLBCL], GBM). Preliminary P1/2 safety and tolerability outcomes for the overall study population and P2 response for select tumor types (SCCHN, MEL, OVC, CRC) are reported. **Methods:** In P1 dose escalation, pts received E (25, 50, 100, 300 mg BID) + N (3 mg/kg Q2W); in P2 cohort expansion, pts received E (100 or 300 mg BID) + N (240 mg Q2W). Safety/tolerability was assessed in pts receiving ≥1 E + N dose. Response was assessed in RECIST v1.1 evaluable pts; for recently enrolled pt subgroups, only preliminary DCR (CR+PR+SD) is presented. **Results:** As of 29OCT2016,241 pts (P1, n = 36; P2, n = 205) were enrolled. No DLT was observed in P1. Most common TRAEs (≥15%) in pts treated with E 100 mg (n = 70) and E 300 mg (n = 135) were rash (33% and 22%, respectively), fatigue (26% and 31%), and nausea (24% and 19%). Rash was the most common grade ≥3 TRAE in E 100 mg and E 300 mg subgroups (10% and 12%). TRAEs led to discontinuation in 7% (E 100 mg) and 13% (E 300 mg) of pts. There were no TR-deaths. For the 23 recently enrolled, efficacy-evaluable SCCHN pts treated with E 300 mg, preliminary DCR was 70% (n = 16). Of 30 MEL pts, 8 were treated with E 100 mg and 22 were more recently enrolled and treated with E 300 mg. ORR (CR+PR) and DCR in MEL pts treated with E 100 mg were 75% (n = 6; all PR) and 100% (n = 8; 2 SD), respectively. Preliminary DCR in MEL pts treated with E 300 mg was 64% (n = 14). Of 29 OVC pts, 18 were treated with E 100 mg and 11 with E 300 mg.ORR and DCR for OVC pts treated with E 100 mg were 11% (n = 2; 2 PR) and 28% (n = 5; 3 SD); for 11 OVC pts treated with E 300 mg, ORR and DCR were 18% (n = 2; 2 PR) and 36% (n = 4; 2 SD).For 25 CRC pts (all E 100 mg), ORR and DCR were 4% (n = 1; PR) and 24% (n = 6; 5 SD).Safety/efficacy evaluations are ongoing for all cohorts. **Conclusions:** E + N was generally well tolerated up to the maximum E 300-mg dose. P2 ORR/DCR outcomes are promising, particularly in SCCHN and MEL pts. Updated data will be presented at the meeting. Clinical trial information: NCT02327078.

3004 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Safety and clinical activity of adenosine A2a receptor (A2aR) antagonist, CPI-444, in anti-PD1/PDL1 treatment-refractory renal cell (RCC) and non-small cell lung cancer (NSCLC) patients. *First Author: Lawrence Fong, University of California, San Francisco, San Francisco, CA*

Background: Adenosine production in the tumor leads to immunosuppression through A2aR on infiltrating immune cells. CPI-444 is an oral A2aR antagonist with single agent(SA) anti-tumor activity in pre-clinical models. This phase 1/1b clinical trial uses a 2-step adaptive design to evaluate CPI-444 as a SA and in combination (combo) with the anti-PDL1 antibody, atezolizumab (atezo). We report results of RCC and NSCLC cohorts. **Methods:** Primary objectives: safety, efficacy and to identify optimal dose/schedule. Step 1 utilized 3 SA and 1 combo cohort to select dose/schedule. Step 2 included disease-specific expansion cohorts including RCC and NSCLC. Eligible pts had selected advanced cancers and failed standard therapies including checkpoint inhibitors. **Results:** 34 pts have enrolled and 25 pts were evaluable for response (Table 1). Median prior regimens: 3 (range,1-5) and most pts were resistant/refractory to anti PD1/PDL1 therapy (R/R). Most common AEs were Gr 1 nausea (n = 3) and pyrexia (n = 3); Gr 3 tachycardia was the only possibly related SAE. The selected Step 2 doses were CPI-444 100mg BID as a SA and in combo with atezo 840mg IV q2 weeks. The disease control rate (DCR, CR+PR+SD; duration 2 mo to $>$ 8 mo) for pts with RCC and NSCLC cohorts were 86% and 50%, (100% and 43% for R/R pts), respectively. DCRs were similar in the SA and combo cohorts. Of 7 evaluable RCC pts, 1 pt has an ongoing PR (SA cohort, $>$ 4 mo) and 5 have ongoing SD, duration 3 mo to $>$ 8 mo (2 SA, 3 combo). Biopsy of the PR pt showed no detectable tumor and infiltration with CD8+ lymphocytes. In 18 evaluable NSCLC pts, 1 PR (PDL1 negative pt) and 8 SD were seen. PRs and SDs were seen in R/R pts and in PDL1 negative pts in both diseases. **Conclusions:** CPI-444 is well tolerated and shows anti-tumor activity in RCC and NSCLC pts as a SA and in combo. Pts who are R/R to anti PD1/PDL1 therapy and who are PDL1 negative can also benefit. Clinical trial information: NCT02655822.

	RCC	NSCLC
n	8	26
Median age (range)	64 (44-73)	72 (41-85)
% PD1/PDL1 R/R	75% (6/8)	68% (18/26)
Regimen: SA/Combo (n)	5/3	15/11
Median followup(range)	15 wks (6-32)	11 wks (1-19)
Disease Control Rate		
All	86% (6/7)	50% (9/18)
SA	75% (3/4)	36% (4/11)
Combo	100% (3/3)	71% (5/7)

3005 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

CX-1158-101: A first-in-human phase 1 study of CB-1158, a small molecule inhibitor of arginase, as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor in patients (pts) with solid tumors. *First Author: Kyriakos P. Papadopoulos, START, San Antonio, TX*

Background: Arginase is secreted by myeloid-derived suppressor cells (MDSCs) and polymorphonuclear cells (PMNs) in the tumor microenvironment, depleting arginine, an amino acid required for T-cell activation and proliferation. CB-1158 is an oral small molecule inhibitor of arginase. CB-1158 reverses PMN- and MDSC-mediated suppression of T-cells in *ex vivo* human models, and increases plasma and tumor arginine levels in mouse syngeneic tumor models leading to increased pro-inflammatory markers and activated CD8 T-cells in the tumor. CB-1158 has single agent efficacy in mouse tumor models and synergistically enhances the antitumor efficacy of checkpoint inhibitors. **Methods:** This is an ongoing phase 1 study to evaluate safety and tolerability of CB-1158 as a monotherapy and in combination with anti-PD-1 in pts with solid tumors. Pharmacokinetics (PK), anti-tumor effects, and biomarkers, including plasma arginine, arginase activity, and effects on immune function in blood and in tumors will be evaluated. CB-1158 was administered BID orally in 28-day cycles. Escalating doses were administered to cohorts for safety evaluation. Additional pts were enrolled at dose levels determined to be safe to support biomarker objectives. **Results:** Nine pts have been enrolled across two monotherapy dose escalation cohorts (50 and 100 mg) and biomarker cohorts. CB-1158 was rapidly absorbed (T_{max} = 4 h) and was cleared with a half-life of 6 h. At doses of 50 and 100 mg, steady-state plasma trough levels were 1.6 and 4.5 μM, sufficient to achieve $>$ 90% arginase inhibition, and plasma arginine levels increased 2.4- and 4-fold, respectively. CB-1158 has been well tolerated with no DLTs or drug-related Grade 3 AEs. Dose escalation is ongoing and updated safety, PK and biomarker data will be presented. **Conclusions:** CB-1158 is a first-in-class inhibitor of the myeloid-derived immunosuppressive enzyme arginase. CB-1158 has been well tolerated and achieves on-target inhibition resulting in increases in plasma arginine, an amino acid required for T-cell immune responses. Clinical trial information: NCT02903914.

3006 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Preliminary results from a phase 1 trial of M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in advanced solid tumors. *First Author: James L. Gulley, Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: M7824 (MSB0011359C) is a novel bifunctional fusion protein comprised of a fully human IgG1 monoclonal antibody against programmed death ligand 1 (PD-L1) fused to the soluble extracellular domain of transforming growth factor-β (TGF-β) receptor II, which acts as a TGF-β trap. We report preliminary data from a phase 1 trial of M7824 in patients (pts) with advanced solid tumors. **Methods:** NCT02517398 is a phase 1, open-label, 3+3 dose-escalation study. Eligible pts receive M7824 at 1, 3, 10, or 20 mg/kg Q2W until confirmed progressive disease, unacceptable toxicity, or trial withdrawal; treatment beyond progression is generally allowable. The primary objective is to determine the safety and maximum tolerated dose of M7824; secondary objectives include pharmacokinetics (PK), immunogenicity, and best overall response per RECIST v1.1. **Results:** 16 heavily pretreated pts with ECOG performance status 0-1 have received M7824. Our PK data show a dose-linear increase in exposure starting at a dose of 3 mg/kg; furthermore, M7824 saturates peripheral PD-L1 and sequesters any released plasma TGF-β1, -β2, and -β3 throughout the dosing period in a dose-dependent manner. Grade 3 drug-related treatment-emergent adverse events (TEAEs) occurred in 3 pts (skin infection secondary to grade 2 bullous pemphigoid [BP], lipase increased, and colitis with associated anemia); there were no grade 4-5 drug-related TEAEs. BP and colitis responded well to steroids. Colitis and its secondary events of anemia and rectal hemorrhage (in a previously radiated area) were considered dose limiting in 1 pt. There was preliminary evidence of efficacy across all dose levels, including 1 ongoing confirmed complete response (cervical), 1 durable partial response (pancreatic), a 25% reduction in the sum of diameters of target lesions after 2 doses of M7824 (cervical), and 2 cases of prolonged stable disease (pancreatic; carcinoid). **Conclusions:** Preliminary data from this phase 1 dose-escalation study suggest that M7824 has a manageable safety profile in pts with heavily pretreated advanced solid tumors. Early signs of clinical efficacy warrant further study. Clinical trial information: NCT02517398.

3007 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Clinical results with combination of anti-CD27 agonist antibody, varlilumab, with anti-PD1 antibody nivolumab in advanced cancer patients. *First Author: Rachel E. Sanborn, Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR*

Background: A phase 1 trial to assess the safety and immunological activity of the combination of varlilumab (V) and nivolumab (N), and recommend a dose of V for the phase 2 study was conducted. **Methods:** The study was performed using the approved dose of N (3 mg/kg Q2W) and escalating doses of V (0.1, 1, or 10 mg/kg Q2W) in anti-PD-(L)1 naïve patients with advanced cancer. **Results:** A total of 36 patients (21 CRC, 8 ovarian [OVA], 4 melanoma and 3 SCCHN) were enrolled. Toxicity was consistent with the safety profile of each agent individually; no unexpected toxicities were seen with the combination. No MTD was identified. An OVA cancer patient in the 10 mg/kg cohort had a DLT: hepatitis (G4) and acute kidney injury (G3). A CRC patient in the 10 mg/kg cohort had a drug-related SAE of mixed motor sensory neuropathy (G2) and a CRC patient in the 1 mg/kg cohort had rash (G3). No additional drug related SAEs or DLTs were reported. The majority of tumors were PD-L1 negative (24/27) by IHC at baseline. For patients with post treatment biopsies, PD-L1 expression was observed in 43.5% (10/23) and correlated with increases in CD8 T cell infiltration, consistent with the generation of anti-tumor immunity. Other treatment related biomarker changes included transient increases in serum chemokine levels, and a prominent decrease in circulating Tregs. Biomarker analysis did not clearly differentiate between dose levels, or delineate an optimal V dose. Three patients had objective PR by RECIST [CRC MSI-low (1 mg/kg V), SCCHN (10 mg/kg V) and OVA (10 mg/kg V, uPR)]. The response in the CRC patient is ongoing with a 94% decrease in target lesion diameter and a PFS of 19+ months. There were also 11 patients with SD. Phase 2 cohorts are ongoing in RCC, SCCHN, OVA, CRC and GBM. The Phase 2 portion includes exploration of different dose/regimens of V, including high and low exposure, to better characterize the optimal dosing strategy for V, in combination with a fixed dose of N (240 mg Q2W). **Conclusions:** The combination of V and N was well tolerated, associated with strong biological signals, and has evidence of clinical activity in subsets of patients with tumor types that are typically resistant to PD-1 inhibitor monotherapy. Clinical trial information: NCT02335918.

3008 Oral Abstract Session, Mon, 1:15 PM-4:15 PM

Association of the diversity and composition of the gut microbiome with responses and survival (PFS) in metastatic melanoma (MM) patients (pts) on anti-PD-1 therapy. *First Author: Jennifer Ann Wargo, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Significant advances have been made in cancer therapy with immune checkpoint blockade. However, responses in pts with MM are variable, and insights are needed to identify biomarkers of response and strategies to overcome resistance. There is a growing appreciation of the role of the microbiome in cancer, and evidence in murine models that modulation of the gut microbiome may enhance responses to immune checkpoint blockade, though this has not been well studied in pts. Thus we evaluated the microbiome in a large cohort of pts with MM, focusing on responses to anti-PD-1. **Methods:** We collected oral (n = 234) and gut microbiome samples (n = 120) on a large cohort of of MM patients (n = 221). Of note, the majority of pts were treated with PD-1 based therapy (n = 105). Pts on anti-PD1 were classified as either responders (R) or non-responders (NR) based on RECIST criteria, and 16S rRNA and whole genome shotgun (WGS) sequencing were performed. Immune profiling (via immunohistochemistry, flow cytometry, cytokines and gene expression profiling) was also done in available pre-treatment tumors at baseline. **Results:** Significant differences in diversity and composition of the gut microbiome were noted in R vs NR to anti-PD-1, with a higher diversity of bacteria in R vs NR ($p = 0.03$). Differences were also noted in the composition of gut bacteria, with a higher abundance of Clostridiales in R and of Bacteroidales in NR. Immune profiling demonstrated increased tumor immune infiltrates in R pts , with a higher density of CD8+T cells; this correlated with abundance of specific bacteria enriched in the gut microbiome ($r = 0.59, 0.014$). Other features of enhanced immunity were also noted, and WGS revealed differential metabolic signatures in R vs NR. Furthermore, diversity ($p = 0.009$; HR = 7.67) and abundance of specific bacteria in R ($p = 0.007$; HR = 3.88) was associated with improved PFS to anti-PD-1 therapy. **Conclusions:** Diversity and composition of the gut microbiome differ in R vs NR pts with MM receiving anti-PD-1 therapy. These have potentially far-reaching implications, though results need to be validated in larger cohorts across cancer types.

3009 Poster Discussion Session; Displayed in Poster Session (Board #104), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A phase I/II clinical trial of E6 T-cell receptor gene therapy for human papillomavirus (HPV)-associated epithelial cancers. *First Author: Christian S. Hinrichs, National Institutes of Health, National Cancer Institute, Bethesda, MD*

Background: Engineered T-cell therapy has shown promise in B-cell malignancies and melanoma, but clinical investigation in epithelial cancers has been limited. **Methods:** We conducted a phase I/II clinical trial of T cells genetically engineered to express a T-cell receptor that targets an HLA-A*02:01-restricted epitope of E6 (E6 TCR T Cells) for patients with metastatic HPV-16+ carcinoma. The cell dose was escalated in cohorts of single patients (1×10^9, 1×10^{10}, and $1\text{-}2 \times 10^{11}$cells). Patients received a nonmyeloablative conditioning regimen of cyclophosphamide and fludarabine, a single infusion of E6 TCR T Cells, and systemic high-dose aldesleukin. **Results:** Twelve patients were treated, 9 at the highest cell dose, plus one retreatment. The cancer types were 6 cervical, 4 anal, 1 oropharyngeal, and 1 vaginal. No dose-limiting toxicity, autoimmune adverse events, or cytokine storm were observed. Two patients with anal cancer treated at the highest cell dose experienced partial tumor responses lasting 6 and 3 months after treatment. The patient with a 6-month response had complete regression of one tumor and partial regression of two tumors that were resected upon progression; she has no evidence of disease 22 months after treatment. T-cell receptor gene transfer efficiency was 45 and 51% in the responding patients, and 47-76% (median 61%) in the non-responding patients. Responding patients showed robust levels of E6 TCR T cell memory (30 and 46% of circulating T cells 1-month after treatment). Non-responding patients showed wide-ranging levels of E6 TCR T cell memory (range 4-53%, median 29%). Expression of programmed cell death protein 1 (PD-1) by circulating E6 TCR T Cells 1-month after treatment was low in all patients ($< 5\%$). The patient with a 6-month response had 7% E6 TCR T Cells in a resected tumor 10 months after treatment, 25% of which expressed PD-1. A patient with no response had no detectable E6 TCR T Cells in a resected tumor 3 months after treatment. **Conclusions:** E6 TCR T-cell therapy was safe at doses up to 2×10^{11} cells. Regression of metastatic HPV+ carcinoma occurred in two patients following treatment, suggesting that TCR T-cell therapy can mediate epithelial cancer regression. Clinical trial information: NCT02280811.

3010 Poster Discussion Session; Displayed in Poster Session (Board #105), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

First-in-human multicenter study of bb2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: Updated results. *First Author: Jesus G. Berdeja, Sarah Cannon Research Institute, Nashville, TN*

Background: To test the safety and efficacy of the CAR T cell modality in relapsed/refractory multiple myeloma (MM), we have designed a second-generation CAR construct targeting B cell maturation antigen (BCMA) to redirect T cells to MM. bb2121 consists of autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-BCMA scFv, a 4-1BB costimulatory motif and a CD3-zeta T cell activation domain. We will report updated safety and efficacy following initial results (Berdeja et al, ENA 2016). **Methods:** CRB-401 (NCT02658929) is a multi-center phase 1 dose escalation trial of bb2121 in patients with relapsed and/or refractory MM who have received $\geq$ 3 prior regimens, including a proteasome inhibitor and an immunomodulatory agent, or are double-refractory, and have $\geq$ 50% BCMA expression on plasma cells. Peripheral blood mononuclear cells are collected via leukapheresis. Patients undergo lymphodepletion with Flu (30 mg/m^2) / Cy (300 mg/m^2) daily for 3 days then receive 1 infusion of bb2121. The study follows a standard 3+3 design with planned dose levels of 5, 15, 45, 80 and 120×10^7 CAR+ T cells. **Results:** As of November 18, 2016, 11 patients had been infused with bb2121 in the first 4 dose cohorts, and 9 patients had reached at least 1 month of follow-up. As of data cut-off, no dose-limiting toxicities and no $>$ Grade 2 neurotoxicities or cytokine release syndrome (CRS) had been observed. Grade 1-2 CRS had been reported in 8/11 (73%) treated patients. All patients treated with doses of 15.0×10^7or higher remained on study and the overall response rate (ORR) in the 6 evaluable patients at these doses was 100%, including 2 sCRs and 2 MRD-negative responses (1 sC, 1 VGPR). CAR+ T cell expansion has been demonstrated consistently. An additional 6 months of follow up on previously reported results and initial data from an additional ~10 patients will be presented. **Conclusions:** bb2121 shows promising efficacy at dose levels above 5×10^7 CAR+ T cells, including 2 sCRs and ongoing clinical responses at 6 months, with mild and manageable CRS to date. These initial data support the potential of CAR T therapy with bb2121 as a new treatment paradigm in MM. Study sponsored by bluebird bio. Clinical trial information: NCT02658929.

3011 Poster Discussion Session; Displayed in Poster Session (Board #106), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Effect of chimeric antigen receptor (CAR) T cells on clonal expansion of endogenous non-CAR T cells in patients (pts) with advanced solid cancer. *First Author: Rebecca H Kim, University of Pennsylvania, Philadelphia, PA*

Background: CAR T cells have produced remarkable responses in heme malignancies, but efficacy in solid cancers is limited. Poor in vivo persistence and heterogeneous expression of the CAR target on tumors are potential barriers to the success of CAR T cell therapy. However, even with transient persistence, CAR T cells may elicit a "vaccine" effect by inducing cancer cell death and subsequent release of tumor antigens that could stimulate tumor-specific T cell activity. **Methods:** 6 pts with pancreatic ductal adenocarcinoma (PDAC) received repeated 3x per week intravenous (iv) infusions of mRNA-transfected mesothelin-redirected CAR T cells (CARTmeso). Pts with PDAC (n = 5), ovarian carcinoma (n = 5), and mesothelioma (n = 5) received iv infusion of lentiviral-transduced (lenti) CARTmeso with or without cyclophosphamide (Cy) preconditioning. Peripheral blood samples were collected from pts at baseline and defined time points after treatment. Genomic DNA from these samples or from pre-infused CAR T cell product was used for deep sequencing of the TCRbeta chain using the ImmunoSEQ platform. A TCRbeta clone was considered to have expanded from baseline to defined time points after treatment if it showed a two-fold change from baseline and met statistical significance by Fisher's exact test ($p < 0.05$). **Results:** mRNA CARTmeso cells persisted *in vivo* for $<$ 24 hrs. Unexpectedly, therapy induced clonal T cell expansion detected in the blood by day 14 in all 6 pts. Expanded clones underwent contraction by day 28 in 3 pts. In one pt, peripherally expanded clones were also detected in a tumor biopsy, but without significant intratumoral clonal expansion. Lenti CARTmeso therapy also induced peripheral expansion of T cell clones both present and not present in the infused CAR T cell product. However, with Cy preconditioning, clonal expansion seen after lenti CARTmeso therapy was predominately restricted to clones detected in the CAR T cell product. **Conclusions:** In pts with advanced solid cancers, CARTmeso stimulates clonal expansion of endogenous T cells, which is lost with Cy conditioning. Findings suggest that CAR T cells may elicit a "vaccine" effect with potential therapeutic implications.

3012 Poster Discussion Session; Displayed in Poster Session (Board #107), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Safety of epacadostat 100 mg bid plus pembrolizumab 200 mg Q3W in advanced solid tumors: Phase 2 data from ECHO-202/KEYNOTE-037. *First Author: Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA*

Background: The immunosuppressive enzyme indoleamine 2, 3-dioxygenase 1 (IDO1) facilitates immune tolerance in cancer via T-cell suppression, and IDO1 overexpression is associated with poor survival. Epacadostat, an oral inhibitor of IDO1, has been shown to be well tolerated as monotherapy and in combination with checkpoint inhibitors. ECHO-202/KEYNOTE-037 is a phase 1/2 study evaluating the safety and efficacy of oral epacadostat plus IV pembrolizumab in patients (pts) with advanced tumors. Based on phase 1 outcomes, epacadostat 100 mg BID plus pembrolizumab 200 mg Q3W was selected for phase 2 evaluation. This analysis summarizes phase 2 safety experience in the overall population of ECHO-202/KEYNOTE-037 (pooled across tumor types) at an October 29, 2016 data cutoff. **Methods:** Phase 2 pts were ≥18 years of age with advanced or recurrent melanoma (MEL), non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial carcinoma (UC), triple-negative breast cancer, squamous cell carcinoma of head and neck (SCCHN), ovarian cancer, diffuse large B-cell lymphoma, or microsatellite instability–high colorectal cancer. **Results:** The overall safety population comprised 244 pts receiving ≥1 study treatment dose. Median age was 63 years, 52% were women, and 91% were white. As of data cutoff, 134 study pts (55%) discontinued study treatment, primarily due to disease progression (n = 97). Median exposure to study treatment was 86 days (range, 1–374 days). TRAEs occurring in ≥5% of pts were fatigue (23%); rash (16%); diarrhea and nausea (7% each); increased alanine aminotransferase, increased aspartate aminotransferase, and pruritus (6% each); and pyrexia (5%). A total of 37 pts (15%) had grade ≥3 TRAEs; the most common grade ≥3 TRAEs were increased lipase (asymptomatic) and rash (3% each). TRAEs led to discontinuation in 3% of pts. **Conclusions:** Epacadostat 100 mg BID plus pembrolizumab 200 mg Q3W was associated with an acceptable safety profile in pts with advanced cancers, supporting continued evaluation of the combination. The phase 3 ECHO-301/KEYNOTE-252 MEL study is ongoing and additional phase 3 studies (NSCLC, UC, RCC, SCCHN) are planned. Clinical trial information: NCT02178722.

3013 Poster Discussion Session; Displayed in Poster Session (Board #108), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A phase 1b study of the anti-PD-1 monoclonal antibody BGB-A317 (A317) in combination with the PARP inhibitor BGB-290 (290) in advanced solid tumors. *First Author: Michael Friedlander, The Prince of Wales Hospital, Randwick, Australia*

Background: The release of tumor-associated antigens may enhance the response to immunotherapy. BGB-A317, a humanized IgG4 variant monoclonal antibody engineered to have no Fc gamma receptor binding, targets the programmed cell death-1 (PD-1) receptor. It is being developed in solid and hematologic malignancies at a dose of 200 mg IV Q3W. BGB-290, a potent inhibitor of PARP 1/2, is hypothesized to promote neoantigen release that will potentially increase the efficacy of BGB-A317. A phase 1 study identified 60mg BID as the recommended Phase 2 dose (RP2D) for BGB-290. This study consists of initial dose escalation to determine the maximum-tolerated dose (MTD), safety, PK profile, and preliminary anti-tumor activity of the combination, followed by expansion into ovarian, breast, prostate, gastric, bladder, pancreatic and small cell lung cancers. **Methods:** Cohorts of 6 -12 pts with advanced solid tumors were treated in each of 5 planned dose levels (DLs). In DLs 1-3, BGB-290 doses ranged between 20-60mg PO BID with BGB-A317 2mg/kg IV Q3W. In DLs 4 - 5, BGB-290 doses were 40 or 60 mg BID; A317 was given at 200 mg IV Q3W based on PK data from a single agent Phase 1 study. **Results:** As of 16 Jan 2017, 38 pts [median age 59 years (34-75)] were treated in DLs 1-4; enrollment to DL5 is ongoing. One DLT of persistent Gr 2 nausea was reported in DL 4. The most common adverse event (AE) considered related to both study drugs was fatigue (10.5%). Immune-related AEs were Gr 3 hypophysitis (n = 1), Gr 3 or 4 autoimmune hepatitis(n = 2), and Gr 2 elevated AST/ALT (n = 1). Decreases in tumor burden have been observed in 16 pts; 7 achieved a PR (5 with ovarian and one each with uterine and pancreatic cancer) and one CR was observed in ovarian cancer. Six pts had SD for > 6 months including 2 pts with pancreatic cancer who received BGB-A317+BGB-290 for 189 and 281 days. Plasma/serum exposure of BGB-290 and BGB-A317 were consistent with those in single-agent trials. **Conclusions:** BGB290 and BGB-A317 can be combined. Dose expansion in multiple tumor types is planned to commence in 2017 once the RP2D is determined. Clinical trial information: NCT02660034.

3014 Poster Discussion Session; Displayed in Poster Session (Board #109), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Activity of a novel immunotherapy combination of intralesional Coxsackievirus A21 and systemic ipilimumab in advanced melanoma patients previously treated with anti-PD1 blockade therapy. *First Author: Brendan D. Curti, Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR*

Background: CAVATAK is a novel bio-selected oncolytic and immunotherapeutic strain of Coxsackievirus A21 (CVA21) that when injected into melanoma lesions can increase immune-cell infiltration, up-regulation of γ-INF response and immune-checkpoint genes, including CD122, which may be a potential marker for enhanced anti-tumor activity by anti-CTLA-4 blockade. Intratumoral replication of CVA21 may act as a strong "immune-sequestration signal" to circulating activated T-cells following CTLA-4 blockade. A large unmet need exists for active therapies in melanoma patients (pts) following treatment (tx) with anti-PD1 therapies. We present in a Phase 1 study, the clinical activity of a CVA21/ ipilimumab (ipi) combination following anti–PD1 therapy in advanced melanoma pts. **Methods:** The Phase Ib MITCI study (NCT02307149) investigated the efficacy and safety of i.t. CVA21 and i.v. ipi in 26 pts with unresectable Stage IIIB/C-IVM1c melanoma with 13 pts previously treated with anti-PD1 therapies. Pts received up to 3 x 10^8 $TCID_{50}$CVA21 i.t. on study days 1, 3, 5, 8 and 22, and then q3w for a further 6 series of injections. Ipi (3 mg/kg) q3w was given as 4 i.v. infusions starting at Day 22. **Results:** Analysis of the prior anti–PD1 treated pts (n=13) revealed that the combination tx was generally well-tolerated with one case of Gr 3 ipi-related liver toxicity observed. Of the tx population, 54% (7/13) had received prior ipi tx in addition to anti-PD1, 85% (11/13) of pts were stage IV M1b/c, with the median time between the last anti-PD1 and first CVA21 and ipi doses being 5.7 and 8.7 weeks, respectively. The mean number of prior systemic therapies including anti-PD1 tx was 2.6. For all pts completing at least the first investigator response assessment (irWHO criteria at Day 106) we observed a confirmed BORR of 38.0% (3/8) and a DCR (CR+PR+SD) of 88% (7/8). **Conclusions:** Intratumoral CVA21 + ipilimumab treatment in anti–PD1 treated pts has displayed promising clinical activity together with low adverse toxicity and as such this regimen may represent a valuable tx option for pts that have been administered previous lines of immune checkpoint therapy. Clinical trial information: NCT02307149.

3015 Poster Discussion Session; Displayed in Poster Session (Board #110), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Antibiotics prescription to decrease progression-free survival (PFS) and overall survival (OS) in patients with advanced cancers treated with PD1/PDL1 immune checkpoint inhibitors. *First Author: Lisa Derosa, Department of Cancer Medicine, Gustave Roussy Cancer Campus, Paris-Sud University, Villejuif, France*

Background: Use of antibiotics (ATB) alters the gut microbiota composition and decreases bacterial diversity. Pre-clinical evidences demonstrated the impact of the microbiota in the efficacy of immune checkpoint blockades (ICB) in cancer. Interaction between ATB and ICB has not been extensively investigated in cancer patients (pts). Our study evaluated the effect of ATB in cancer pts treated with PD-1/PD-L1 inhibitors. **Methods:** We conducted a retrospective analysis of pts treated with PD-1/PD-L1 inhibitors for advanced Renal Cell Carcinoma (RCC), Urothelial Cancer (UC) and Non-Small Cell Lung Cancer (NSCLC) and data on ATB use were collected. ATB(+)/(-) groups were defined as pts treated or not with ATB before (2 months period) or within the first month of ICB. PFS and OS were compared between both groups among all pts and then according to tumor site. Statistical analyses were performed using the Kaplan-Meier method. Cox regression analyses were performed separately for each cancer type adjusting for its specific risk factors. **Results:** Among 175 pts included, 51 (29%) received ATB (mostly beta-lactamases and fluoroquinolones). ATB(+) group had shorter PFS and OS when compared to ATB(-) group: 3.4 vs. 5.2 months, $p < 0.013$, and 12.2 vs. 20.8 months, $p < 0.001$, respectively. According to tumor type, ATB(+) group translated into decrease OS (7.0 vs. 13.8 months, $p < 0.038$) in NSCLC. In RCC and UC pts, ATB (+) group had shorter PFS when compared to ATB(-) group (4.3 vs. 7.4 months, $p < 0.013$ and 1.8 vs. 4.3 months, $p = 0.048$, respectively). The negative impact of ATB was maintained after multivariate analyses adjusting for risk factors in each tumor type. **Conclusions:** ATB prescription preceding or concomitant to the first injection of PD-1/PD-L1 inhibitors impaired the outcome in patients with advanced cancers. This reduction in efficacy seems to be independent of classical prognostic factors in RCC, UC and NSCLC. These data should be validated in larger cohort. In addition, the role of gut composition to explain this interaction is ongoing, as well as novel diagnosis tools based on microbiota to predict response/resistance to ICB.

3016 Poster Discussion Session; Displayed in Poster Session (Board #111), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Loss-of-function of PBRM1 to predict response to anti-PD-1/PD-L1 therapy in metastatic renal cell carcinoma. *First Author: Diana Miao, Dana-Farber Cancer Institute, Boston, MA*

Background: Immune checkpoint inhibitors targeting programmed cell death-1 (PD-1) substantially improve patient survival in clear-cell renal cell carcinoma (ccRCC), but predictive biomarkers for efficacy have not yet been identified. **Methods:** We analyzed whole exome sequencing (WES) from a clinical trial of anti-PD-1 monotherapy (nivolumab) for ccRCC (N = 34) to discover genomic predictors of response to immune checkpoint therapy, and validated our findings in 28 ccRCC patients from 2 institutions treated with anti-PD-1 or anti-PD-L1 therapies. We defined 3 response groups: clinical benefit (CB) – complete or partial response by RECIST or stable disease with objective decrease in tumor burden and progression free survival (PFS) $>$ 6 months - and no clinical benefit (NCB) – progressive disease with PFS $<$ 3 months, with all other patients in intermediate benefit (IB). We further validated our findings in WES from 212 melanoma patients treated with immune checkpoint therapies in 3 published cohorts. **Results:** Biallelic loss of the chromatin remodeling subunit *PBRM1*, mutated in 34/62 (55%) patients across both cohorts and up to 41% of ccRCC overall, was the only gene mutation associated with CB in both the training (p = 0.0064; Pearson's chi-squared) and validation cohorts (p = 0.043), and predicted both PFS and overall survival (OS) (p = 0.042 and 0.014, respectively; Kaplan-Meier). In 212 melanomas, truncating alterations in *ARID2* – a closely related chromatin remodeler - were also enriched in responders after correcting for tumor mutational burden (p = 0.036), and having a truncating alteration in either *PBRM1* or *ARID2* significantly predicted overall survival (p = 0.022). In this ccRCC cohort, tumor mutational burden and loss of antigen presentation machinery were not associated with CB or NCB. **Conclusions:** Loss of chromatin remodeling subunits may impact response to immune checkpoint therapy in both ccRCC and melanoma. Further study in larger cohorts of immunotherapy-treated patients and functional characterization of *ARID2* and *PBRM1* in the context of the tumor-immune microenvironment will help to determine potential for further biomarker development.

3017 Poster Discussion Session; Displayed in Poster Session (Board #112), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Expression quantitative trait loci (eQTLs) as germline determinants of melanoma immunotherapy response. *First Author: Robert Ferguson, New York University, New York, NY*

Background: Approximately 40-60% of metastatic cutaneous melanoma (CM) patients do not respond to the current immunotherapy (IT) regimens, pointing to other yet unknown factors conferring IT resistance. Based on our recent findings showing that germline expression quantitative trait loci (eQTLs) in immune pathways associate with overall CM survival, in this study we tested whether germline immune-specific eQTLs also impact IT outcomes in CM. **Methods:** By interrogating a healthy twin cohort expression dataset (MuTHER), we have identified 50 eQTLs most significantly associated with the expression of 265 immune genes. Using the MassARRAY system, these 50 SNPs were genotyped in 138 anti-CTLA-4 treated patients, 59 PD-1 treated patients and 38 patients from combined (COMBO) treatments collected from multi-institutional collaborations. To test the association of SNPs with IT response, logistic regression was performed for each treatment group adjusting by demographic and clinical covariates. **Results:** We found significant associations with COMBO IT resistance for rs6673928 (OR = 4.249, p = 0.0167), an eQTL in *IL10/IL19* which we have recently identified for association with melanoma survival; interestingly, it is a previously established locus associated with the risk of several autoimmune diseases. Additionally, we also identified eQTLs that are associated with IT sensitivity: rs4848306 in *IL1-β* with resistance to anti-CTLA-4 (OR = 0.373, p = 0.000733) and rs2071304 in *SPI1* with resistance to anti-PD-1 (OR = 0.3328, p = 0.0271). **Conclusions:** In this study we report that rs6673928, an eQTL from the *IL19/IL10* locus previously shown to predict autoimmunity risk and CM survival, is also a surrogate marker of response to COMBO IT. The associations of rs6673928 with both IT response and CM survival indicate a strong relationship between interleukin pathways and the level of tumor immunogenicity. In addition to its apparent function in immune response, the putative multi-faceted role of this locus in predicting better survival and IT outcomes indicates high potential as a novel clinical target. Additional genetic and functional validation of these findings is currently underway in a large collaborative setting.

3018 Poster Discussion Session; Displayed in Poster Session (Board #113), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

FDA analysis of patients with baseline autoimmune diseases treated with PD-1/PD-L1 immunotherapy agents. *First Author: Chana Weinstock, U.S. Food and Drug Administration, Silver Spring, MD*

Background: With FDA approval of three novel agents targeting the PD-L1/PD-1 checkpoint pathway in multiple tumor types, use of these agents in the clinical setting is becoming increasingly common. However, little is published on their use in patients with a history of autoimmune diseases. We therefore aimed to collect safety data on patients with a history of autoimmune diseases treated with PD-1/PD-L1 immunotherapy agents in a clinical trial setting. **Methods:** Data on patients with a history of autoimmune disease were collected for four different PD-1/PD-L1 immunotherapy agents. Information collected included name of autoimmune disease, corticosteroid dependency at baseline, duration of dosing, immune-related adverse events (iRAEs) and worsening of underlying autoimmune disease. **Results:** In total, 552 patients enrolled in 22 clinical trials of PD-1/PD-L1 immunotherapy agents were identified with a history of autoimmune disease. None were known to be dependent on systemic corticosteroids at baseline. The most common autoimmune diseases identified were thyroid disorder (n = 188), psoriasis (n = 70), and vitiligo (n = 44). For the four agents identified, mean duration of dosing was 183, 187, 196, and 145 days. Worsening of underlying autoimmune disease occurred in 16%, 6%, 13% and 6%. There were two grade 4 cases of hyperglycemia in patients with diabetes, three cases each of grade 3 AEs related to the underlying disorder in patients with psoriasis, interstitial lung disease, and hypothyroidism, and one grade 3 AE in a patient related to ankylosing spondylitis.For two of these agents, data were available on the development of grade 1-4 irAEs (per investigator) that required treatment with systemic steroids, which occurred in 8% and 9% of patients. **Conclusions:** Clinical trial data demonstrates relative safety of the use of PD-1/PD-L1 immunotherapy agents in patients with a history of autoimmune disease compared to their use in patients without such history. No consistent pattern of worsening of baseline autoimmune disease was identified. These results should be interpreted with caution, as diagnostic method and clinical manifestations of reported baseline autoimmune conditions are not known.

3019 Poster Discussion Session; Displayed in Poster Session (Board #114), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Biomarkers associated with neurotoxicity in adult patients with relapsed or refractory B-ALL (R/R B-ALL) treated with CD19 CAR T cells. *First Author: Bianca Santomasso, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: CD19-specific chimeric antigen receptor (CAR) modified T cells produce high and durable anti-tumor activity, but can be associated with treatment-related toxicities including cytokine release syndrome (CRS) and neurotoxicity (NTX). NTX is poorly understood and it hasn't been clear where to focus further research. We report cerebrospinal fluid (CSF) data and neuroimaging characteristics of patients (pts) who developed severe NTX (sNTX) during our phase I clinical trial of CD19-specific 19-28z CAR T cells for adult pts with R/R B-ALL, which suggest new avenues for future research. **Methods:** 51 adult pts with R/R B-ALL were treated with 19-28z CAR T cells following conditioning chemotherapy at MSKCC. We analyzed the incidence and grade of NTX, CRS and correlative biomarkers in blood and CSF. **Results:** 21/51 treated pts developed sNTX (grade $\geq$3) complications such as encephalopathy, aphasia, depressed level of consciousness, myoclonus, and seizure. No pt developed grade 5 NTX and, in all but one case, neurologic symptoms fully resolved. We collected CSF by lumbar puncture and blood from 14 pts at the time of peak NTX. sNTX was correlated with pre-infusion disease burden (p = 0.013) and peak CAR T cell expansion in the blood (p = 0.0001), but we found no significant correlation between NTX grade and the CAR T cell concentration in the CSF during NTX. Instead CSF protein level was correlated with neurotoxicity grade (p = 0.0109). The cytokines IL6, IL8, IL10, IFNγ and GCSF were elevated in CSF over serum at the time of NTX and correlated with CSF protein levels (all p $<$ 0.005). These were distinct from serum cytokines significantly associated with sNTX at d3 of T cell infusion: GMCSF, IFNγ, IL15, IL5, IL10, and IL2 (all p $<$ 0.01). 4/21 patients developed a pattern of reversible MRI T2/FLAIR hyperintensity involving the bilateral thalami, dorsal pons, and medulla. **Conclusions:** NTX is predominantly reversible. MRI findings suggesting transient toxicity to deep grey structures and findings of a CSF-specific cytokine profile expand the hypotheses on the mechanism of NTX. Future studies will focus on determining the etiology of the CSF protein elevation and the distinct cytokine profile. Clinical trial information: NCT01044069.

3020 Poster Discussion Session; Displayed in Poster Session (Board #115), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Cytokine release syndrome (CRS) and neurotoxicity (NT) after CD19-specific chimeric antigen receptor- (CAR-) modified T cells. *First Author: Cameron John Turtle, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: CD19 CAR-T cells have produced impressive responses in $CD19^+$ ALL, NHL and CLL. Detailed understanding of the presentation and pathogenesis of CRS and NT will facilitate safe CAR-T cell use in multicenter trials. **Methods:** We treated 161 adults with B-ALL, NHL or CLL with anti-CD19 CAR-T cells, formulated in a 1:1 CD4/CD8 ratio and infused after lymphodepletion chemotherapy in a dose finding study (NCT 01865617) to identify a MTD in each disease. **Results:** 133 patients (pts) completed toxicity assessment. CRS developed in 71% (60% gr 1-2, 4% gr 3, 8% gr $\geq$4). Fever was the first sign of CRS and preceded organ toxicity, allowing safe outpatient administration of CAR-T cells. NT was observed in 40% (19% gr 1-2, 16% gr 3, 5% gr $\geq$4) and gr $\geq$3 NT presented a median of 4.5 days after CRS onset. The time from onset to peak of NT was 2 days. CRS and NT were reversible with the exception of 6 pts who died, 4 during the dose-finding phase of the study. In multivariable analyses, higher CAR-T cell dose and malignant B cells in marrow (BM) were associated with CRS; and CAR-T cell dose, malignant BM B cells, more intensive lymphodepletion, and prior neurologic comorbidities were associated with NT. Probability curves of response, CRS and NT in relation to blood CAR-T cell counts show that toxicity mitigation by CAR-T cell dose reduction may be feasible in B-ALL without impairing BM response; however, dose reduction may reduce nodal response in NHL and CLL. Analysis of clinical parameters revealed that pts who later developed severe CRS or NT could be identified early after CAR-T cell infusion by higher fever, greater vascular instability, and more severe hypoalbuminemia. Paired serum-CSF studies and autopsy data suggest blood-brain barrier disruption in severe NT. High serum IL-6, IL-15, MCP-1 and IL-10, and endothelial activation markers on day 1 after infusion correlated with subsequent toxicity, which identifies pts for early intervention to prevent severe toxicity. **Conclusions:** CAR-T cells can be safely administered in the outpatient setting. Clinical and laboratory biomarkers allow early identification of a small subset of pts who might develop serious toxicity, facilitating study of preventive strategies. Clinical trial information: NCT 01865617.

3021 Poster Session (Board #116), Mon, 8:00 AM-11:30 AM

Maintenance immunotherapy in stage IV cancer patients who have a clinical benefit from chemotherapy. *First Author: Francesco Recchia, Fondazione Carlo Ferri, Monterotondo, Italy*

Background: Even if patients with stage IV cancer (AC) may have prolonged remissions with chemotherapy (CT), the majority of them, will eventually relapse. In vitro studies suggest that natural killer (NK) cells mediate lytic activity against cancer cell lines and that high expression of vascular endothelial growth factor (VEGF) promotes tumor progression through neoangiogenesis. We have shown that low-dose interleukin-2 (IL-2) and 13-cis retinoic acid (RA) increased NK cells and decreased VEGF, in patients with AC and a clinical benefit on CT (Clin Cancer Res 7: 1251, 2001). We hypothesized that IL-2 and RA, increasing NK and decreasing VEGF, could improve disease-free survival (DFS) and overall survival (OS) in a minimal residual disease setting. Primary endpoint was the evaluation of NK cells and VEGF; secondary endpoints were DFS, OS and toxicity. **Methods:** 500 patients with AC, and a clinical benefit from CT, were given subcutaneous IL-2, 1.8×10^6 IU and oral RA, 0.5 mg/Kg, 5 days/week, 3 weeks/month, until progression. NK cells, VEGF, response and toxicity were assessed every 4 months. **Results:** After a median follow-up of 112 months (range 63-200), a total of 4400 courses of CT and 2634 courses of immunotherapy were delivered. A statistically significant improvement of NK cells [from a mean of $309 \pm 76/mm^3$ to a mean of $579 \pm 74/mm^3$ ($p < 0.001$)] and a decrease of VEGF [from a mean of 520 ± 75 pg/mm^3 to a mean of 150 ± 12 pg/mm^3, ($p < 0.001$)], were observed. Eighteen-years DFS and OS were 29% and 32%, respectively. A significant improvement, with respect to NCI SEER data (*), was observed in the 5-year OS rate for the most common treated AC: Breast cancer 55% vs. 6% *; Lung cancer 22% vs. 4.3% *; Colorectal cancer 43.5% vs. 21%*. No WHO grade 3 or 4 toxicity was observed, while grade 2 cutaneous toxicity and fever occurred in 20% and 13% of patients, respectively. **Conclusions:** Our data show that immunotherapy with IL-2/RA, may determine, with an acceptable toxicity profile, a statistically significant improvement of NK cells, a decrease of VEGF, and better 5-year survival rates with respect to NCI SEER data, for all major stage IV cancers.

3022 Poster Session (Board #117), Mon, 8:00 AM-11:30 AM

PRKDC: A new candidate for checkpoint blockade immunotherapy? *First Author: Ming Huang Chen, Taipei Veterans General Hospital, Taipei, Taiwan*

Background: Immunologic checkpoint blockade with antibodies that target CTLA-4 or PD-1/PD-L1 have demonstrated promise in a variety of malignancies. However, the treatment response rate of these immunologic checkpoint blockades remains low. Identifying predictive biomarkers to assist patient selection for immunotherapy have become a priority in both clinical and research settings. **Methods:** Mutations in patients who responded to immunotherapy were identified by Next-Generation Sequencing (NGS). Relationship between mutation of *PRKDC*, mutation load and known immune biomarkers were analyzed using datasets from The Cancer Genome Atlas (TCGA). Following up, the PRKDC protein expression was evaluated in 439 gastric cancer patients by immunohistochemical staining and their MSI statuses were evaluated by PCR. **Results:** We first identified *PRKDC* mutations in two responders to immune checkpoint therapy (1 HCC, 1 gastric cancer). From published literature, we further discovered that 66.7% (2/3) of lung cancer patients and 63.6% (7/11) of melanoma patients whose tumor harbored *PRKDC* mutation and responded to immunotherapy. Most of these mutations detected in responders were either truncating or located in functional domains. Further analysis showed that *PRKDC* mutation is significantly associated with high mutation load in cervical cancer, colon adenocarcinoma, head and neck squamous cell carcinoma, lung adenocarcinoma, gastric adenocarcinoma and endometrial cancer ($p = 0.008$, $p = 0.0108$, $p = 0.0166$, $p = 0.0183$, $p < 0.001$ and $p < 0.001$, respectively). Interestingly, gastric cancer patients harboring *PRKDC* mutations or with MSI-H demonstrated significantly higher gene expression in *PDL1, TIM3, LAG3, IFNG, CXCL9, CXCL10, GZMA* and *PRF1*, compared to MSS patients ($p = 0.0016$, $p = 0.0142$, $p = 0.0017$, $p = 0.0034$, $p = 0.0118$, $p < 0.0001$, $p = 0.0001$, $p < 0.0102$, respectively). Finally, we discovered low expression of PRKDC was a poor prognostic factor and significantly correlated with MSI-H in gastric cancers. **Conclusions:** PRKDC may be a potential biomarker that can identify responders to immune checkpoint inhibition.

3023 Poster Session (Board #118), Mon, 8:00 AM-11:30 AM

Product characteristics associated with in vivo expansion of anti-CD19 CAR T cells in patients treated with axicabtagene ciloleucel (axi-cel). *First Author: Frederick Lundry Locke, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: Axi-cel (formerly KTE-C19) is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy. ZUMA-1 is a multicenter, registrational trial of axi-cel in patients (pts) with refractory aggressive non-Hodgkin lymphoma. In a prespecified interim analysis, ZUMA-1 met its primary endpoint, with a 76% objective response rate and a 47% complete response rate (*Blood* 2016;128:LBA-6). Post-treatment CAR T cell blood levels were associated with objective response. Here, we describe novel associations between product characteristics and CAR T cell levels in pts. **Methods:** CAR T cell characteristics in axi-cel produced from 62 pts were analyzed by flow cytometry and modeled against CAR T cell levels. *In vivo* CAR T cell levels were measured by qPCR. T cell expansion during production (fold expansion/total days in culture) was compared with CAR T cell blood levels, using a partition analysis with expansion rates of $\geq$1 vs $<$ 1. Wilcoxon 2-sample test and linear regression were used. **Results:** Axi-cel contained CCR7+ T cells (median, 42%; range, 15–73%), with naïve (CD45RA+/CCR7+; median, 12%; range, 1–57%), central memory (CD45RA−/CCR7+; median, 29%; range, 12–49%) phenotypes, and more differentiated CCR7− effector memory and effector T cells. On infusion, CAR T cells expanded rapidly, reaching peak levels within 2 weeks (median, 43 cells/μL; range, 1–1513), and were also measurable in all pts at 1 month (median, 2 cells/μL; range, 0.03–89). The CCR7+/CCR7− T cell ratio in axi-cel associated positively with peak (P=0.001) and cumulative (P=0.003) CAR T cell levels through 1 month. Axi-cel lots that expanded more rapidly during production ($\geq$1.0-fold/d; n = 18/62) associated with higher cumulative levels of CAR T cells (P=0.03). Other product characteristics, eg, CD4/CD8 ratio or number of infused T cells, were not significantly associated with CAR T cell blood levels. **Conclusions:** An association was observed between CAR T cell expansion *in vivo* and both the T cell growth rate during production and product cell phenotype pretreatment. A key attribute of axi-cel product was the presence of CCR7+ naïve/central memory T cells, without upfront T cell subset selection. Clinical trial information: NCT02348216.

3024 Poster Session (Board #119), Mon, 8:00 AM-11:30 AM

Updated results from ZUMA-3, a phase 1/2 study of KTE-C19 chimeric antigen receptor (CAR) T cell therapy, in adults with high-burden relapsed/refractory acute lymphoblastic leukemia (R/R ALL). *First Author: Bijal D. Shah, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: Promising results have been observed with KTE-C19, an anti-CD19 CAR T cell therapy, in refractory aggressive NHL in the ZUMA-1 trial (Blood 2016;128:LBA-6). We present here updated results from the ZUMA-3 phase 1 trial of KTE-C19 in adult patients (pts) with R/R ALL. **Methods:** Adult (≥18 y) pts with R/R ALL (Ph+ eligible), ≥25% bone marrow (BM) blasts, adequate organ function and ECOG status 0-1 received 1 or 2×10^6 CAR T cells/kg after conditioning with cyclophosphamide + fludarabine. Phase 1 primary endpoint is incidence of dose-limiting toxicity (DLT). Secondary endpoints include efficacy outcomes and biomarker associations. **Results:** As of Nov 1, 2016, 11 pts were enrolled; 10 received KTE-C19. One pt had a serious adverse event (SAE) prior to dosing and was not treated. KTE-C19 was successfully manufactured in all pts across a broad range of baseline absolute lymphocyte counts in 6 days in a centralized facility, with an approximate 2-week turnaround time. Pts were 60% men with 1-4 prior lines of therapy and high disease burden (median, 70% BM blasts). No pt (0/3) experienced a DLT at the 2×10^6 dose. Phase 1 was expanded to 6 pts at the same dose; 1 grade (Gr) 5 AE (multiorgan failure due to cytokine release syndrome [CRS]) was observed. Subsequent pts (4) received 1×10^6 CAR T cells/kg. Overall, the most common Gr≥3 AEs were cytopenias (80%), febrile neutropenia (50%), pyrexia (40%), and transaminitis (40%). Gr≥3 CRS and neurologic events (NEs) were reported in 20% and 40% of pts, respectively. Cerebral edema was not observed. All CRS (except Gr5) and 5 of 6 NEs (1 Gr3 ongoing at cut-off) resolved. Of the 8 efficacy evaluable pts, 6 achieved an MRD-negative (MRD^-) complete response (CR, or CR + partial or incomplete hematopoietic recovery). Updated results will include additional pt follow-up and biomarker data. **Conclusions:** No DLTs were observed with KTE-C19 in adult pts with high BM disease burden; one pt had G5 CRS after the DLT cohort. Manufacturing was successful in all pts; most pts achieved an MRD^- CR. Based on these results, ZUMA-3 continues to enroll pts with additional measures implemented to further enhance safety. Clinical trial information: NCT02614066.

3025 Poster Session (Board #120), Mon, 8:00 AM-11:30 AM

Characterization of anti-CD19 chimeric antigen receptor (CAR) T cell-mediated tumor microenvironment immune gene profile in a multicenter trial (ZUMA-1) with axicabtagene ciloleucel (axi-cel, KTE-C19). *First Author: Jerome Galon, Laboratory of Integrative Cancer Immunology, INSERM, Paris, France*

Background: Axi-cel is an autologous anti-CD19 CAR T cell therapy. ZUMA-1 is a multicenter, registrational trial of axi-cel in patients (pts) with refractory/aggressive B-cell non-Hodgkin lymphoma (NHL). In a pre-specified interim analysis, ZUMA-1 met its primary endpoint with 76% objective response rate and 47% complete response (Blood 2016;128:LBA-6). We describe, for the first time, a tumor microenvironment immune gene signature associated with CAR T cell treatment (tx) of NHL pts. **Methods:** Paired biopsies, pre- and within 3 weeks post-axi-cel tx, were analyzed by digital gene expression followed by a pre-specified bioinformatics algorithm applied to IGES15 and IGES21 genes involved in immune-mediated tumor regression (Immunosign; Galon Immunity 2013). Immunosign profiles expression of a pre-defined set of effector T cell, Th1, chemokine, and cytokine genes. Expression analysis and hierarchical clustering were used to define an axi-cel-related tumor immune gene signature. Wilcoxon signed rank test with multiple test correction by FDR (Benjamini-Yekutieli) was used. **Results:** Gene expression profile comparisons of pre- and post-axi-cel tx biopsies from 14 pts showed profound changes in gene expression within the tumor environment after infusion. The most upregulated genes post-axi-cel tx were CCL5 (RANTES), CTLA4, and GZMA ($\log_2$ fold change > 2, $P< 0.05$, FDR < 0.050). Immune checkpoints PD-L1 and LAG3 were also upregulated post-axi-cel ($\log_2$ fold change > 1.6, $P< 0.05$, FDR < 0.055). Other genes associated with T cell proliferation, homing, and effector function were also upregulated: IL-15, GZMK, CXC3CL1 (Fractalkine), CD8A, and STAT4 ($\log_2$ fold change > 1.6; $P< 0.05$, FDR $<$ 0.074). Additional baseline tumor characteristics and associative analysis will be presented. **Conclusions:** We define a mechanistic tumor immune gene signature in NHL pts associated with axi-cel tx. This signature comprises upregulation of T cell activation, effector, chemokine, and immune checkpoint genes. These data will potentially lead to rational optimization of T cell interventions in cancer Clinical trial information: NCT02348216.

3026 Poster Session (Board #121), Mon, 8:00 AM-11:30 AM

Response to first-line chemotherapy regimen to predict efficacy of nivolumab in lung cancer. *First Author: Coureche Guillaume Kaderbhai, Centre Georges-François Leclerc, Dijon, France*

Background: Nivolumab is a monoclonal antibody, targeting PD-1 receptor and demonstrating durable clinical benefit in 20% of metastatic NSCLC patients in second and further treatment lines. The expression of one of the PD-1 ligand, PD-L1 assessed by IHC is associated with better outcome. However, robust predictive markers of efficacy are lacking. **Methods:** 115 pts with stage IV NSCLC (42 squamous, 73 adenocarcinoma) were included in this retrospective study in 4 different institutions. They received nivolumab (3 mg/kg IV Q2W) after at least one line of systemic platinum-based chemotherapy. Response to first line chemotherapy and to nivolumab (RECIST 1.1) was determined on CT scan by two physicians. Association between best response to first-line regimen and PFS, OS or response to nivolumab was determined using both Chi2 and Cox analysis. **Results:** 46 (40%), 44 (38%) and 25 (22%) patients experimented PR, SD and PD to first-line platinum-based chemotherapy. 25 (22%), 34 (29.5%), 56 (48.5%) experimented PR, SD and PD to nivolumab. 59.5% (53/89) of patients who experimented clinical benefit (SD+PR) to first-line also experimented clinical benefit to nivolumab while only 20% (5/25) of patients with PD as best response to chemotherapy experimented clinical benefit to nivolumab (Chi2 test p = 0.002). The type of first-line doublet chemotherapy did not influence the response rate to nivolumab. Cox uni and multivariate models included age, histology and performance status underlined that patients with clinical benefit from chemotherapy had improved PFS with nivolumab (P = 0.002) (median PFS on nivolumab regimen of 4.9, 3.3 and 1.8 months for patients with PR, SD and PD to first-line, respectively). Similar results were obtained for OS (P = 0.03). **Conclusions:** Our data suggest that response to first-line chemotherapy may be a good surrogate marker of response, PFS and OS to post-platinum nivolumab in metastatic NSCLC.

3027 Poster Session (Board #122), Mon, 8:00 AM-11:30 AM

The relationship of pharmacodynamics (PD) and pharmacokinetics (PK) to clinical outcomes in a phase I study of OX40 agonistic monoclonal antibody (mAb) PF-04518600 (PF-8600). *First Author: Anthony B. El-Khoueiry, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: PF-8600 is a novel fully human IgG2 agonistic mAb against human OX40, a TNF receptor superfamily member expressed primarily on activated T cells. This ongoing phase 1 study (NCT02315066) is investigating the safety, efficacy, PK and PD of PF-8600 in patients (pts) with solid tumors. **Methods:** PF-8600 (0.01–10 mg/kg) was given IV every 14d. Expression of free/total OX40 receptor, proliferation marker ki67 and activation markers HLA-DR/CD38 were measured in T cell subsets in peripheral blood by flow cytometry in all pts. CD4, CD8, OX40 and FOXP3 were evaluated in paired tumor biopsies (bx), collected from a subset of pts (≥0.1 mg/kg) at baseline (BL) and Wk6, by immunohistochemistry. **Results:** As of 21Sep2016, 48 pts with melanoma (n = 14), hepatocellular carcinoma (HCC, n = 19), head and neck squamous cell (n = 6) or renal cell carcinoma (n = 9) enrolled in the dose-escalation cohorts (0.01-3 mg/kg). No immune related adverse events (AE) were reported. The most frequent treatment related AEs in > 3 pts were fatigue (27.1%) and nausea and vomiting (8.3% each); all Gr 1-2. 2 pts had a partial response: melanoma at 0.1 (Pt1) and HCC at 0.3 (Pt2) mg/kg. 25 pts had best ORR (BOR) of stable disease (SD; 3 pts ≥24 wks). A majority of pts at 0.1, 0.3, and 3 mg/kg, including Pt1 and Pt2, had increases in ki67 and HLA-DR/CD38 expression in peripheral CD4+ central memory T cells. Pt1, Pt2 and all pts at ≥0.3 mg/kg had full receptor occupancy. Paired bx were only available from pts with BOR of SD or progressive disease. In 10 pts with available paired tumor bx and defined date of radiographic progression (rPD), longer time to rPD correlated with increases in %OX40+ in bx from BL to Wk6, regardless of dose level, tumor type or prior immunotherapy (R^2= 0.52, p = 0.0188); no correlation between rPD and CD4+, CD8+ or FOXP3+ expression changes was observed. Updated efficacy, safety, PK and PD data will be presented. **Conclusions:** PF-8600 is well tolerated with evidence of single agent efficacy. Initial observations of PD markers that change with treatment and correlate with rPD support efforts to confirm these findings as more clinical outcomes and larger sample sizes become available. Clinical trial information: NCT02315066.

3028 Poster Session (Board #123), Mon, 8:00 AM-11:30 AM

Epitope mapping of PD-L1 primary antibodies (28-8, SP142, SP263, E1L3N). *First Author: Kelly Schats, HistoGeneX, Antwerp, Belgium*

Background: Currently, programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) assays received approval in combination with an anti-PD-1 or anti-PD-L1 compounds. However, the FDA blueprint and other publications revealed differences in staining pattern between PD-L1 IHC assays. More precisely the SP142 assay detects less tumor cells (TC), but more immune cells (IC), while the 28-8 assay is more sensitive for TC and less appropriate for IC detection. SP263 stains TC and IC equally well. E1L3N IHC reveals IC and slightly more TC staining than SP142. This study investigates whether these staining discrepancies can be partly explained by specific epitope recognition. **Methods:** Linear epitope mapping was performed for PD-L1 antibody clones 28-8, E1L3N, SP142 and SP263. In brief, the PD-L1 sequence (Q9NZQ7, Uniprot) was split into 15 amino acid (AA) peptides with a peptide overlap of 14 AA . Each peptide was printed in duplicate on the PD-L1 microarray. The microarray was exposed to different concentration of the four PD-L1 antibodies. For the detection, sheep anti-rabbit IgG DyLight800 was used. **Results:** Epitope mapping for the E1L3N antibody revealed a linear epitope in the intracellular domain. The other clones showed weaker binding to multiple peptides. The 28.8 clone demonstrated binding to predominantly intracellular epitopes, while SP142 and SP263 clones showed binding to both intracellularly and extracellularly located epitopes. Blasting the epitope sequences of the PD-L1 antibodies did not disclose identity with another (non-PD-L1) human protein. **Conclusions:** Different binding characteristics were found for all four PD-L1 antibody clones in a linear epitope mapping experiment. This could lead to particular staining patterns depending on PD-L1 conformation (folding) or isoform expression. Two PD-L1 isoforms are known, with isoform 2 lacking AA 19-132 of the extracellular domain. Especially SP142 binding can be impacted in the case of dominant isoform 2 presence, since epitopes were observed in this spliced domain. Further investigation is needed into the potentially conformational epitopes of SP142, SP263 and 28.8 antibody clones as well as in the PD-L1 conformation and isoform expression in TC and IC.

3029 Poster Session (Board #124), Mon, 8:00 AM-11:30 AM

Overall survival prognosis of patients in immuno-oncology phase I trials: The Gustave Roussy score. *First Author: Frederic Bigot, Drug Development Department (DITEP), Gustave Roussy, Villejuif, France*

Background: The evaluation of patient's life expectancy is crucial to select patients who may benefit from phase I studies. The Royal Marsden Hospital (RMH) prognostic score, based on 3 objective variables (number of metastatic sites, LDH and serum albumin) was validated in patients treated with cytotoxic and targeted therapies. We aimed to determine if those factors were applicable to immunotherapy (IT) phase I trials. **Methods:** A retrospective analysis for risk factors of survival was conducted in a discovery cohort of 155 patients enrolled into IT phase I trials at our institution. We computed univariate and multivariate analysis (MVA) of demographics, clinical and biological data to assess their prognostic value for overall survival (OS). MVA results were used to build a prognostic score for OS. A validation cohort of 113 patients enrolled in IT phase I trials was used to prospectively re-validate this score. **Results:** 155 patients receiving an experimental IT between March 2012 and January 2016 were included in the discovery cohort. A MVA assessing the RMH Score variables showed that albumin < 35 g/dL (HR 1.73, 95% CI 1.05-2.86) and LDH $>$ upper normal limit (1.88, 95% CI 1.12-3.15) were independent negative prognostic factors for OS. As opposed to the RMH score, number of metastases was not associated with a poorer outcome for this IT cohort (0.83 95% CI 0.51-1.35). Interestingly, a neutrophil to lymphocyte ratio (N/L) > 6 (1.75, 95% CI 1.04-2.95) was associated with a worse OS. A risk analysis based on the results of the MVA showed that patients presenting a high score (2-3) had a significantly shorter OS (20.4 weeks; 95% CI 5.7-35.2) compared to those with a low score (0-1) (68.9 weeks; 95% CI 50-83.7) (HR = 2.9 95% CI 1.87-4.64). In the validation cohort of 113 patients, the patients presenting a high score showed an inferior OS (HR = 6.3, 95% CI 2.7-14.8). **Conclusions:** In phase I trials of IT, traditional prognostic variables included in the RMH Score are suboptimal to determine patient's prognosis. In this context, the N/L ratio, which reflects the immune contexture, is a significant prognostic variable. The new Gustave Roussy Score, based on albumin, LDH and N/L ratio allows to better select patients for IT phase I trials.

3030 Poster Session (Board #125), Mon, 8:00 AM-11:30 AM

Very early molecular marker of tumor response to PD-1 inhibition in plasma of patients with advanced non-small cell lung cancer (NSCLC). *First Author: Thijo Jeroen Nicolaas Hiltermann, University Medical Center Groningen, Groningen, Netherlands*

Background: Nivolumab shows a durable tumor response in 20 % of advanced NSCLC patients. While a PD-L1 immunohistochemistry complementary diagnostic has been approved, there is a need to identify a predictive biomarker with greater diagnostic accuracy. **Methods:** In an ongoing study of patients, treated with nivolumab every 2 weeks for advanced recurrent NSCLC and a known KRAS mutation in the primary tumor, liquid biopsies were taken by a simple blood draw at baseline (before treatment), 1, 2, 4, 6 and thereafter every 12 weeks until disease progression. Circulating tumor DNA (ctDNA) was extracted from cell free plasma and tested with a specific digital droplet PCR (ddPCR)-KRAS G12/G13 screenings assay (BIORAD). Mutation levels in plasma were compared with tumor response on CT scans by RECIST v.1.1. CT scans were performed at baseline and thereafter every 6 weeks until disease progression. **Results:** Patient characteristics are shown in table 1. In this prospective analysis specific patterns could be demonstrated in plasma ctDNA testing of KRAS mutation levels. All 4 responders showed an increase of mutant copies/ml plasma in the first week followed by a clear drop to non-detectable KRAS mutations at all CT evaluated tumor responses. The 2 non-responders however, did not show the increase in mutant copies/ml at one week and showed a gradual increase in mutant copies/ml in the following weeks. **Conclusions:** Specific plasma ctDNA testing seems a very promising early biomarker (1 week) for tumor response to PD-1 therapy.

	Sex	Age	KRAS mutation (plasma)	Cycles of Nivolumab	Responder (RECIST)	ECOG PS	PFS (weeks)	Deceased
Patient 1 (980)	M	59	c.34G>T; p.G12C	28+	R	0	NR	No
Patient 2 (1032)	F	59	c.35G>A; p.G12D	9	R	0	42	No
Patient 3 (1035)	M	68	c.34G>T; p.G12C	27+	R	1	NR	No
Patient 4 (1067)	F	64	c.34G>T; p.G12C	3	NonR	1	5	Yes
Patient 5 (1083)	F	60	c.34G>T; p.G12C	2	NonR	0	7	Yes
Patient 6 (1096)	F	53	c.35G>A; p.G12D	16+	R	1	NR	No

R=responder; NonR= non-responder; NR= not reached.

3031 Poster Session (Board #126), Mon, 8:00 AM-11:30 AM

Association of changes in T regulatory cells (Treg) during nivolumab treatment with melanoma outcome. *First Author: Jeffrey S. Weber, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY*

Background: PD-1 blocking antibodies have significant efficacy in the treatment of melanoma; however, many patients fail to respond and resistance mechanisms remain unknown. We addressed the role of T_{regs}, an immunosuppressive T-cell population, in patient outcome after treatment with nivolumab. **Methods:** Peripheral blood mononuclear cells (PBMC) were obtained from patients on trials with nivolumab as adjuvant therapy for resected disease or as treatment for metastatic melanoma. To measure suppression, T_{regs} were flow-sorted from PBMC and evaluated in allogeneic mixed lymphocyte reactions. T_{regs} and conventional CD4 T-cells were evaluated for gene expression changes by RNA-sequencing. T_{reg} percentages and phosphorylated STAT3 (pSTAT3) expression were evaluated by flow cytometry. The effects of PD-1 blockade with nivolumab were evaluated *in vitro* using T-cells from baseline patient PBMC samples. **Results:** T_{regs} from responding patients or adjuvant patients without evidence of disease (NED) had reduced suppressive function post-nivolumab ($p < 0.05$), but no changes were observed in relapsing/non-responding patients; their T_{regs} were more suppressive than NED/responding T_{regs} ($p < 0.001$). NED T_{regs} had unique gene expression changes and associated pathways post-nivolumab compared to relapsing patient T_{regs} and conventional CD4 T-cells, including up-regulation of proliferation pathways ($q < 8e\text{-}19$) and downregulation of oxidative phosphorylation ($q < 7e\text{-}5$). NED T_{regs} had upregulation of pSTAT3 expression post-nivolumab ($p < 0.05$), which was not observed in relapsing patients. Evaluation of T_{regs} from patients with active disease also showed upregulation of pSTAT3 in responders ($p < 0.05$) but not non-responders. The relative increase in T_{reg} pSTAT3 was associated with increased overall survival ($R^2 = 0.49$, $p < 0.05$). *In vitro* assays using PD-1 blocking antibodies recapitulated the increase in pSTAT3 ($p < 0.05$) and T_{reg} percentages ($p < 0.001$), which were diminished with the addition of a STAT3 inhibitor ($p < 0.01$). **Conclusions:** These results demonstrate previously unknown roles of decreased T_{reg} suppressive function and induction of STAT3 as biomarkers of patient's outcome to nivolumab therapy.

3032 Poster Session (Board #127), Mon, 8:00 AM-11:30 AM

Excision repair cross complementation group 1 (ERCC-1) gene polymorphisms and response to nivolumab in advanced non-small cell lung cancer (NSCLC). *First Author: Marco M. Aiello, Medical Oncology, University Hospital Policlinico, Vittorio Emanuele, Catania, Italy*

Background: Anti PD1 antibodies showed significant clinical activity in different cancer types. Recently, it was observed that cancers with higher somatic mutation burden, as tumors with genome instability due to DNA repair defects, develop more elevated anti PD1 induced neoantigen specific T cell reactivity which results into increased susceptibility to PD1 blockade. We hypothesize that NSCLC pts with single nucleotide polymorphisms (SNPs) of the ERCC-1 gene, a key enzyme of DNA nucleotide excision repair pathway, may be more responsive to PD-1 blockade due to their genetic instability. **Methods:** We evaluated the rs11615 and rs3212986 ERCC1 SNPs by pyrosequencing analysis on tumor DNA of stage IIIb-IV previously treated NSCLC patients receiving Nivolumab (Nivo) 3 mg/kg q2w. To be eligible for this study, pts had to have a complete record of clinical and radiological parameters. Objective tumour response was assessed according to RECIST 1.1 criteria. **Results:** Between Jul 2015 and Jan 2016, 45 NSCLC pts received Nivo. Pts characteristics were as follows: M/F = 37/8; median age (range) = 64 (38-80); ECOG PS, 0/1/2 = 33/9/3; Stage IIIb/IV = 8/37; sqNSCLC/non sq NSCLC = 11/34; current-former smokers/non-smokers = 40/5; EGFR status, mutant/wildtype/unknown = 4/35/6; median cycles (range) = 12 (1-28). Only two pts presented the rs11615 SNP. 16 pts were positive for the rs3212986 SNP. ORR for all pts was 26.6% (95% CI, 10 to 47). The ORR was significantly higher in NSCLC pts positive for the rs3212986 SNP than for wild-type NSCLC patients (62.5% vs. 6.9%. p = 0.0001). For all pts median PFS was 4.3 mos (95% CI, 1.2 to 7.4)and median OS not-reached. Among pts positive for the rs3212986 SNP, median PFS and OS were 8.2 mos and not-reached respectively. In contrast wild-type patients presented a median PFS of 3.1 mos (HR = 0.21 95% CI, 0.07 to 0.57; p = 0.02) and a median OS of 6.5 mos (HR = 0,403 95% CI = 0,131-1,237 p = 0.11). Multivariate analyses confirmed the effect of rs3212986 SNP after adjustment for age, PS, sex and disease stage for PFS. **Conclusions:** This study suggests that genetic instability due to tumor ERCC1 SNPs in advanced NSCLC pts may be of value to predict clinical benefit from Nivo.

3033 Poster Session (Board #128), Mon, 8:00 AM-11:30 AM

Phase 1 safety of ICOS agonist antibody JTX-2011 alone and with nivolumab (nivo) in advanced solid tumors; predicted vs observed pharmacokinetics (PK) in ICONIC. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Nashville, TN*

Background: JTX-2011 is an agonist monoclonal antibody that targets ICOS, Inducible CO-Stimulator of T cells. A dual mechanism of action is intended to activate antigen-specific CD4 T effector cells and selectively deplete intratumoral T regulatory cells. JTX-2011 is equally potent across human, rodent, and non-human primate species. **Methods:** A quantitative systems pharmacology (QSP) model describing target binding by JTX-2011 and target mediated drug disposition in blood, tumor and non-tumor tissues was based on preclinical potency and non-linear PK data across species. The model was translated to predict PK and target engagement (TE) in humans to facilitate dose selection. The QSP model predicts $>$ 95% TE for 21 days at the top planned dose. We present safety and actual/predicted PK from a Phase 1 study of JTX-2011 alone (Part A) and safety in combination with nivo (Part B). **Results:** 25 subjects have been dosed, 19 in 4 cohorts of JTX-2011 alone at .003, .01, .03, and .1 mg/kg IV q 21 days, and 6 in 2 cohorts of JTX-2011 .01 mg/kg and .03 mg/kg IV plus nivo 240 mg IV q21 days. Safety data from $\geq$ 1 cycle is available for 12 subjects in Part A (7 $\geq$ 3 cycles), and 3 in Part B (all $\geq$ 3 cycles). PK data is available for cycle 1 of Part A. Mean age ($\pm$SD) is 60 ($\pm$10.6). Mean prior systemic therapies is $>$ 5 (range 1-11). Tumor types include endometrial, triple negative breast, melanoma, lung, pancreatic and colorectal cancers. No dose limiting toxicities have been reported. 3 Grade 3 adverse events (AEs) were reported in 2 Part A subjects: anemia and hypoxia (unrelated SAE) at .003 mg/kg and JTX-2011 related diarrhea at .1 mg/kg. Grade 1-2 AEs in $\geq$2 subjects are chills, pyrexia, neck pain, dizziness, and nausea. 5 subjects had JTX-2011 related Grade 1-2 infusion reactions up to 6 hours post infusion. Non-linear exposure increase was observed. While PK at lower doses is consistent with model predictions, AUC and $t_{1/2}$at 0.03 and 0.1 mg/kg doses are higher than predicted, suggesting higher than predicted TE. **Conclusions:** JTX-2011 has been well tolerated up to 0.1 mg/kg and with nivo at .01 mg/kg IV q 21 days. Greater than linear exposure increase was observed and TE may be higher than QSP model prediction. Clinical trial information: NCT02904226.

3034 Poster Session (Board #129), Mon, 8:00 AM-11:30 AM

Non-invasive clinical visualization of tumor infiltrating lymphocytes in patients with metastatic melanoma undergoing immune checkpoint inhibitor therapy: A pilot study. *First Author: Svetomir Markovic, Mayo Clinic, Rochester, MN*

Background: Unique to modern immune therapy for cancer is that early in the course of treatment, patients frequently exhibit transient tumor enlargement (pseudo-progression, pPROG) due to tumor infiltration by lymphocytes (TIL). Currently, pPROG cannot be reliably distinguished from true tumor progression (PROG). There is a need for biomarker techniques to discriminate pPROG (effect of therapy) and PROG (therapy failure). Nuclear medicine offers radiopharmaceuticals capable of imaging immune cells; images can be fused to evaluate functional and anatomic characteristics of tumors, and potentially discriminate pPROG from PROG. **Methods:** In our study of metastatic melanoma patients, SPECT/CT imaging with ^{99m}Tc-interleukin-2 (^{99m}Tc-IL2) was performed to visualize TIL. Images were collected before/after 12 weeks of ipilimumab (IPI) or pembrolizomab (PEMBRO) therapy. The ^{99m}Tc-IL2 tracer was synthesized by conjugating succinimidyl-6-hydrazinopyridine-3-carboxylate (HYNIC-NHS) with commercial interleukin-2 (Aldesleukin). HYNIC-IL2 was incubated with tricine, $^{99m}TcO_4^-$ (370-740 MBq) and $SnCl_2$. After labelling ^{99m}Tc-IL2 was purified by reverse-phase chromatography and diluted in 5% glucose with 0.1% human albumin before injection. Five patients were enrolled in this study. Two patients failed to complete the 12 week ^{99m}Tc-IL2 scan due to discontinuation of IPI after: 1) grade 3 colitis and 2) patient refusal for adverse events attributed to IPI. No adverse events attributable to the tracer infusion were reported. **Results:** Metastatic lesions could be visualized by the tracer. Some lesions decreased in size, while others increased. A positive correlation was found between size and ^{99m}Tc-IL2 uptake, before and after therapy, suggesting the potential discrimination of tumor PROG (no ^{99m}Tc-IL2 uptake) from pPROG (high ^{99m}Tc-IL2 uptake). Immunohistochemical staining for TIL of ^{99m}Tc-IL2 positive and negative lesions are illustrated. **Conclusions:** The results demonstrate feasibility of ^{99m}Tc-IL2 imaging as a clinically useful tool capable of discriminating tumor PROG from pPROG. A clinical validation study is in progress. Clinical trial information: NCT01789827.

3035 Poster Session (Board #130), Mon, 8:00 AM-11:30 AM

Tumor shrinkage and increased overall survival are associated with improved albumin, neutrophil lymphocyte ratio (NLR) and decreased durvalumab clearance in NSCLC and UC patients receiving durvalumab. *First Author: Thomas Powles, Barts Cancer Institute, London, United Kingdom*

Background: Progression of cancer is often associated with biomarkers of cancer inflammation, cachexia, and increased protein catabolism. Anti-PD1 and PD-L1 therapy have demonstrated durable responses across a number of tumor types. Durvalumab is a human monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 and CD80. The primary objective of this analysis was to prospectively assess potential correlations of longitudinal changes in ALB and NLR and durvalumab clearance (CL) rate to maximum decrease in tumor size and overall survival (OS) in patients (pts) with NSCLC and UC receiving durvalumab. **Methods:** Longitudinal target lesion size, serum chemistry, hematology and pharmacokinetic data were obtained from 3L+ NSCLC pts (n = 418) in study ATLANTIC and 2L+ UC pts (n = 182) in study 1108 during durvalumab treatment. Nonparametric correlations (Spearman's rho) were evaluated between OS, maximum percent change in target lesion size, and the maximum percent change from baseline observed in ALB, NLR, and CL. **Results:** In NSCLC, maximum decrease in tumor size was correlated with increased ALB ($r = 0.46$, $p < 0.0001$), decreased NLR ($r = 0.44$, $p < 0.0001$), and decreased CL ($r = 0.66$, $p < 0.0001$). OS was similarly correlated with increased ALB ($r = 0.47$, $p < 0.0001$), decreased NLR ($r = 0.41$, $p < 0.0001$), and decreased CL ($r = 0.76$, $p < 0.0001$). In UC, decreased tumor size also correlated with increased ALB ($r = 0.43$, $p < 0.0001$), decreased NLR ($r = 0.38$, $p < 0.0001$), and decreased CL ($r = 0.65$, $p < 0.0001$). OS in UC also correlated with increased ALB ($r = 0.50$, $p < 0.0001$), decreased NLR ($r = 0.33$, $p < 0.0001$) and decreased CL ($r = 0.82$, $p < 0.0001$). **Conclusions:** In NSCLC and UC pts receiving durvalumab, tumor shrinkage and longer survival are associated with increased ALB, decreased NLR and decreased clearance of durvalumab. These findings support the hypothesis that durvalumab may be associated with a decrease in protein catabolism, inflammation and cachexia among pts who benefited from therapy. Additional biomarkers of cancer, inflammation and cachexia will be evaluated for relationships to clinical outcomes.

3036 Poster Session (Board #131), Mon, 8:00 AM-11:30 AM

Metabolomic correlates of response in nivolumab-treated renal cell carcinoma and melanoma patients. *First Author: Marios Giannakis, Dana-Farber Cancer Institute, Boston, MA*

Background: Immune-checkpoint inhibition has been shown to be effective in a variety of cancers, including renal cell carcinoma (RCC) and melanoma. However, only a subset of patients with RCC and melanoma respond to anti-PD1 therapy. Given the importance of metabolism in the tumor immune microenvironment, we performed serum metabolomics in nivolumab-treated patients towards identifying novel non-invasive correlates of response and progression-free survival in immunotherapy-treated patients. **Methods:** We performed liquid chromatography-mass spectrometry on pre- and on-treatment serum samples from 79 patients with advanced melanoma (CA209-038 study) and 82 patients with metastatic RCC (CA209-009 study) receiving nivolumab. We precisely measured more than one-hundred named metabolites at baseline (prior to starting nivolumab), at 4 weeks and at 6 (melanoma) or 9 weeks (RCC) after initiation of treatment and correlated these with best overall response as well as progression-free survival (PFS). **Results:** In melanoma patients treated with nivolumab, the difference in mean levels of kynurenine (the product of IDO / TDO activity in tryptophan catabolism) between weeks 4 and 6 compared to baseline was significantly different between responders and non-responders (t-test with unequal variance p-value = 0.043 and p-value = 0.044 respectively). In RCC patients, we observed that patients with no response to nivolumab had significantly higher adenosine levels, than those who responded, at baseline and at 4 weeks after initiation of treatment (158% and 138% higher, t-test p-value = 0.0019 and p-value = 0.0011 respectively). RCC nivolumab-treated patients with higher (top quartile) baseline adenosine levels also had a significantly worse PFS (log rank test p-value = 0.004). **Conclusions:** In this first-of-its kind metabolomic analysis of peripheral blood from nivolumab-treated patients, we find that the change in kynurenine levels in melanoma patients correlates to response. In addition, higher baseline levels of adenosine in RCC patients are associated with worse PFS and lack of response to nivolumab. These results suggest a possible role for serum metabolites as biomarkers of benefit to PD1 inhibition.

3037 Poster Session (Board #132), Mon, 8:00 AM-11:30 AM

Biologic and clinical relevance of an IFNG mRNA signature (IFNGS) and PD-L1 protein expression in tumor and immune cells in urothelial cancer (UC) patients (pts) treated with durvalumab (D). *First Author: Carlos Bais, MedImmune, Gaithersburg, MD*

Background: PD-L1 can be induced by IFNG in tumor cells (TC) and immune cells (IC). TC PD-L1 expression prevalence in UC is low and the relevance of scoring TC (in addition to IC) is not fully understood. We recently reported a positive correlation between high levels of an IFNGS and outcome in a cohort of 30 UC pts treated with D. Here, we assessed the potential predictive value of the IFNGS in an additional 32 pts (total N = 62) and further explored the relationship between the IFNGS and TC and/or IC PD-L1 IHC expression patterns. **Methods:** Study CP1108 was a phase 1/2 trial evaluating D in pts with solid tumors; 191 UC pts received 10 mg/kg D with median follow up of 8.4 mo. 144 of these pts have available ORR and PD-L1 data and 62 pts have ORR, PD-L1 and IFNGS data. Pts with ≥25% TC or IC were scored as PD-L1 high (TC+ or IC+). Pts within the top tertile of IFNGS (*LAG3*, *PDL1*, *CXCL9*, and *IFNG* mRNAs) tumor expression were scored positive. Cox proportional hazards models were used adjusting for age, gender, ECOG, smoking status, line of therapy, and liver metastasis at baseline. ORR was evaluated using RECIST v1.1. **Results:** IFNGS+ pts had increased ORR (45 vs 16%) and improved PFS (adj HR 0.3; p = 0.005) and OS (adj HR 0.18; p = 0.016) over IFNGS- pts. IFNGS expression was significantly higher in pts who were PD-L1 high (TC+/IC+) compared with TC-/IC- (low/negative) pts (mean IFNGS expression 3.5 vs 1.1; p = 0.0155) and also in TC+ or IC+ vs TC-/IC- (mean IFNGS 2.2 vs 1.1; p = 0.000127). TC-/IC+ and TC+/IC- groups had a mean IFNGS expression of 2 and 2.2 respectively. ORR in all 1108 UC pts with available IHC and ORR data (N = 144) was 29% for TC+/- pts, 36% in TC-/IC+ pts, and 7% in the TC-/IC- pts. **Conclusions:** IFNGS predicted improved outcomes in a cohort of 62 2L+ UC pts treated with D. TC-/IC- PD-L1 pts had lowest levels of IFNGS expression. Observations that TC+ (and IC+) pts contribute to IFNGS enrichment and that TC+/IC-, and TC-/IC+ pts have increased response vs TC-/IC-pts provides rationale for TC+ inclusion (in addition to IC+) in the SP263 PD-L1 scoring algorithm for UC. IFNGS is an additional potential predictive biomarker in UC pts that warrants further investigation.

3038 Poster Session (Board #133), Mon, 8:00 AM-11:30 AM

Association of liver metastases (LM) with survival in NSCLC patients treated with durvalumab (D) in two independent clinical trials. *First Author: Luis G. Paz-Ares, Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain*

Background: Immunotherapies have improved survival in NSCLC but not all pts benefit. Besides baseline PDL1 expression, routinely measured clinical factors may predict clinical outcomes in immunotherapy trials. LM are associated with poor prognosis in melanoma and bladder cancer pts treated with anti-PD1/L1, respectively. We examined correlation between pretreatment LM and survival in D-treated NSCLC pts. **Methods:** CP1108/NCT01693562 and ATLANTIC/NCT02087423 were nonrandomized phase 1/2 and 2 trials, respectively, of D 10 mg/kg Q2W in advanced NSCLC. As of Oct 24/Jun 3 2016, 304/265 primarily pretreated pts were enrolled in CP1108/ATLANTIC Cohort 2. Cox proportional hazards analysis was conducted, first among LM+/− pts, then LM+/− and PDL1 high/low pts. Both models accounted for tumor stage, ECOG/WHO PS, histology, sex, age, smoking and PDL1 status. PDL1 high was defined as ≥25% tumor cells immunostained for PDL1 at any intensity. **Results:** LM absence was a positive independent predictor of OS and PFS in both trials. LM− and PDL1 high or low pts had improved OS and PFS vs PDL1 low/LM+; PDL1 high/LM+ pts had improved PFS vs PDL1 low/LM+. An independent tumor kinetic model indicated LM as a predictive covariate of rapid tumor growth in D-treated pts. **Conclusions:** LM are associated with shorter survival in D-treated NSCLC pts in 2 trials irrespective of PDL1 status. Clinical trial information: NCT02087423 and NCT01693562.

CP1108	N	OS adjusted HR; p	Median OS, mo (95% CI)	PFS adjusted HR; p	Median PFS, mo (95% CI)
LM+	86	1.91; 0.0002	5.6 (3.3, 9.5)	1.63; 0.0009	1.4 (1.4, 1.9)
LM−	218		15.7 (13.6, 24.1)		3.4 (2.7, 5.3)
PDL1 high/LM−	119	0.33; <0.0001	19.4 (15.6, 28)	0.35; <0.0001	4.8 (2.8, 5.7)
PDL1 low/LM−	85	0.55; 0.014	9.1 (7.5, 15.7)	0.51; 0.002	2.4 (1.4, 3.9)
PDL1 high/LM+	46	0.66; 0.14	6.1 (3.4, 19.2)	0.50; 0.007	1.7 (1.4, 2.9)
PDL1 low/LM+	35		4.3 (1.9, 6.5)		1.4 (1.2, 1.5)
ATLANTIC					
LM+	47	2.2; <0.0001	5.1 (3.5, 8.3)	1.92; 0.0005	1.8 (1.7, 1.9)
LM−	216		10.4 (9.3, 13.0)		3.1 (1.9, 3.6)
PDL1 high/LM−	120	0.27; <0.0001	13.2 (9.3, 17.4)	0.23; <0.0001	3.6 (2.5, 3.9)
PDL1 low/LM−	77	0.46; 0.011	10.2 (7.2, 12.1)	0.36; 0.0008	1.9 (1.9, 3.5)
PDL1 high/LM+	29	0.61; 0.17	5.3 (3.5, 11.3)	0.37; 0.004	1.9 (1.7, 2.4)
PDL1 low/LM+	16		4.3 (2.0, 8.3)		1.8 (1.5, 1.9)

All HRs vs PDL1 low/LM+ subgroup

3039 Poster Session (Board #134), Mon, 8:00 AM-11:30 AM

Mutational burden of tumors with primary site unknown. *First Author: Laurie M. Gay, Foudation Medicine, Inc., Cambridge, MA*

Background: Higher levels of tumor mutational burden (TMB) can predict sensitivity to immunotherapies (IO), which are FDA approved to treat NSCLC, melanoma, and urothelial carcinoma (Ca). TMB may be a biomarker for sensitivity to IO, irrespective of tumor type. TMB has not been explored widely for tumors of unknown primary site, but may reveal additional treatment options. **Methods:** Comprehensive genomic profiling of DNA from FFPE tissue samples was performed using hybrid-capture, next-generation sequencing. TMB was calculated by counting all coding short variant alterations (base substitutions and indels), including synonymous alterations, and subtracting from this functionally oncogenic or germline alterations (per ExAC, dbSNPT, or internal algorithmic analysis). To calculate the TMB per Mb, the total number of relevant mutations is divided by the coding region of the bait set (0.8 Mb, 1.1 Mb, or 1.2 Mb). High, intermediate, and low TMB were defined as ≥20 mut/Mb, ≥6 and <20 mut/Mb, or <6 mut/Mb, respectively. Tumor types with >100 samples were analyzed. **Results:** From a database of 102,878 samples sequenced during routine clinical care, 6116 samples for which the primary tumor site was unclear at sequencing were identified. Table shows TMB metrics (mut/Mb) and median patient age for these cohorts. **Conclusions:** Significant numbers of patients with each tumor type have high TMB that may indicate benefit from IO, excepting GIST. As expected, urothelial tumors have higher than average TMB and more patients have high TMB. SCC tumors are commonly TMB high (23%), as are tumors difficult to define histologically (15%). For ACUP or CUP, the most common tumors, 8-11% have high TMB. Analysis of responses to treatment with IO are ongoing.

Unknown Primary Tumor Type	Total Cases	TMB-High (%)	Average TMB	1st Quartile TMB	Median TMB	3rd Quartile TMB	90th Percentile TMB	Max TMB	Median Age
Adenocarcinoma (ACUP)	2530	8	7.8	1.8	3.8	8.1	17.1	278.4	63
Ca NOS (CUP)	1366	11	11.5	2.7	5.4	10.8	21.6	445	62
Squamous cell Ca (SCC)	618	23	18.2	3.6	7.2	16.2	51.4	344.1	64
Neuroendocrine Ca	720	6	6.2	1.3	2.7	6.3	12.6	109	60
Malignant Neoplasm NOS	454	15	12.5	1.8	3.8	10.1	29.1	421.1	59
Urothelial Ca	180	13	11.3	3.6	6.3	13.6	24.3	108.1	67
GIST	131	0	2.6	0.9	2.5	3.6	5	10.8	59
Small Cell Ca	117	9	8.8	2.7	6.3	11.7	18.9	56.8	63

3040 Poster Session (Board #135), Mon, 8:00 AM-11:30 AM

Germ-line biomarkers disrupting microRNA regulatory pathways to predict toxicity and response to anti-PD-1 and anti-PD-L1 therapies. *First Author: Joanne B. Weidhaas, University of California, Los Angeles, Los Angeles, CA*

Background: Identifying responders to developing immune therapies is of high priority, yet identifying patients who will suffer from toxicity, which represents a unique spectrum of side effects, termed immune-related adverse events (irAEs), is critical. The complex host-specific response to immune therapies led us to hypothesize that germ-line mutations, present in both the tumor and in the host's immune system, may be a source of biomarkers. As there is compelling evidence that recently discovered germ-line mutations disrupting microRNA (miRNA) networks act as biomarkers of treatment response and baseline immune status, we evaluated such mutations in patients treated with these therapies. **Methods:** Patients treated with anti-PD1 or anti-PDL1 therapy alone and clinically documented response and toxicity were tested with a panel of over 150 vetted germ-line miRNA based biomarkers. Of 85 patients evaluated for response, 75 had melanoma, and 10 had NSCLC. For analysis of toxicity, an additional 4 patients with other cancer types were included. Subjects were classified as responders (Complete, Partial) versus non-responders (Progressive, Stable), or as experiencing low irAEs (grade 0 and 1) versus high irAEs (grade 2 and above). We used Chi-squared analysis for base evaluation and then compared three classification techniques including classification trees, random forests and Bayesian probit regression with non-local priors. We estimated classification performance via leave-one-out cross validation. **Results:** By Chi-Squared analysis we found over a dozen biomarkers associated with response, and a dozen biomarkers associated with toxicity. These included germ-line mutations in 3' untranslated regions as well as in miRNA promoter regions. We found that both classification trees and Bayesian probit compared reasonably well with random forests. We found a response signature with a specificity of 89% by Random Forests, and a toxicity signature with a specificity of 76% by Random Forests. **Conclusions:** We have shown that a new class of germ-line mutations disrupting miRNA regulatory networks can act as biomarkers of response and toxicity to anti-PD1 and anti-PDL1 therapy.

3041 Poster Session (Board #136), Mon, 8:00 AM-11:30 AM

Gene expression analysis of tumor biopsies from a trial of durvalumab to identify subsets of NSCLC with shared immune pathways. *First Author: Katie Streicher, MedImmune, Translational Medicine (currently with EMD Serono), Gaithersburg, MD*

Background: We previously reported that NSCLC pts with high pretreatment tumoral IFNG mRNA signature (sig) expression have improved outcomes (ORR, PFS, OS) to the anti-PD-L1 therapy durvalumab (D). To explore the relationship of other immunotherapy targets with the IFNG sig, we evaluated expression of *CD137, PD1, PDL1, CTLA4, GITR, OX40, TLR7, TLR8, CD73, TIM3, NKG2A, IDO1, CD40, LAG3, A2AR, CXCR4, iNOS, ARG1, and STAT3* in D-treated NSCLC. **Methods:** CP1108/NCT01693562 was a nonrandomized phase 1/2 trial evaluating D (10 mg/kg Q2W) in advanced NSCLC. As of 24OCT16, 304 primarily previously-treated pts were enrolled. RNA sequencing was conducted on available tumor specimens from 98 pts. ORR was evaluated using RECIST v1.1. 19 genes were z-scored, scaled and clustered across pt tumors. Each gene was coded binary using 0 as a cut point. The proportion of tumors with concordant or discordant over-expression between a gene and the IFNG sig was calculated. **Results:** In 43% of evaluable NSCLC pts, mRNAs for *PD-1, IDO1, PD-L1, CD40, CTLA4, LAG3, TIM3, TLR8, NKG2A*, and *CD137* were co-expressed with IFNG sig (Spearman's rho $>=$ 0.7). In 34% of evaluable pts, *TLR7, OX40, GITR, A2AR*, and *CXCR4* mRNAs had moderate concordance with IFNG sig ($0.5 <$ rho < 0.7) and in 23% of evaluable pts *iNOS, CD73, ARG1*, and *STAT3* had low concordance (rho < 0.5). Within the cluster of pts including high IFNG sig, a small subset expressed high *iNOS* and *CD73*; however, pts with high *STAT3* or *ARG1* formed a distinct cluster within the low IFNG sig subset. The subset with high IFNG sig had an ORR of 24% compared to only 10% in all other subsets combined. **Conclusions:** Our findings enrich understanding of the immune microenvironment of NSCLC by identifying three broad categories of tumors: tumors with pre-existing immunity that have high IFNg sig and select other IO pathways with enhanced responses to D; tumors with moderate expression of IO genes in which the local microenvironment is crucial; finally a distinct "cold" subset of tumors with high expression of *STAT3* or *ARG1* and characterized by low or no expression of IFNG sig and other IO genes. These results may aid in identifying the right pts for anti-PD-L1 and in prioritizing immunotherapy combinations.

3042 Poster Session (Board #137), Mon, 8:00 AM-11:30 AM

CD133-redirected chimeric antigen receptor engineered autologous T-cell treatment in patients with advanced and metastatic malignancies. *First Author: Yao Wang, Department of Molecule and Immunology, Bio-therapeutic Ward, Chinese PLA General Hospital, Beijing, China*

Background: Expressed by cancer stem cells of various epithelial cell origins, CD133 is an attractive therapeutic target for cancers. Autologous chimeric antigen receptor-modified T cells directed CD133 (CART-133) were firstly tested in this clinical trial. We aimed to determine the safety dosage, toxicity and biological activity of CART-133 in epithelium-derived solid tumors. **Methods:** The initially enrolled 8 patients with sorafenib-refractory hepatocellular carcinoma (HCC), treated by CART-133 monotherapy, were assigned into 3 dose cohorts (1, $0.5\text{-}1.5\times10^5$/kg; 2, $5\text{-}10\times10^5$/kg; 3, $1\text{-}2\times10^6$/kg). For the additional 16 patients (6 HCCs, 7 pancreatic carcinomas, 2 colorectal carcinomas, and 1 cholangiocarcinoma), all non-HCCs were conditioned by regimen (Nab-pacitaxel/cyclophosphamide or anti-PD1 antibody) before cell infusions. **Results:** For the initial 8 HCCs, 1 from cohort 2 occurred hemoglobin/platelet decline and direct hyperbilirubinemia (Grade 3), 4 from cohort 2/3 reported delayed low fever, nausea accompanied with elevation of CRP and serum cytokines. The 4-6 week persistence of relatively higher CAR copy numbers and its reverse relationship with the count of $CD133^+$ cells harboring pro-metastatic epithelial progenitor cells in peripheral blood led to the determination of acceptable cell infusion dose from 0.5 to 2×10^6/kg and reinfusion cycle in 24 patients. Similar toxicities ($\leq$ Grade 3) were observed in 15 cases. The cholangiocarcinoma patient who uniquely received 1 cycle of CART-133 infusion after anti-PD1, developed Grade 3 skin/mucosal vasculature damage, blood three-lineage decline and cytokine release syndrome, whereas, obtained a 4.5 month-lasting partial remission. Although no marked reduction of tumor volume was observed in most patients, 21 out of 23 patients had an 8-22 week progression-free survival, 2 patients without bulky tumor burden attained 8/10-month ongoing stable disease by the cut-off data (Jan 1, 2017). **Conclusions:** This trial showed the feasibility, controllable toxicities and effective biological activity of CART-133 transfer for the treatment of late-stage tumor patients. Clinical trial information: NCT02541370.

3044 Poster Session (Board #139), Mon, 8:00 AM-11:30 AM

Augmentation of adoptive T-cell therapy for Merkel cell carcinoma with avelumab. *First Author: Kelly Garneski Paulson, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: 80% of Merkel cell carcinomas (MCCs) are caused by Merkel cell polyomavirus (MCPyV) oncoproteins. Although absent in most cases, abundant MCPyV-specific CD8+ TIL are associated with good MCC outcomes, implying tumor susceptibility to immune attack. Indeed, anti-PD-1 axis blockade has a response rate of 32-56%. However, half of patients do not respond, suggesting a lack of adequate MCPyV-specific T cells and/or tumor evasion from MCC-related reduced HLA expression. We hypothesized the combination of adoptive transfer of MCPyV-specific T cells with HLA upregulation and PD1 axis blockade would be more effective than either approach alone. **Methods:** 8 adult patients with MCPyV-associated metastatic MCC without pre-existing immune deficiencies were enrolled. The safety and efficacy of *ex vivo* expanded MCPyV-specific T-cells plus HLA-upregulation (radiation or interferon) with (triple therapy) and without (double therapy) avelumab (mAb against PD-L1, dose 10 mg/kg IV q2weeks) were compared in 2 related phase I/II studies. **Results:** All 4 patients who received triple therapy (100%) are alive (median follow-up 10 months), and experienced objective responses (RECIST 1.1) with 3 of 4 sustained complete responses (CRs) at last follow-up (longest 13 mo). This compared favorably to outcomes among the 4 patients who received double therapy (3 with progression and 1 CR (25%) for 14 months before progression) and published data for avelumab monotherapy – response rate 32% and CR rate 9% in patients who had failed chemotherapy (Kaufman et al, *Lancet Oncol*, 2016). Grade 3-4 T cell-related adverse events were similar and anticipated in both groups, including transient lymphopenia (n = 7) and modest cytokine release syndrome lasting $<$ 24 hours, manageable on the general ward (n = 4). No grade 3-4 toxicities were attributed to avelumab. Among patients receiving triple therapy, transferred T cells persisted, and peak frequencies correlated with rate of tumor regression. **Conclusions:** The combination of MCPyV-specific T cells, avelumab and HLA upregulation is safe and correlative studies suggest avelumab enhances the T cell responses to MCC. This strategy has potential for MCC treatment, and can be readily applied to other solid tumors. Clinical trial information: NCT01758458 and NCT02584829.

3045 Poster Session (Board #140), Mon, 8:00 AM-11:30 AM

Efficacy of single administration of tumor-infiltrating lymphocytes (TIL) in heavily pretreated patients with metastatic melanoma following checkpoint therapy. *First Author: Amod Sarnaik, Moffitt Cancer Center, Tampa, FL*

Background: Adoptive cell therapy with TIL involves collection of autologous lymphocytes from the tumor via surgical resection, *ex vivo* expansion of TIL, lymphodepletion of the patient prior to infusion of TIL using Fludarabine and Cyclophosphamide, followed by infusion of TIL. Up to 6 doses of IL-2 (600,000 IU/kg) is administered to support multiplication of TIL and engraftment. Here, we present the preliminary results from an ongoing, multi-site Phase 2 study of TIL for advanced metastatic melanoma. **Methods:** Patients with advanced metastatic melanoma who have failed at least one prior systemic therapy were enrolled. Primary objective of the study was to characterize safety profile of LN-144. At baseline, patients had a median age of 56 (41-72) years; 44% were ≥ 60 years old. Median sum of tumor diameters for the target lesions was 10.4 cm, and median of 3 prior therapies. All enlisted patients had prior anti-PD1 as well as anti-CTLA4 and 67% had received ≥ 3 prior therapies. Responses were assessed by RECIST 1.1. TIL products were centrally manufactured. No complications arose from shipment of tumors or TIL. **Results:** Results are presented through 31 Jan 2017 for the first 9 infused patients evaluable by two assessments. Eight of 9 patients received all 6 doses of IL-2 per protocol. The most common (≥3 patients) non-hematologic grade 3-4 TEAE was hypophosphatemia. No neurotoxicity of grade ≥ 3 was reported. There were no deaths or discontinuations due to SAEs related to study treatment. ORR was 33% (CR = 11%, PR = 22%, SD = 22%, PD = 33%, NE = 11%). Mean time to best response was 3.0 months and median duration of follow up was 3.6 months (1.1+, 12.1). Responses were observed in patients with tumors carrying wild type or BRAF mutations. All patients demonstrated persistence of TIL on day 14 post-infusion. **Conclusions:** Cell therapy with TIL is an effective treatment with acceptable safety profile for advanced metastatic melanoma patients who are refractory to anti-PD1. TIL products can be centrally manufactured for broad clinical application. This study will be expanded to enroll patients with a shorter manufacturing process as well as offering retreatment for study patients. Clinical trial information: NCT02360579.

3046 Poster Session (Board #141), Mon, 8:00 AM-11:30 AM

Feasible and efficient identification of neoantigens for personalized cancer immunotherapy in advanced refractory epithelial cancer patients. *First Author: Fangjun Chen, The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University and Clinical Cancer Institute of Nanjing University, Nanjing, China*

Background: Recent genomic and bioinformatic technological advances have made it possible to dissect the immune response to personalized neoantigens encoded by tumor-specific mutations.However, rapid and efficient identification of neoantigens is still fraught with difficulty, and a systematic evaluation of personalized neoantigens based immunotherapy in advanced refractory epithelial tumors is lacking. **Methods:** Tumor and ctDNA samples from 16 advanced epithelial cancer patients were underwent mutational profiling by cancer-associated genes panel. Neoantigens identification were performed by two strategies: As classic mode, somatic mutations were subjected to in silico analysis to predict potential high-affinity epitopes and mutated peptides were denovo synthesized; Hotspot mutations were matched to our customized driver mutation-derived neoantigens peptide library. Candidate neoepitopes were identified. Approximately 10^8 neoantigen loaded DC vaccine and 10^{10} bulk T cells composed of 10^9 neoantigen reactive CD8+T cells were generated for personlized immunotherapy. **Results:** Among the sequenced patients, 3 of 4 patients who utilized the classic mode and 6 of 12 patients who performed customized neoantigens library have successfully identified 1~2 neoantigens recognized by autologous T cells, respectively. Subsequently, a total number of 6 patients received immunotherapy targeting personalized neoantigen. To date, one patient with metastatic thymoma is achieving a complete and durable response beyond 9 months. In addition, immune related partial response was observed in another advanced pancreatic cancer patient. The remaining 4 patients achieved prolonged stabilization of disease with median PFS of 8.6 months. **Conclusions:** Our costomized neoantigens library can provide a novel approach for neoantigens screening in advanced epithelial cancer patients. Besides, targeted sequencing is sufficient for somatic variant and neoantigen identification. The combination of two strategies can accelerate the neoantigen-based translational immunotherapy research into the paradigm of precision medicine.

3047 Poster Session (Board #142), Mon, 8:00 AM-11:30 AM

Anti-PD-1 monoclonal antibody combined CD3-retronectin activated T cell in heavy-treated renal cell cancer. *First Author: Lingdi Zhao, Cancer Hospital Affiliated to Zhengzhou University and Henan Cancer Hospital, Zhengzhou City, China*

Background: Metastatic renal cell carcinoma (MRCC) has a poor prognosis after failure of multitargeted tyrosine kinase inhibitors. New immunomodulators, such as anti-programmed death (PD)-1 antibody drugs, have made progress in the treatment of MRCC, but their objective response rate is only about 25%. Therefore, it is important to enhance the response rate of anti-PD-1 therapy. **Methods:** Patients with MRCC were eligible if they were failed to at least one kinase inhibitors, ECOG PS 0-2. Patients received nivolumab (2mg/kg, q2w) or keytruda (2mg/kg, q3w), followed by CD3-retronectin activated T cell, and the total number of CD3-retronectin activated T cell each time was about 5×10^9/L. The primary objective was to determine the objective response rate, secondary objectives included time to symptom relief, time to efficacy, safety. **Results:** 8 pts were enrolled (median age 58 [31-79], male 6). Pts had received a median of 2 (1-4) prior regimens. To date there is 2 patients that the efficacy can not be evaluated. The other 6 pts got remission (3 complete remission and 3 partial remission), the median time to efficacy was 10 weeks (6-12 weeks) and the time to symptom relief was 4 weeks (3-6 weeks). There was no grade 3/4 adverse effects. family:'';font-size:12.0000pt;mso-font-kerning:1.0000pt;" $> 10^9$/L. The primary objective was to determine the objective response rate, secondary objectives included time to symptom relief, time to efficacy, safety. **Conclusions:** CD3-retronectin activated T cell might improve the efficacy of anti-PD-1 therapy without increasing the side effects. This combination therapy has many implications in the age of immunotherapy, and should be explored across cancer types. mily:'';font-size:12.0000pt;mso-font-kerning:1.0000pt;" $> 10^9$/L. The primary objective was to determine the objective response rate, secondary objectives included time to symptom relief, time to efficacy, safety.

3048 Poster Session (Board #143), Mon, 8:00 AM-11:30 AM

High-fidelity genome editing using NextGEN CRISPR (Clo51-dCas9) system for the production of allogeneic CAR-T cells. *First Author: Xinxin Wang, Poseida Therapeutics, Inc., San Diego, CA*

Background: Autologous chimeric antigen receptor (CAR) T therapies are highly efficient at targeting hematological malignancies, but the clinical applications have been limited by individualized manufacturing. Furthermore, there has been little success in treating solid tumors due to immunosuppressive microenvironments. Currently, genome editing technologies are being used to address both issues. However, the CRISPR/Cas9 system has significant safety concerns due to high incidence of off-target mutations and TALEN only works sufficiently in activated cells. A hybrid gene editing system, NextGEN (NG) Clo51-dCas9, can be targeted using gRNA, like CRISPR/Cas9, but exhibits little-to-no off-target cutting like TALEN, thereby overcoming limitations in the genome editing of resting T cells. **Methods:** We successfully developed a platform for production of allogeneic CAR-T cells with reduced receptivity to inhibitory signaling. Here, T cells were modified by piggyBac-mediated BCMA CAR gene delivery, along with NG reagents to knock out critical genes mediating rejection responses. Gene edited CAR-T cells were assessed by mixed lymphocyte reaction (MLR) and tumor killing. In addition, NG was used to knockout multiple checkpoint inhibitory receptors known to mediate key suppressive signals in T cells. **Results:** NG demonstrated high gene disruption efficiencies for all targets (84% for TCRα, 91% for TCRβ, 64% for β-2 microglobulin, and 40-60% for the surface inhibitory receptors PD-1, CTLA-4, Tim3, Lag-3, and TGFBRII). In contrast to CRISPR/Cas9, no off-target mutations were detected for multiple targets by deep-sequencing. In MLRs, disruption of TCR eliminated the GvHD response, while disruption of MHCI completely abrogated graft-rejection. Lastly, TCR/MHCI double knockout did not affect the ability to kill BCMA+ multiple myeloma cells *in vitro*. **Conclusions:** NG overcomes significant limitations of the CRISPR/Cas9 and TALEN systems with highly efficient genome editing in resting T cells. NG has great potential and flexibility for the manufacture of allogeneic CAR-T cells and for enhancing efficacy against solid tumors.

3049 Poster Session (Board #144), Mon, 8:00 AM-11:30 AM

A phase I study of anti-GPC3 chimeric antigen receptor modified T cells (GPC3 CAR-T) in Chinese patients with refractory or relapsed GPC3+ hepatocellular carcinoma (r/r GPC3+ HCC). *First Author: Bo Zhai, Department of Interventional Oncology, Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China*

Background: HCC was commonly diagnosed and identified as leading causes of cancer death in China. Using a 10% cutoff score, GPC3 was detected in 63.6% of HCCs. Safety and preliminary efficacy of a GPC3 CAR-T was evaluated in 13 Chinese patients (pts) with r/r GPC3+ HCC in a Phase I trial. **Methods:** Pts between 18 and 70 yrs old with histopathological confirmed r/r GPC3+ HCC, Child-Pugh score≤B7, ECOG≤1, lymphocyte ≥□0.7 x10^9, post-transduction positive T cells □≥30%, amplification by α CD3/CD28 ≥5□, and without ascites and HIV infection were enrolled. Eligible pts undergo leukapheresis or whole blood colletion, which further developed into GPC3 CAR-T via lentiviral transduction. Standard release tests were conducted before administering GPC3 CAR-T in pts. Adverse events were graded per NCI CTCAE v.4.03. Efficacy was evaluated per modified RECIST (mRECIST). **Results:** All 13 pts, who received at least one infusion of GPC3 CAR-T, tolerated the treatment well. No dose-limiting toxicity (DLT) was identified, and only one SAE of grade 3 fever was reported. Preliminary analysis compared the clinical outcomes in pts who received GPC3 CAR-T without lymphodepleting conditioning (LDC) (Group A) vs. with LDC (Group B) at baseline. In Group A (N = 5), all pts developed progressive disease (PD) shortly after received a total infusion of GPC3 CAR-T ranging from 0.92x10^7 to 8.72 x10^7 cells/kg. In Group B (N = 8), following the LDC with fludarabine and cyclophosphamide, pts received a total infusion of GPC3 CAR-T ranging from 0.013x10^7 to 14.68 x10^7 cells/kg. Except two non-evaluable pts, the best response for the rest 6 pts are 1 PR, 3 SD, 2 PD. As of Feb 1, 2017, the PR pt remains alive for 385 days; 2 SD pts remain alive for 384 and 562 days, respectively; and one SD deceased at 108 days. Also worth to mention, one pt in Group A decided to remain on the study after PD, further received a total of 6.23 x10^7cells/kg infusions following a LDC given around Day 150, remains stable for 571 days as of Feb 1, 2017. **Conclusions:** Phase I trial shows GPC3 CAR-T is feasible and safe for Chinese pts with r/r GPC3+ HCC, and holds promising antitumor potential when LDC is applied along with GPC3 CAR-T. Clinical trial information: NCT02395250.

3050 Poster Session (Board #145), Mon, 8:00 AM-11:30 AM

Chimeric antigen receptor (CAR) T cells genetically engineered to deliver IL-12 to the tumor microenvironment in ovarian cancer. *First Author: Oladapo O. Yeku, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chimeric antigen receptor (CAR) T cell therapy for solid tumor malignancies has not shown the same degree of clinical efficacy observed in hematologic malignancies. The presence of an immunosuppressive cytokine and cellular microenvironment has been hypothesized as one reason for the failure of adoptive immunotherapy for solid tumors. In ovarian cancer, the presence of tumor associated macrophages (TAMs) and immunosuppressive cytokines in the ascitic microenvironment have been reported. IL-12 is a proinflammatory cytokine produced by macrophages, dendritic cells (DC) and NK cells, and has been shown to increase proliferation of T cells and enhance antigen presentation by macrophages. We hypothesized that CAR T cells genetically modified to constitutively secrete IL-12 would overcome a hostile tumor microenvironment in a peritoneal carcinomatosis model of ovarian cancer. **Methods:** CAR T cells were generated from retroviral transduction of second generation and IL-12 modified CAR's directed to either an irrelevant CD-19 antigen or $Muc16^{ecto}$. **Results:** Here we report increased production of IL-12, improved proliferation and cytotoxic activity of 4H1128-IL12 CAR T cells. We show increased levels of inflammatory cytokines at 24 and 48hrs after treatment of tumor-bearing mice, leading to increased survival at advanced stages of disease. Mice treated with 4H1128-IL12 CAR T cells had decreased levels of $F4/80^+$ $CD11b^+$TAM's. Genetic analysis of recovered TAM's from the ascites of treated animals showed skewing towards an M1-phenotype via upregulation of cytokines, chemokines, MHC-II and down-regulation of Arg1. Recovered 4H1128-IL12 CAR T cells showed upregulation of FAS-L and recovered TAMs showed increased expression of FAS suggesting FAS/FAS-L engagement was responsible for decreased TAMs. Blocking the FAS/FAS-L pathway led to recovery of TAM populations in 4H1128-IL12 treated mice. Finally, clodronate-mediated depletion of TAM's further enhanced survival in mice treated with 4H1128-IL12 CAR T cells. **Conclusions:** These results demonstrate the mechanisms of efficacy of localized delivery of IL-12 to the tumor microenvironment by 4H1128-IL12 CAR T cells.

3051 Poster Session (Board #146), Mon, 8:00 AM-11:30 AM

Peritoneum metastasis (PM) as a prognostic factor in metastatic gastric cancer (MGC) treated with anti-PD-1/PD-L1 monotherapy. *First Author: Yukiya Narita, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*

Background: Anti-PD-1 monotherapy has proven effective for the patients (pts) with MGC. However, the identification of biomarkers for predicting clinical outcomes remain as critical needs. We aimed to identify baseline characteristics associated with time to treatment failure (TTF) or overall survival (OS) for anti-PD-1/PD-L1 monotherapy as second- or later-line therapy in MGC. **Methods:** Routine blood count parameters and clinical characteristics at baseline were retrospectively investigated in 31 pts with MGC in Aichi Cancer Center Hospital. Endpoints were TTF and OS following anti-PD-1/PD-L1 monotherapy. Kaplan-Meiyer and Cox regression analysis were applied for survival analyses. **Results:** Patient characteristics were as follows: median age (range), 68 (47–83); ECOG performance status (PS) 0/1, 21/10; PM +ve/-ve, 12/19; No. of metastatic sites 1–2/≥3, 18/13; No. of prior chemotherapy regimens 1–2/≥3, 11/20; and absolute eosinophil count (AEC) <150/≥150 /μl, 14/17. Objective response rate and disease control rate (RECIST ver. 1.1) were 26% vs. 0% (odds ratio [OR], 3.76; $P = 0.12$) and 79% vs. 50% (OR, 3.58; $P = 0.12$) in the PM -ve group (Cohort A) and the PM +ve group (Cohort B), respectively. On univariate analysis, the pts with poor PS, PM +ve, and high AEC were significantly poor TTF; and poor PS and PM +ve were significantly identified as prognostic factors of poor OS. On multivariate analysis, only PM +ve was independent negative impact not only for TTF but also for OS. Median TTF and OS were 5.4 vs. 1.3 months (M) (adjusted hazard ratio [HR], 4.29; 95%CI, 1.60–11.5; $P < 0.01$) and 28.2 vs. 7.5 M (adjusted HR, 3.68; 95%CI, 1.25–10.8; $P = 0.02$) in Cohort A and Cohort B. Six-months TTF probabilities of 42% vs. 0% ($P = 0.03$) and one-year OS probabilities of 58% vs. 8% ($P < 0.01$) were observed in Cohort A compared to in Cohort B. **Conclusions:** PM -ve in the pts treated with anti-PD-1/PD-L1 monotherapy was associated with better efficacy. In the pts with PM -ve, anti-PD-1/PD-L1 monotherapy could be adapted in first-line therapy.

		TTF	OS
		Multivariate HR (*P* value)	
ECOG PS	0 vs. 1	1.58 (0.42)	1.95 (0.21)
Peritoneum metastasis	No vs. Yes	4.29 (< 0.01)	3.68 (0.02)
Absolute eosinophil count	<150 vs. ≥150 /μL	2.28 (0.12)	

3052 Poster Session (Board #147), Mon, 8:00 AM-11:30 AM

Durvalumab and tremelimumab in metastatic breast cancer (MBC): Immunotherapy and immunopharmacogenomic dynamics. *First Author: Cesar Augusto Santa-Maria, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: PD-1/PD-L1 inhibitors produce modest responses in MBC; adding CTLA-4 inhibitors can augment anti-tumor activity in other cancers. Immunopharmacogenomics characterize immune-cancer cell interactions and may predict response. **Methods:** A single arm study was designed to determine the efficacy of durvalumab (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor), and immunopharmacogenomics in pts with metastatic ER+ or TNBC. The primary clinical endpoint was to assess ORR using a Simon 2-stage design (28 pts needed for type 1 error rate of 4%, 80% power). 18 pts were enrolled in the first stage; ≥4 responses were needed to proceed with the second stage. Pts were treated with durvalumab 1500mg IV and tremelimumab 75mg IV monthly for 4 doses, then durvalumab 750mg every 2 weeks to complete 1 year of therapy (option to renew for an additional year); biopsies at baseline and 2 months were collected. T-cell receptor (TCR) sequencing using mRNA isolates was conducted at baseline and 2 months, whole exome sequencing and immune-gene expression profiling were conducted at baseline. **Results:** From 01-09/2016, 18 evaluable pts were accrued (11 ER+; 7 TNBC). Responses are shown in the table below; the ORR did not meet criteria to proceed to the second stage. Notably, one pt with TNBC with PD had pseudoprogression, thus 5/7 (71%) pts with TNBC had clinical benefit. Median PFS was 3.8 months (95%CI 2.2-11.2) for the entire cohort (TNBC not reached), and median OS has not been reached. No grade 4 AEs were observed; grade 3 immune-related AEs included hepatitis (n = 3), nephritis (n = 1), and myocarditis (n = 1). Proportions of abundant TCR-β clonotypes (≥ 0.5% frequency) were increased in 2-month samples compared to baseline in TNBC compared to ER+, p = 0.004, and associated with responses. Remaining correlative analysis is ongoing and will be presented at ASCO. **Conclusions:** Response rates to PDL-1 and CTLA-4 inhibition were low in unselected MBC, however, high rates of clinical benefit were observed in TNBC. Immunopharmacogenomic may help identify phenotypes most likely to respond. Future studies in TNBC are warranted to confirm findings. Clinical trial information: NCT02536794.

	All pts (n = 18)	TNBC (n = 7)	ER+ (n = 11)
PR	3	3	0
SD ≥6 months	1	1	0
PD	14	3*	11
ORR	17%	43%	0%

3053 Poster Session (Board #148), Mon, 8:00 AM-11:30 AM

Paracrine wnt-β-catenin signaling inhibition as a strategy to enhance the efficacy of anti-PD-1 antibody (Ab) therapy in a transgenic model of melanoma. *First Author: Nicholas C. DeVito, Tufts Medcl Ctr, Medford, MA*

Background: Activation of the Wnt-β-catenin signaling pathway is associated with poor T cell infiltration of tumors. We have previously demonstrated that paracrine Wnt5a-β-catenin signaling is a critical trigger of dendritic cell (DC) tolerization and regulatory T cell (Treg) differentiation in the melanoma microenvironment. In a transgenic $BRAF^{V600E}PTEN^{-/-}$ model, the genetic silencing of melanoma-derived Wnt5a potently enhances infiltrating $CD8^{+}$T cell effector function and promotes responses to anti-PD-1 Ab therapy. Ipafricept (IPA) is a recombinant Wnt decoy receptor and Vantictumab (VAN) is a Fzd receptor monoclonal Ab. Both molecules inhibit Wnt-β-catenin signaling and have been well-tolerated in ongoing phase I/Ib clinical trials. We explored the ability of IPA/VAN to reverse tumor-mediated immune tolerance and enhance the efficacy of anti-PD-1 Ab immunotherapy in a pre-clinical model that closely recapitulates human melanoma. **Methods:** Both IPA and VAN were utilized to investigate Wnt-β-catenin inhibition as a strategy for suppressing melanoma-induced DC indoleamine 2,3-dioxygenase (IDO) expression and Treg differentiation in vitro. These agents were further tested for their ability to enhance anti-tumor T cell responses and to augment the efficacy of anti-PD-1 Ab therapy in syngeneic and autochthonous models of $BRAF^{V600E}PTEN^{-/-}$ melanoma. **Results:** IPA and VAN effectively inhibit Wnt5a and melanoma-induced DC IDO expression and Treg differentiation in vitro. Further studies demonstrate that IPA and VAN significantly augment anti-PD-1 Ab-mediated suppression of primary and metastatic tumor progression in both syngeneic and autochthonous $BRAF^{V600E}PTEN^{-/-}$ melanoma models. These anti-tumor effects correlated with suppressed IDO enzymatic activity, enhanced tumor-infiltrating $CD8^{+}$T cell/Treg ratios, and increased activation of TRP2 antigen-specific effector T cells. **Conclusions:** The pharmacological inhibition of paracrine Wnt-β-catenin signaling with IPA and VAN augment the anti-tumor efficacy of anti-PD-1 Ab therapy and represent a promising strategy for further phase I testing in melanoma and other solid tumors.

3054 Poster Session (Board #149), Mon, 8:00 AM-11:30 AM

Phase 2 study of pembrolizumab in combination with azacitidine in subjects with metastatic colorectal cancer. *First Author: James J. Lee, Division of Hematology-Oncology, Department of Medicine, University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA*

Background: Microsatellite stable (MSS) metastatic colorectal cancer (mCRC) has relatively poor tumoral infiltration of $CD8^{+}$ T cells and is resistant to pembrolizumab (Pembro) when compared to MSI-H mCRC. DNA hypomethylating agent induces epigenetic expression of multiple genes including cancer-testis antigens in CRC, which are recognized by cytotoxic $CD8^{+}$ T cells *in vitro* and *in vivo*. This trial tested whether concurrent treatment with azacitidine (Aza) could enhance the anti-tumor activity of Pembro. **Methods:** This is a phase 2 trial to evaluate anti-tumor activity and safety of Pembro plus Aza in patients (pts) with previously treated mCRC without any further standard chemotherapy option. Pts received Pembro 200 mg IV on day 1 of each cycle Q3W and Aza 100 mg daily SQ injection on days 1-5 of each cycle Q3W. Primary endpoint was response rate (ORR) using RECIST v1.1. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Tumor tissues were collected for correlative studies. **Results:** Thirty-one pts were enrolled [median age, 61 years (range, 30-79); 17 M/14 F; ECOG PS 0/1 (58%/42%); 30 pts with MSS mCRC]. Pts received at least 2 lines of prior systemic chemotherapy for mCRC (median, 3; range, 1-5). Thirty pts received at least one dose of study therapy (median, 3 cycles; range, 1-8). Ten pts could not complete the first 3 cycles due to rapid symptomatic tumor progression. One pt with MSS mCRC achieved PR and 3 pts had SD as best response. The ORR was 3% (1/30; 95% CI, 0.1-17%). Seven pts with PD at the end of cycle 3 continued on study therapy, and 2 pts had stabilization of tumor progression. Median PFS was 2.1 months (95% CI, 1.8-2.8), and median OS was 6.2 months (95% CI, 3.5-8.7). While treatment-related adverse events (TRAEs) were reported in 63% of pts, most of the TRAEs were Gr 1/2 (96%). Frequent TRAEs possibly related to Aza were anemia (n = 5), constipation (n = 5), and leukopenia (n = 4); and possibly related to both Aza and Pembro were nausea (n = 5) and fatigue (n = 5). Gr 3 TRAEs included anemia (n = 1), ALT elevation (n = 1), and alkaline phosphatase elevation (n = 1). **Conclusions:** Pembro plus Aza is feasible with a tolerable safety profile but appears to have minimal anti-tumor effect for MSS mCRC. Clinical trial information: NCT02260440.

3055 Poster Session (Board #150), Mon, 8:00 AM-11:30 AM

Predictive and prognostic value of systemic inflammatory response biomarkers in patients receiving nivolumab for metastatic non-small cell lung cancer (NSCLC). *First Author: Claire Gervais, Department of Medical Oncology, Cochin Hospital, Paris Descartes University, AP-HP, CARPEM, Immunomodulatory Therapies Multidisciplinary Study group (CERTIM), Paris, France*

Background: Nivolumab is the first checkpoint immunotherapeutic agent approved for NSCLC. By enabling host immune-mediated cytotoxic activity against tumor cells, nivolumab induces a tumor response in 15% of patients (pts). However, host-related parameters to predict nivolumab activity are still missing. We evaluated the predictive and prognostic value of the presence of a systemic inflammatory response. **Methods:** From July 2015 to December 2016, we measured at nivolumab initiation the Glasgow Prognostic Score (GPS), a cumulative prognostic score based on C-reactive protein and albumin, the neutrophil-lymphocyte ratio (NLR), the Nutrition Risk Index (NRI) and the Prognostic Nutritional Index (PNI). Univariate and multivariate analyses tested the association between initial patient characteristics and clinical outcome. **Results:** The characteristics of the 57 consecutive pts analyzed are: median age of 66 years (range 41-78), 65% non-squamous cell lung cancer, 61.4% males and 52.6% Performance Status (PS) 0-1. GPS was 0 in 27 (47.4%), 1 in 21 (36.8%) and 2 in 9 (15.8%) pts. In multivariate analysis, parameters associated with disease progression (per RECIST 1.1) were GPS (1-2 vs 0; HR 1.45 [1.11-1.90], p= 0.009) and number of metastatic sites (>2 vs ≤ 2; HR: 0.75 [0.57-0.98], p = 0.04). Overall survival was significantly worse for pts with PS 2-3 vs PS 0-1 (p=0.01) and for pts with GPS 2 vs GPS 0-1 (p=0.01). The GPS was an independent predictive marker of progression and was superior to other inflammation-based prognostic scores in our cohort (Table). **Conclusions:** The Glasgow Prognostic Score (GPS) allows identifying patients with disease progression and long survivors among metastatic NSCLC patients treated with nivolumab.

	GPS 0 n=27 (47.4%)	GPS 1 n=21 (36.8%)	GPS 2 n=9 (15.8%)	HR (GPS 1-2 versus 0)	univariate p
Median overall survival (months)	6.30 [2.17-15.10]	4.87 [1-11.77]	3.77 [2.17-10.50]	3.30 [1.43-7.61]	0.05
Median number of cycles	8.5 [4-22]	4 [1-22]	3 [1-14]		$<10^{-4}$
Progression	10 (37%)	14 (67%)	8 (89%)	4.54 [1.33-16.83]	0.008
Disease control rate	17 (63%)	7 (33%)	1 (11%)		

3056 Poster Session (Board #151), Mon, 8:00 AM-11:30 AM

The scope of possible combination therapy with immunotherapy and targeted therapy. *First Author: Leandro Machado Colli, National Cancer Institute, National Institutes of Health, Rockville, MD*

Background: Combination treatment of two recent trends in cancer therapy, namely immunotherapy with checkpoint inhibitors and drugs that target specific gene mutations, could improve cancer survivorship overall. Targeted drugs usually induce rapid tumor death leading to the release of neoantigens, and can affect immune development pathways, which could increase the efficacy of checkpoint inhibitor treatment. Assessment of somatic mutation profiles from large public databases provides an estimate of the prevalence of targetable somatic mutations and the burden of somatic nonsynonymous mutations (NsM), used as a surrogate for overall neoantigen load, which, in turn, correlates with clinical utility of checkpoint inhibitors for melanoma and lung adenocarcinoma. The rational design of these combinations based on somatic genomic profiles offers a prioritization scheme for new clinical trials. **Methods:** We surveyed 13,349 genomic profiles from public databases for cases with specific mutations targeted by current agents and/or a burden of exome-wide non-synonymous mutations (NsM) that exceeds a recently suggested threshold for response to checkpoint inhibitors. **Results:** Overall, 8.9% of cases have profiles that could benefit from combination therapy, which corresponds to approximately 11.2% of US annual incident cancer cases; the most commonly targetable mutations were observed in *PIK3CA*, *BRAF*, *NF1*, *NRAS*, and *PTEN* genes. Interestingly, cases with mutations in *SMO*, *DDR2*, *FGFR1*, *PTCH1*, *FGFR2*, and/or *MET* appear to be enriched in those with high burdens of NsM, who have a higher likelihood of responding to immunotherapy. Of the 13,349 cases that could benefit from combination therapy, 50.9% had *BRAF*, *NF1*, *GNAQ* and/or *GNA11* mutations which can be targeted by Trametinib; 26.1% by Taselisib (targets *PIK3CA* mutations); and 19.8% by Afatinib (*EGFR* and *ERBB2* mutations). **Conclusions:** Our results indicate a significant proportion of solid tumor patients are eligible for combination therapy and suggest prioritizing specific cancers for combination trials using target drugs and checkpoint inhibitor therapy.

3057 Poster Session (Board #152), Mon, 8:00 AM-11:30 AM

Atezolizumab (A) + cobimetinib (C) in metastatic melanoma (mel): Updated safety and clinical activity. *First Author: Wilson H. Miller, Segal Cancer Centre, Jewish General Hospital, McGill University, Montreal, QC, Canada*

Background: A, an anti–programmed death-ligand 1 (PD-L1) monoclonal antibody, inhibits PD-L1/programmed death-1 (PD-1) and PD-L1/B7.1 binding and shows promising clinical activity in patients (pts) with cutaneous mel (objective response rate [ORR] 33%; median progression-free survival [mPFS] 5.5 months; Hodi et al SMR 2014). C promotes intratumoral T-cell infiltration, major histocompatibility complex 1 upregulation, and PD-L1 expression via targeted MEK inhibition in preclinical models (Ebert et al *Immunity* 2016) and tumor biopsy specimens (Bendell et al ASCO 2016). Therefore, clinical benefits may be enhanced by combining A + C vs A. This Phase Ib dose-escalation and -expansion study (NCT01988896) suggested higher ORR/disease control rate (DCR, ORR + stable disease) and longer PFS may be achieved with A + C vs A or C alone in mel. We present updated safety and efficacy data. **Methods:** Oral C, escalated 20 mg→40 mg→60 mg, was given qd for 21 days followed by 7 days off. Intravenous (IV) A was given at 800 mg q2w. Tumor-specific expansion cohorts were enrolled at maximum tolerated doses (C 60 mg/d 21/7; A 800 mg IV q2w). No prior anti–PD-L1 or –PD-1 therapy was allowed. **Results:** Data cut-off was Oct 12, 2016; 22 patients were safety-evaluable (two ocular, 20 non-ocular [ten each *BRAF*-mutant and -wild-type]). Median safety follow-up was 14.4 months (range 2.1–23.2). Adverse events (AEs) were experienced in all pts (diarrhea [20 pts, 90.9%] and rash [15 pts, 68.2%] were most common); related grade (G)3–4 AEs in 54.5% (diarrhea [three pts, 13.6%] and dermatitis acneiform [two pts, 9.1%] were most common; no related G5 AEs); related serious AEs in 13.6%. All were manageable. One pt discontinued A + C due to an AE. RECIST v1.1-confirmed ORR was 45.0% in pts with non-ocular mel (median duration of response was not reached); DCR was 75.0%; mPFS was 12.0 months (95% CI 2.8–not evaluable). ORR was similar for pts with *BRAF*-mutant and wild-type mel. **Conclusions:** Updated results confirm previous findings that suggest higher ORR/DCR and longer PFS may be achieved with A + C vs A or C monotherapy for mel. Together with biomarker data from other cohorts, our data suggest that the immune contexture may be altered by C, enhancing A activity. Clinical trial information: NCT01988896.

3058 Poster Session (Board #153), Mon, 8:00 AM-11:30 AM

Immune related adverse events (irAE) with platinum chemotherapy (CT) with durvalumab (D) ± tremelimumab (T): CCTG IND226. *First Author: Nathalie Daaboul, Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

Background: CT is immunomodulatory and requires corticosteroids (CS) premedication. We hypothesized that the incidence of irAE may be lower when D ± T is given with CT or CS. **Methods:** Patients (pts) receive CT (pemetrexed, nab-paclitaxel, etoposide or gemcitabine + cisplatin or carboplatin; usual 4-6 cycles) with D ± T, followed by D ± T alone (1 year total); pts with ≥ g2 (selected) or ≥ g3 irAE discontinued D ± T. Cycles were coded as CT + D ± T or D ± T; pts could contribute to both. CS: high (dexamethasone > 10mg/day for 5 days) or low CS. irAE were D ± T related gastrointestinal (GI), skin, endocrine, neurologic, hypersensitivity, pneumonitis (PN) or other immune (nephritis (GN), pancreatitis, hepatitis). Biochemistry (BIO; all causality): creatinine, transaminases/bilirubin (LFTS) and amylase/lipase was summarised. **Results:** In this ongoing study, 118 pts received 723 cycles. Pts had good performance status (PS 0-1), 78 had thoracic malignancies and 84 no prior CT. 44 pts continue on D ± T alone; 32 pts continue on CT + D ± T while 76 pts discontinued D ± T primarily due to disease progression; 15 discontinued for ≥ g2 irAE [PN (3), hepatitis (1), GN (2), adrenal (1), myocarditis (1), GI (3), thrombocytopenia (1), hyperthyroidism (1), encephalitis (1), pt decision (1)]. 67 pts had high CS cycles while 78 pts had low. 50% pts had irAE and 10% had ≥ g3 irAE, most commonly skin and GI. GI (15 vs 11%), skin (26 vs 20%) and PN (3 vs 0%) were reported in more pts during CT + D ± T cycles (non significant (NS)) ; hypothyroidism was more common with D ± T alone (18 vs 10%; p = NS). IrAE rates and severity were similar between high (67 pts) or low CS (78 pts) except for GI (19 vs 10%; p = NS). BIO were more common during CT + D ± T (74% of pts vs 48% p = 0.003); rates in high CS were similar to low CS. LFTs (ALT/AST - 41% vs 16%; 38% vs 9%; p = 0.005) and amylase/lipase (18 vs 9%; 19 vs 14%; p = NS) were more common in pts with CT + D ± T cycles vs pts with D ± T alone cycles. **Conclusions:** There is no evidence that CT or CS abrogates irAE in this exploratory analysis. GI, skin, pneumonitis, LFTS and amylase/lipase were more common during CT + D ± T suggesting additive/multifactorial causes; hypothyroidism is more common in D ± T cycles, which may reflect time on treatment. Clinical trial information: NCT02537418.

3059 Poster Session (Board #154), Mon, 8:00 AM-11:30 AM

Safety profile of avelumab in patients with advanced solid tumors: A JAVELIN pooled analysis of phase 1 and 2 data. *First Author: Karen Kelly, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Avelumab is a fully human IgG1 anti–PD-L1 antibody with clinical activity in several tumor types. Pooled safety data from a large phase 1 trial in various tumors and a phase 2 trial in Merkel cell carcinoma (NCT01772004, NCT02155647) were analyzed to further characterize the safety profile of avelumab. **Methods:** Patients (pts) received avelumab 10 mg/kg 1-hour IV Q2W until progression, unacceptable toxicity, or withdrawal. Treatment-related adverse events (TRAEs) were graded by NCI CTCAE. In post hoc analyses, immune-related adverse events (irAEs) were identified via an expanded AE list and medical review, and infusion-related reaction (IRR) events were identified based on prespecified MedDRA terms, occurring within 1 day or related symptoms that resolved within 2 days of infusion. **Results:** In 1,738 pts analyzed (phase 1, n = 1,650; phase 2, n = 88) who received ≥1 dose of avelumab for a median of 12 weeks (range 2-138), the most common any grade TRAEs were fatigue (n = 307, 18%), IRR (n = 295, 17%), and nausea (n = 150, 9%). 177 pts (10%) had a grade ≥3 TRAE; most common were fatigue and elevated lipase (17 [1%] each). TRAEs led to discontinuation in 107 pts (6%). Four pts (0.2%) died due to a TRAE. Any grade irAEs occurred in 247 pts (14%), which were grade ≥3 in 39 pts (2%) and considered serious in 43 pts (2%). The most common any grade irAEs were thyroid disorder (n = 98, 6%) and rash (n = 90, 5%). Other irAEs (eg, colitis, hepatitis, pneumonitis, adrenal insufficiency, myositis) each occurred in < 2%. irAEs led to discontinuation in 34 pts (2%). IRR or related symptoms (eg, chills, pyrexia, hypersensitivity) occurred in 439 pts (25%), which were grade 3 in 9 pts (0.5%) and grade 4 in 3 pts (0.2%). An IRR occurred at first infusion in 79% and within first 4 doses in 99%; 63/439 pts (14%) had IRR recurrence in later cycles. IRR led to dose interruption in 152 (9%), infusion rate reduction in 124 (7%), and discontinuation in 35 pts (2%). **Conclusions:** This large pooled analysis confirms that avelumab has an acceptable safety profile. A minority of pts experienced a grade ≥3 TRAE or irAE and discontinuation due to TRAEs was uncommon. IRRs mostly occurred at first infusion and the rate of recurrence was low. Clinical trial information: NCT01772004, NCT02155647.

3060 Poster Session (Board #155), Mon, 8:00 AM-11:30 AM

PD-1 blockade using pembrolizumab in adolescent and young adult patients with advanced bone and soft tissue sarcoma. *First Author: Tahlia Scheinberg, Chris O'Brien Lifehouse, Camperdown, Australia*

Background: Sarcomas represent 1015% of cancers in adolescent and young adult (AYA) patients, and survival for those with metastatic disease or after relapse is poor. Immunotherapy with checkpoint inhibition has improved outcomes in multiple tumour types, but there are limited data on the efficacy of immunotherapy in advanced sarcomas, particularly within the AYA population. **Methods:** We retrospectively reviewed AYA patients with advanced bone and soft tissue sarcoma who received self-funded pembrolizumab at Chris O Brien Lifehouse and Children s Hospital Westmead. Initial response was evaluated after cycle three or four using RECIST v1.1 criteria. **Results:** Fourteen AYA patients with sarcoma received pembrolizumab 2mg/kg IV every 3 weeks from May 2015 to December 2016. Median age was 24 (14 35), male to female was 7:7, ECOG PS was 0 1 in 6 patients, 2 in 6 patients and 3 4 in 2 patients. Malignancy type included three patients with osteosarcoma (OS), five patients with Ewing sarcoma (ES), two patients with synovial sarcoma (SS), two patients with alveolar soft part sarcoma (ASPS), and one patient with each of embryonal rhabdomyosarcoma (RMS) and clear cell sarcoma (CCS). The median number of pembrolizumab doses was four (range 1 16), with one patient still receiving treatment at the time of last follow up. Treatment was generally very well tolerated with no G3-4 toxicity. One patient with ES had an excellent, sustained response; of the two patients with ASPS one had a radiological partial response with an excellent clinical response and one patient achieved stable disease. Three patients (two ES, one RMS) died of disease prior to first scheduled assessment and thus their response was not evaluable. The remaining 8 patients had progressive disease. **Conclusions:** Our data suggest further evaluation of the role of pembrolizumab in AYA patients with advanced sarcoma is warranted.

3061 Poster Session (Board #156), Mon, 8:00 AM-11:30 AM

Sustained oligoclonal T cell expansion correlates with durable response to anti-PD1 therapy. *First Author: Sope Omowale Olugbile, University of Chicago, Chicago, IL*

Background: Immune checkpoint blockers have demonstrated durable response in many tumor types including lung cancer. This clinical benefit is however restricted to a subset of patients in whom longitudinal assessments of their tumor microenvironment have revealed increase CD8+ T cell infiltration. However detailed characterization of this T cell dynamics at clonal levels in a large population of patients is yet to be reported. Such analyses will provide vital insight into the mechanism of tumor eradication in responders. **Methods:** We performed next-generation sequencing of T cell receptor β chain in longitudinal tumor and peripheral blood samples obtained from lung cancer patients treated with immunotherapies. We first extracted RNA from these samples and synthesized cDNA with 5'RACE adapter using SMART library construction kit (Clontech). We then amplified TCR β gene products to prepare sequence libraries which were analyzed with MiSeq system (Illumina). **Results:** Here we report on TCR receptor β chain sequencing data for 29 patients in whom we had 3 or more serial samples. Thirteen (45%) of the selected patients in this cohort had durable response and seven (24%) had radiological complete response. We confirmed that there is concordance between the expanded T cell clone at tumor site and the peripheral blood. In one responder, we found expansion of a dominant T cell clone (20%) at a metastatic site where he had pathological complete response on day 17 of treatment and the same clone remained persistent in his peripheral blood (24%) at week 48 of therapy. Similarly in other responders, there were T cell clonal expansions detected as early as week 2 after only one cycle of treatment and such clones remained at high frequencies several months afterwards. Such pattern of early and sustained clonal expansions were absent among non-responders even while they remained on therapy. **Conclusions:** We found durable response to immune checkpoint blockade to correlate with early and sustained expansion of one to two dominant T cell clones in this selected patient cohort.

3062 Poster Session (Board #157), Mon, 8:00 AM-11:30 AM

A randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab, a PD-L1 antibody, to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). *First Author: Sibylle Loibl, German Breast Group, Neu-Isenburg, Germany*

Background: Adding an anti-PD-L1 checkpoint inhibitor durvalumab to standard chemotherapy (CT) may increase pathological complete response (pCR) in patients (pts) with TNBC. **Methods:** GeparNuevo randomizes pts to durvalumab (D) 1.5 g i.v. or placebo (pl) every 4 weeks (wks). D/pl monotherapy (0.75 g i.v.) is given for the first 2 wks (window phase), followed by a biopsy and D/pl plus nab-paclitaxel (nP) 125 mg/m^2 weekly for 12 wks, followed by D/pl plus epirubicin/cyclophosphamide (EC) q2 wks for 4 cycles. Randomization is stratified by stromal TILs (sTILs) (low (≤10%), intermediate (11-59%), high (≥60%)). Pts with primary cT1b-cT4a-d disease, centrally confirmed TNBC, and sTILs status can be included. Primary objective compares pCR (ypT0 ypN0) rates. Secondary objectives are pCR rates in stratified subpopulations and according to other pCR definitions; response rates; breast conservation rate; toxicity; compliance and survival. Change in sTILs, Ki67 and other immune biomarkers before CT, after the window phase and after CT will be correlated with outcome. The first 10, 20 and 30 pts will be included in safety interim analyses (SIA). Sample size was planned assuming a pCR rate of 48% for pl (nP treated TNBC cohort in GeparSepto) and of 66% for D (as clinically meaningful benefit), requiring 158 pts to show superiority of D (2-sided $\alpha = 0.2$, 80% power). Assuming a 10% drop-out rate 174 pts will be randomized. **Results:** Since 6/2016, 50 pts were recruited within 16 sites; data are presented as available until 01/2017. Median age is 49 years; 86% NST and G3 tumors; sTILs categories 40% low, 40% intermediate and 20% high. Blinded SIA was performed. No pt interrupted D/pl, one nP and one EC. Treatment delay was observed in 9 pts (20.0%) in D/pl, 18 (41.9%) in nP and 2 (13.3%) in EC; dose was reduced in 10 pts (23.3%) in nP and in 4 (26.7%) in EC. 10 pts (20%) had at least one grade 3-4 AE: 4 haematological and 6 non-haematological AEs. 4 SAEs and 5 immune related AEs were reported. 2 pts discontinued study treatment prematurely in the EC phase. **Conclusions:** The addition of D to standard nP-EC is feasible and does not result in an increased toxicity. Clinical trial information: NCT02685059.

3063 Poster Session (Board #158), Mon, 8:00 AM-11:30 AM

Atezolizumab (A) + cobimetinib (C) + vemurafenib (V) in BRAF^{V600}-mutant metastatic melanoma (mel): Updated safety and clinical activity. *First Author: Ryan J. Sullivan, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Targeted inhibition of MEK with C and BRAF with V in BRAF^{V600}-mutant mel can lead to both anticancer immune activation and direct tumor cell death. A, an anti–PD-L1 monoclonal antibody, inhibits PD-L1/PD-1 signaling. Combining C + V with A may enhance antitumor activity, potentially leading to improved clinical responses and durability. Preliminary data from this phase Ib study (NCT01656642) showed that A + C + V had a manageable safety profile and promising antitumor activity in patients (pts) with untreated BRAF^{V600}-mutant unresectable/metastatic mel, with increases in CD8-positive T-cell infiltration observed after C + V (Sullivan et al SMR 2016). We present updated safety and efficacy data. **Methods:** Pts received A + C + V after a 28-day run-in with C + V. A was given at 800 mg q2w, C at 60 mg qd for the first 21 days of each 28-day cycle, and V at 960 mg bid during day 1–21 of run-in and 720 mg thereafter. Safety was evaluated in pts who had ≥1 dose of A; efficacy, in pts who had ≥1 dose of A by the data cutoff date and received ≥1 dose of A, C, or V by the dosed-by date. **Results:** Thirty-four patients were treated and evaluated for both safety and efficacy. Median survival follow-up was 7.1 months (range 2.5–19.9). Elevated AST/ALT, diarrhea, arthralgia, fatigue, photosensitivity, pyrexia, nausea, flu-like symptoms, maculopapular rash, and pruritus were reported as A- and/or C- and/or V-related in > 20% of pts at any grade (G). A/C/V-related G3–4 adverse events (AEs) were seen in 15 pts (44.1%) with the triple combination (none G5). Three serious AEs were A-related. All AEs were manageable and reversible. Elevated ALT/AST (three pts each) and rash (one pt) led to discontinuation of any drug. Unconfirmed RECIST V1.1 responses were observed in 29 pts (85.3%; six complete, 23 partial). Three pts with confirmed partial responses had resolution of target lesions. Twenty of the 29 responding patients continue to respond at the time of the data cutoff. **Conclusions:** Updated results confirm preliminary findings that A + C + V has a manageable safety profile and promising antitumor activity in pts with BRAF^{V600}-mutant metastatic mel. Continued exploration of A + C + V is warranted. Clinical trial information: NCT01656642.

3064 Poster Session (Board #159), Mon, 8:00 AM-11:30 AM

DETERRED: PD-L1 blockade to evaluate the safety of lung cancer therapy using carboplatin, paclitaxel, and radiation combined with MPDL3280A (atezolizumab). *First Author: Steven H. Lin, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint blockade in non-small cell lung cancer (NSCLC) may be enhanced when combined with radiation therapy. Atezolizumab (atezo) is a humanized and Fc receptor modified monoclonal antibody that blocks programmed death-ligand-1 (PD-L1) interacting with PD-1 or B7.1 sparing PD-L2, which may result in less pulmonary toxicity. We report the early safety data of combining atezo added sequentially after standard concomitant chemoradiation (CRT) for locally advanced NSCLC (LA-NSCLC). **Methods:** This is a phase II study in LA-NSCLC assessing the safety and feasibility of adding atezo to CRT in two parts: I) sequentially (N = 10) with CP after completing CRT, or II) concurrently (N = 30) with CRT followed by consolidation atezo with CP. We report on the early toxicity results from part I of the trial. Atezo was given at 1200 mg IV Q3 weeks with consolidation CP for 2 cycles after CRT followed by atezo monotherapy for up to one year. Radiation dose at 60-66 Gy in 30-33 fractions was combined with weekly low dose CP, followed by 2 cycles of full dose CP. Dose limiting toxicities were defined as any adverse events (AEs) ≥ grade 3 within 15 weeks of start of therapy or any immune-related AEs during atezo treatment. **Results:** From January to December 2016, 10 evaluable patients were enrolled. Seven patients have received consolidation atezo ranging from 1 to 14 doses, with 3 yet to receive atezo after completing CRT. Three patients reported potential immune-related AEs. One patient developed grade 3 arthralgia, and another developed grade 2 radiation-induced pneumonitis, which resolved with steroids. A third patient who experienced grade 3 dyspnea due to COPD exacerbation after 1 dose of atezo discontinued additional therapy. Of the 7 patients who have received atezo, 2 patients developed progression of disease after 6 and 8 doses of atezo. **Conclusions:** Atezo consolidation with 2 cycles of CP after CRT appears to be feasible and well tolerated with manageable toxicities. Additional data from part I will be reported. Conditions for proceeding after part I are met and part II of the study which adds atezo to CRT followed by atezo-CP consolidation is open for accrual. Clinical trial information: NCT02525757.

3066 Poster Session (Board #161), Mon, 8:00 AM-11:30 AM

A phase II randomized, double-blind study of sipuleucel-T followed by IDO pathway inhibitor, indoximod, or placebo in the treatment of patients with metastatic castration resistant prostate cancer (mCRPC). *First Author: Gautam Gopalji Jha, University of Minnesota, Minneapolis, MN*

Background: The indoleamine 2,3-dioxygenase (IDO) pathway is a key counter-regulatory mechanism exploited by tumors in order to prevent and defeat anti-tumor immunity. Sipuleucel-T has overcome this tumor mediated anergy only in part by its ex-vivo sensitization. Small-molecule inhibitors of the IDO pathway, such as indoximod, are an increasingly validated class of potential cancer therapeutics. We tested the hypothesis whether targeting the IDO pathway by indoximod will inhibit Treg and abrogate tumor-mediated immunosuppression permitting a robust and sustained immune response to sipuleucel-T. **Methods:** Patient (pts) with mCRPC received either indoximod or placebo orally for 10 weeks after completion of sipuleucel-T therapy. In the absence of radiographic or clinical progression, pts were continued on study drug for 3 more months. Immune monitoring was done similar to IMPACT study (NEJM 2010; 363:411-422) starting prior to sipuleucel-T therapy. The primary endpoint was augmentation of immune response to PA2024 measured at 14 weeks. Secondary endpoints include safety, clinical efficacy (PFS, OS) and HR-QOL **Results:** Of the 63 pts with CRPC screened, 46 eligible pts were randomized to indoximod (n = 22) or placebo (n = 24). Pts tolerated therapy with indoximod with no significant difference in adverse events between two arms. There was no difference in PSA progression nor difference in the primary endpoint of immune response to PA2024 for 35 pts who have completed study and have samples analyzed. Median OS has not yet been reached in the study. Median radiographic PFS was 10.3 months in the treatment arm vs 4.1 months in placebo arm ($p = 0.011$), 4.1 months being similar to PFS in the pivotal 'IMPACT' study. More Pts continued to complete maximum treatment on indoximod arm (40.9% vs 25%). **Conclusions:** Treatment with indoximod post sipuleucel-T therapy is well tolerated and led to a significant improvement in radiographic and clinical progression. Augmentation of immune response to PA2024 by ELISPOT or ELISA might not be right biomarker for augmented response assessment while studying inhibition of IDO pathway. Clinical trial information: NCT01560923.

3067 Poster Session (Board #162), Mon, 8:00 AM-11:30 AM

A phase I study of JS001, a humanized IgG4 mAb against programmed death-1 (PD-1) in patients with advanced solid tumors. *First Author: Zhihong Chi, Peking University Cancer Hospital and Institute, Beijing, China*

Background: JS001 blocks the interaction between PD-1 and its ligands and eradicates established tumor in human PD-1 Knock-in mouse model. **Methods:** A Phase I open-label study is designed to evaluate the safety and tolerability of JS001 in advanced solid tumor pts who are refractory to standard therapy. The study has a 3+3 dose escalation design with planned cohorts at 1, 3, and 10 mg/kg followed by a dose expansion. (Clinical Trial ID: NCT02836795). **Results:** As of January 27, 2017, pts enrollment has been completed with 36 pts from 3 indications (22 Melanoma; 9 Urothelial Carcinoma; 5 Renal Cell Carcinoma). The majority of melanomas are acral and mucosal origin. No DLT was observed and no MTD was reached in the study. The most common treatment-related AEs were grade 1/2, including hyper- or hypo-thyroidism (42%), rash (39%), fever (28%), leukopenia (22%), elevation of liver enzymes (19%), anorexia (17%), and fatigue (14%). Treatment–related grade 3 AEs include proteinuria (n = 1), and lipase increase (n = 2). The emergence of AEs is not dose related. JS001 PK shows dose-dependent exposure with the elimination half-life of 6 to 12 days. Among 32 evaluable pts, 1 pt have complete response (melanoma), 6 pts have partial response (3 melanoma, 2 RCC and 1 UC), and 10 pts achieve stable disease, for an ORR of 22% and a DCR of 53%. 6 out of 7 CR/PR pts still have ongoing response. Two groups of pts benefited most from JS001 treatment, pts with high tumor-infiltrating lymphocytes (TIL) (50% ORR) and pts with $>$ 1% PD-L1 expression in tumor biopsy (46% ORR). **Conclusions:** JS001 exhibited a favorable safety profile in human. Treatment related AEs are in line with those from approved drugs in the same class. JS001 has demonstrated promising anti-tumor activity, especially in previously under-evaluated acral (20% ORR, 53% DCR) and mucosal (25% ORR, 50% DCR) melanomas. Clinical trial information: NCT02836795.

3068 Poster Session (Board #163), Mon, 8:00 AM-11:30 AM

Racial disparities in the use of programmed death-1 checkpoint inhibitors. *First Author: Jeremy O'Connor, Yale School of Medicine, New Haven, CT*

Background: There are concerns about racial disparities in access to trials of new cancer drugs, including the programmed death 1 checkpoint inhibitors (anti-PD1s). It is unknown whether these disparities extend to anti-PD1 treated patients in real-world practice. **Methods:** We used retrospective data from Flatiron Health's electronic health record database, which includes more than 250 cancer clinics and 1.5 million patients with cancer. We identified patients diagnosed after January 1, 2011 who underwent systemic therapy for: advanced non-small cell lung cancer (aNSCLC; n = 13,473), metastatic renal cell carcinoma (mRCC; n = 1,537), and advanced melanoma (n = 1,221). Within each cohort, we identified treatment type (anti-PD1 versus non-anti-PD1). Therapy lines containing study drugs were excluded. We used logistic regressions to model the use of anti-PD1s by race, adjusting for factors such as age, sex, stage at diagnosis and line of therapy. **Results:** Of 16,231 patients in our sample, 4,643 (28.6%) were treated with anti-PD1s. Racial distributions differed for anti-PD1 treated patients compared to non-anti-PD1 treated patients in the aNSCLC cohort (Table: $p < 0.01$), but not in the mRCC cohort ($p = 0.84$) or the advanced melanoma cohort ($p = 0.96$). In bivariate analyses of patients with aNSCLC, anti-PD1 treatment was associated with other race, male sex, stage II at diagnosis, squamous histology, smoking history and line of therapy (all $p < 0.05$). Adjusted models showed there were no significant differences in likelihood of receiving anti-PD1s when comparing black and white patients undergoing systemic therapy for aNSCLC (aOR for black vs. white: 0.86, 95% CI 0.72-1.02), mRCC (aOR 0.90, 95% CI 0.53-1.49), or melanoma (aOR 2.02, 95% CI 0.42-14.59). **Conclusions:** Among patients undergoing systemic therapy in a large national network of cancer clinics, we found no significant racial disparities in the use of anti-PD1s.

	aNSCLC			mRCC			Melanoma		
	Anti-PD1	Non-Anti-PD1	p-value	Anti-PD1	Non-Anti-PD1	p-value	Anti-PD1	Non-Anti-PD1	p-value
Race	-	-	< 0.01	-	-	0.84	-	-	0.96
White, %	66.8	62.8		67.9	65.0		78.6	78.8	
Black, %	7.4	8.1		6.5	7.2		0.8	0.5	
Asian, %	3.1	3.4		1.3	1.7		0.3	0.2	
Other, %	9.2	10.3		12.4	12.6		6.2	6.9	
Unknown, %	13.5	15.4		11.9	13.6		14.2	13.6	

3069 Poster Session (Board #164), Mon, 8:00 AM-11:30 AM

Phase 1 study to evaluate the safety and tolerability of MEDI4736 (durvalumab, DUR) + tremelimumab (TRE) in patients with advanced solid tumors. *First Author: Margaret K. Callahan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: DUR is a human IgG1 monoclonal antibody (mAb) that blocks PD-L1. TRE is a human IgG2 mAb inhibitor of CTLA-4. Blocking these checkpoints can result in antitumor activity in some solid tumors. The targets for DUR and TRE are non-redundant, providing sound rationale for clinical testing of the combination. **Methods:** This is an ongoing Phase 1, multicenter, open label study (NCT01975831) with a dose escalation (3+3 design) and subsequent expansion phase. Patients (pts) with renal cell carcinoma (RCC), cervical (CC), colorectal (CRC), non-triple-negative breast (NTNBC), ovarian (OC), non-small cell lung, or head and neck cancer are eligible. Primary endpoints are safety/tolerability and identification of maximum tolerated dose (MTD) of the combination. Secondary objectives include tumor response and progression-free/overall survival. **Results:** As of 16 Dec 2016, 105 pts were treated. DUR 1500 mg every 4 weeks (Q4W) and TRE 75 mg Q4W X 4 was the regimen used for opening the expansion phase. Dose-limiting toxicities were reported in 4 pts: diarrhea, colitis, abnormal liver function tests (abn LFTs), and hyponatremia. The majority of treatment-related AEs (TRAEs) were Grades (Gr) 1 and 2. TRAEs $\geq$ Gr 3 were reported in 12 pts; the majority were diarrhea/colitis (n = 5) and abn LFTs (n = 4) and responded to established treatment algorithms. There was 1 Gr 5 TRAE: multi organ failure. No new toxicities were identified. The preliminary responses by tumor type with n $\geq$ 10 pts are shown in the table below. Responses were seen in OC and RCC at the Cohort 2 dose escalation level (DUR 1/TRE 3 mg/kg). There were 4 cases of SD $>$ 24 weeks: CC, n=2; CRC, n=1; OC, n=1. PD-L1 status was not tested. **Conclusions:** The DUR + TRE combination has a manageable safety profile, with preliminary evidence of clinical activity. These data support continued study of the combination therapy; the study is ongoing. Clinical trial information: NCT01975831.

		Preliminary Best Response by irRC		
Tumor Type	Evaluable Pts (n)	Stable Disease* (SD, n)	Partial Response (PR, n)	SD + PR Rate** (%)
CC	13	6	0	46.2
CRC	11	3	1	36.4
NTNBC	10	2	1	30.0
OC	25	10	2	48.0
RCC	11	8	1	81.8

*Includes pts with at least 1 post-baseline assessment (SD $\geq$ 6 weeks); majority observed $<$ 24 weeks; **No complete responses were observed

3070 Poster Session (Board #165), Mon, 8:00 AM-11:30 AM

Validation of the Princess Margaret immune oncology prognostic index (PM-IPI) for patients (pts) treated in immune oncology (IO) early phase trials. *First Author: Daphne Day, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: We previously developed the PM-IPI (ECOG performance status [PS] > / = 1, albumin < lower limit of normal [LLN] and > 2 metastatic sites) from a retrospective cohort of 192 pts treated in phase I IO trials (development cohort). The PM-IPI prognosticated for overall survival (OS), 90-day mortality (90DM) and was associated with improved overall response rate (ORR) and progression free survival (PFS). Our aim was to prospectively validate the PM-IPI in an independent cohort of pts treated on IO trials. **Methods:** We included 152 consecutively treated advanced solid tumor pts at PM from Aug 2015 to Aug 2016 in 24 IO early phase trials, targeting immune checkpoints and/or co-stimulatory molecules. Pts from the development cohort were excluded. The ability of the PM-IPI to prognosticate OS and 90DM, and predict PFS and ORR was compared with the previously published Royal Marsden Hospital prognostic score (RMI: albumin < 35g/L, LDH > upper limit of normal and > 2 metastatic sites) using the C-index (0.5 = no discrimination, 1 = perfect discrimination) and Area Under the Curve (AUC). **Results:** Median age was 59y (range 20-86), 28%/72% of pts were ECOG PS 0/1, and 88% had at least 1 prior systemic therapy (range 0-7). The most common tumor sites were gastrointestinal (23%), gynecological (16%), head and neck (15%) and urological (10%). Median PFS and OS were 9.0 and 39.7 wk respectively and 90DM was 14%. ORR was 7% by RECIST 1.1, immune related RECIST or immune related response criteria. In multivariable analysis, ECOG PS > / = 1 (HR 2.7, p = 0.01), albumin < LLN (HR 2.1, p = 0.01) and > 2 metastatic sites (HR 1.8, p = 0.04) were independently prognostic for OS. Pts with a PM-IPI score of 2-3 compared to 0-1 had significantly shorter OS (HR 3.3, p < 0.0001), PFS (HR 1.7, p = 0.005) and higher 90DM (OR 12.2, p = 0.019), and a trend towards lower ORR (OR 0.4, p = 0.15). The prognostic performance of PM-IPI was superior to the RMI for OS and 90DM, but not PFS and ORR (Table). **Conclusions:** In this independent validation cohort, the PM-IPI prognosticated for OS and 90DM and was associated with PFS. Validation in a large external cohort is ongoing.

	OS	PFS	90DM	ORR
	C-index		AUC	
PM-IPI	0.69	0.57	0.80	0.64
RMI	0.63	0.57	0.70	0.70

3071 Poster Session (Board #166), Mon, 8:00 AM-11:30 AM

Pembrolizumab therapy for microsatellite instability high (MSI-H) colorectal cancer (CRC) and non-CRC. *First Author: Luis A. Diaz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Mismatch repair deficient cancers harbor high levels of microsatellite instability and somatic mutations. Treatment with anti-PD-1 antibodies has resulted in durable objective responses in MSI-H cancer. As part of the ongoing, global, multicenter phase 2 studies KEYNOTE(KN)164 and KN158, we assessed the efficacy of pembrolizumab in patients (pts) with MSI-H tumors. **Methods:** Both studies enrolled pts with MSI-H status determined locally by IHC or PCR. KN164 enrolled pts with MSI-H CRC and ≥2 prior therapies, whereas the multicohortKN158 study included pts with MSI-H non-CRC and ≥1 prior therapy. Eligible pts in both studies received pembrolizumab 200 mg Q3W until progression, unacceptable toxicity, or pt/investigator decision. Tumor response was assessed every 9 wk by independent review per RECIST v1.1. Primary endpoint was ORR. Secondary endpoints included DOR, PFS, OS, and safety. Analyses were performed in pts from KN164 and KN158 who had ≥27 wk of follow-up as of Aug 3, 2016 and Oct 19, 2016, respectively. **Results:** KN164 enrolled 61 pts with MSI-H CRC (90% with ≥2 prior therapies) whereas KN158 included 21 pts with MSI-H non-CRC (42% with ≥2 prior therapies). In KN158 the most common tumor types were endometrial and small intestinal cancer (n = 4 each), cholangiocarcinoma (n = 3), and gastric and pancreatic cancer (n = 2 each). Median follow-up was 7.4 mo for MSI-H CRC and 4.5 mo for MSI-H non-CRC. ORR for MSI-H CRC was 26.2% (95% CI, 15.8%-39.1%), with 15 confirmed responses and 1 unconfirmed response, and ORR for MSI-H non-CRC was 42.9% (21.8%-66.0%), with 8 confirmed responses and 1 unconfirmed response. DCR was 50.8% (n = 31; 37.7%-63.9%) for MSI-H CRC and 66.7% (n = 14; 38.4%-83.7%) for MSI-H non-CRC. Median duration of response was not reached for either MSI-H CRC or non-CRC, and 100% of responses were ongoing. Survival and safety analyses are ongoing. **Conclusions:** Early results from KN164 and KN158 confirm the robust antitumor activity of pembrolizumab in heavily pretreated pts with MSI-H cancers. Clinical trial information: NCT02628067; NCT02460198.

3072 Poster Session (Board #167), Mon, 8:00 AM-11:30 AM

Relationship between liver metastases and PD-1 blockade in melanoma. *First Author: James Chi-Chiang Lee, University of California, San Francisco, San Francisco, CA*

Background: WhilePD-1 blockade is effective in melanoma, durable responses remain elusive. We have previously reported that liver metastasis is associated with reduced response rates and that the fraction of CTLA4 hi/PD-1 hi CD8+ cells ("activated-exhausted" or T-ex cells) within the TIL is predictive of response to PD-1 blockade. Here, we explore the biology behind liver metastasis in human melanoma and in animal models. **Methods:** Patients with metastatic melanoma with or without liver metastasis were biopsied pre- PD-1 treatment and immune infiltrates were analyzed by FACS. The CD8 fraction was gated on CTLA4 and PD-1. C57BL/6 mice were implanted with a "primary" subcutaneous tumor and a "metastatic" tumor in the liver or the lungs (control), and given systemic PD-1 blockade therapy. **Results:** Patients with melanoma and liver metastasis (n = 25) had 15.2% T-ex cells while those without liver metastasis (n = 76) had 26.5 % T-ex cells, p = 0.0092. A T-ex fraction < 20% was significantly associated with lack of PD-1 response, p < 0.005. In C57BL/6 mice implanted with a B16 tumor (subQ & liver) treated with PD-1 antibody, 0/35 mice achieved subQ tumor rejection while in the SubQ only mice 9/30 mice (30%) rejected their tumors. The mean tumor size of mice with Sub Q+liver metastasis was 139.2 mm2 vs subQ only mice 23.4 mm2 at d 14, p = 0.002. Mice with liver metastasis showed a T-ex fraction 31.9% vs 67.3%without liver met, p = 0.0003. In contrast, in mice made lung metastatic, the subQ tumor rejection rate was 7/20 (35%), with T-ex infiltrate at 57.9%. The implantation of liver metastases from an unrelated MC38 tumor does not protect the subQ tumor from immune rejection. **Conclusions:** The presence of liver metastases is associated with reduced response to PD-1 blockade and reduced T-ex infiltrate in patients with stage IV melanoma. Mechanistic studies using a mouse model of syngeneic organ site specific metastasis confirms that the liver metastasis results in reduced antigen specific T cell at distant sites, resulting in reduced response. Site of metastasis may determine immune responsiveness in both mouse models and in humans with melanoma.

3073 Poster Session (Board #168), Mon, 8:00 AM-11:30 AM

Managing immune checkpoint-inhibitor-induced severe autoimmune-like hepatitis by liver-directed topical steroids. *First Author: Mirjana Ziemer, Department of Dermatology, Universtiy of Leipzig, Leipzig, Germany*

Background: The CTLA4-antibody ipilimumab, and PD-1-antibodies pembrolizumab as well as nivolumab have revolutionized antineoplastic therapies. Induction of autoimmune-like drug-induced liver injury (DILI) is within the spectrum of adverse reactions of these new drugs and has been observed in about 1-5 % of patients, developing predominantly within the first 6 to 12 weeks after start of treatment. Immediate application of systemic steroids and a permanent discontinuation of immune checkpoint-inhibition therapy are recommended for any alanine aminotransferase increase ≥ WHO grade 3. In severe autoimmune-like DILI the permanent discontinuation of the immune checkpoint inhibitor is recommended, as drug re-exposure might be associated with a significant risk of a fulminant DILI. **Methods:** We report six patients with severe grade 3 autoimmune-like DILI (according to Common Terminology Criteria for Adverse Events 4.3) treated with long-term application of budesonide, a liver-directed topical steroid. **Results:** Immune checkpoint inhibitors were stopped and methylprednisolone was applied initially with a dose of 1 mg/kg body weight and tapered thereafter. To reduce systemic steroids and to minimize the exposure time to systemic steroids, the topical steroid budesonide 3 mg three times per day was additionally given in combination with N-acetylcysteine and ursodeoxycholic acid. Under this multimodal approach transaminases normalized and the respective immune-checkpoint inhibitor could be re-started without re-manifestation of DILI under the continuous treatment with budesonide. **Conclusions:** Budesonide - a liver-directed topical steroid - might be an interesting approach to target liver related autoimmune adverse reactions induced by immune checkpoint inhibitors without compromising their anti-cancer effect. We were able to safely and effectively re-introduce and continue immune checkpoint inhibitors under the continuous application of the topical steroid without showing any further liver toxicity.

3074 Poster Session (Board #169), Mon, 8:00 AM-11:30 AM

Discovery of COM701, a therapeutic antibody targeting the novel immune checkpoint PVRIG, for the treatment of cancer. *First Author: Spencer Liang, Compugen Ltd., San Francisco, CA*

Background: While inhibitors of CTLA4 and PD1 have emerged as effective cancer therapies, the majority of treated patients do not derive long term benefit. Employing our computational discovery platform, we discovered PVRIG as an immune suppressive molecule expressed on T and NK cells and identified COM701, an antibody (Ab) targeting human PVRIG that enhances T cell function and anti-tumor responses. **Methods:** Anti-human PVRIG Ab COM701 was identified as an antagonistic Ab that enhanced T cell function in multiple assays. Antagonistic anti-mouse PVRIG Abs and PVRIG deficient ($PVRIG^{-/-}$) mice were generated and characterized using syngeneic tumor models. **Results:** PVRIG was induced upon T cell activation, with long term activation leading to the highest expression. PVRL2 was identified as the ligand for PVRIG, placing PVRIG in the DNAM/TIGIT immunoreceptor axis. Compared to normal adjacent tissues, PVRIG and PVRL2 were both induced in the tumor microenvironment of several human cancers. To target PVRIG for therapeutic intervention, we identified COM701, a high affinity Ab that disrupts the interaction of PVRIG with PVRL2. COM701 enhanced CD8 T cell proliferation and IFN-g production *in vitro* and had an additive or synergistic effect on T cell activation when further combined with an anti-PD1 or anti-TIGIT Ab. Consistent with a checkpoint function for human PVRIG, mouse $PVRIG^{-/-}$ T cells showed increased function compared to wild type T cells. A surrogate antagonistic anti-mPVRIG Ab reduced growth of CT26 and B16 tumors when combined with an anti-PDL1 Ab *in vivo*. MC38 tumors also grew slower in $PVRIG^{-/-}$ mice compared to wild type mice and ex vivo analysis pointed to functional differences in anti-cancer immunity. **Conclusions:** We demonstrated that targeting PVRIG with COM701, a high affinity antagonistic Ab, increased human T cell function. We further showed that PVRIG was induced in the tumor microenvironment and that disruption of PVRIG/PVRL2 interaction resulted in reduced tumor growth in preclinical models. These data demonstrate that PVRIG is a promising target for the treatment of cancer and provide the rationale for COM701 as a potential cancer immunotherapy.

3075 Poster Session (Board #170), Mon, 8:00 AM-11:30 AM

Phase 1 open-label, multiple ascending dose trial of AGEN1884, an anti-CTLA-4 monoclonal antibody, in advanced solid malignancies. *First Author: Breelyn A. Wilky, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: AGEN1884 is a fully human IgG1 monoclonal antibody targeting the co-inhibitory protein cytotoxic T lymphocyte-associated protein 4 (CTLA-4). CTLA-4 blockade has been shown to augment T cell activation and proliferation, resulting in immune infiltration of the tumor and subsequent regression. **Objectives:** Assess the safety, maximum tolerated dose (MTD), and pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AGEN1884 in patients (pts) with advanced and refractory malignancies using a "3+3" trial design. **Methods:** Eleven pts have been enrolled and treated to date. AGEN1884 was administered intravenously q3w for 4 doses and then q12w. Three (0.1, 0.3 and 1 mg/kg) of six (3, 6 and 10 mg/kg) planned dose levels have been completed. **Results:** Five pts were accrued at 0.1 mg/kg dose level (2 were not DLT evaluable) and three pts each at doses of 0.3 mg/kg and 1 mg/kg. Median age was 56 years (range 26–70), ECOG 0–2, with a median of 4 (range 1–8) prior therapies. No DLT events have been observed thus far. Data from 5 pts were available for PK evaluation. Half-life of AGEN1884 post first dose was 8.8 and 9.6 days for 0.3 mg/kg and 0.1 mg/kg dose levels, respectively, as measured by ELISA. As of Jan 31, 2017, pts across cohorts were followed for a median of 6 weeks (range 0-28). Six pts (54.5%) have come off study due to disease progression, while 5 (45.5 %) remain on study. One confirmed partial response (80% reduction) by RECIST criteria was seen at 0.1 mg/kg in a patient with angiosarcoma. **Conclusions:** AGEN1884 is safe at 0.1 and 0.3 mg/kg dose levels. Dose escalation is ongoing and updated safety and PK data will be presented. Clinical trial information: NCT02694822.

3076 Poster Session (Board #171), Mon, 8:00 AM-11:30 AM

Molecular characterization of immune-related severe adverse events (irSAE). *First Author: Justin M. Balko, Vanderbilt University Medical Center, Nashville, TN*

Background: Immune checkpoint inhibitors (ICIs; anti-CTLA-4 and anti-PD-1) have shown clinical success in many cancers, but may cause rare irSAE. The molecular features of irSAE have not been extensively explored. Therefore, we characterized the immune composition of tissue affected by ICI-mediated inflammation with a focus on colitis and neurologic toxicity. **Methods:** We performed retrospective T-cell receptor (TCRβ) sequencing, RNA-sequencing (HTG EdgeSeq; $>$ 2500 immune-related genes), and digital spatial profiling (NanoString) for 20 protein markers in 10 regions across tissues representing ICI-induced colitis, autoimmune inflammation (e.g. Crohn's) and normal colon. Matched tumors were also included in a subset. We also analyzed the encephalitic and healthy brain of a unique presentation of anti-PD-1-induced encephalitis. **Results:** Patient-matched melanoma and colitis biopsies (n = 3) demonstrated shared T cell clones in all samples ranging from several shared clones to several hundred (0.4%, 2.7%, and 3% of rearrangements, respectively), including high-frequency clones. Shared TCRβ sequences were also identified among and between colon-irSAE and Crohn's specimens. Gene expression patterns of inflammation in colon-irSAE resembled that of Crohn's disease in principle components and clustering analysis, highlighting likeness between these diseases/SAEs. NanoString digital spatial profiling of regions of inflammation across samples showed higher CD68 and PD-L1 positivity in colon-irSAE specimens versus normal colon or Crohn's specimens and reduced beta-catenin levels in both Crohn's and colon-irSAE specimens relative to normal controls. Finally, we detected a high degree of TCR clonality in the encephalitic brain, including a single sequence present in ~20% of $>$ 12,000 T cells, suggesting a distinct antigen-specific response. **Conclusions:** We report the molecular characteristics of irSAE in colon and brain specimens from patients receiving ICIs. Highly clonal TCRβ sequences were frequently detected, particularly in a unique case of encephalitis-irSAE. Furthermore, we identify molecular distinctions and similarities between autoimmune and colon-irSAEs at the gene expression and proteomic levels.

3077 Poster Session (Board #172), Mon, 8:00 AM-11:30 AM

Interrogating resistance mechanisms to PD-1 blockade therapy with CRISPR. *First Author: Davis Yuri Torrejon, University of California Los Angeles Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: We tested the biological significance of the loss of function (LOF) mutations in JAK1 or JAK2 within the IFN-receptor-pathway and in beta-2-microglobulin (B2M), which had been found in patient biopsies with resistance to anti-PD-1 therapy. **Methods:** We used CRISPR/Cas9 genome editing to generate JAK1, JAK2 and B2M knockout (KO) sublines of HLA-A*02:01 MART-1 or NY-ESO-1 positive human melanoma cell lines, tested using *in-vitro* T cell co-culture systems and in a syngeneic mouse model (MC38) to analyze the *in-vivo* antitumor activity with anti-PD1 therapy. **Results:** The JAK2-KO cell line was insensitive to IFN-gamma induced signaling and growth arrest ($p < 0.001$ compared with IFN-alpha or beta), while the JAK1-KO cell line was insensitive to all three IFNs. Baseline MHC class I expression after JAK1-KO was unaffected (baseline-MFI 1230 JAK1-KO vs 1570 parental, $p = 0.66$), but the magnitude of change was lower upon IFN-gamma exposure compared to the parental (MFI change with IFN-gamma, 26% decrease for JAK1-KO vs 50% increase for parental). There was no difference in *in-vitro* cytotoxicity by NY-ESO-1-TCR transgenic T-cells against JAK1-KO-NY-ESO-1+ melanoma cells compared to the parental (78% vs 82% cytotoxicity at 10:1 E:T ratio, p NS). However, B2M-KO was resistant to killing by MART-1 specific T-cells (2% vs 96% cytotoxicity at 10:1 E:T ratio, $p < 0.0001$). On the other hand, in the MC38 model the significant antitumor activity of anti-PD-1 against the wild type cells was lost in both JAK2-KO and B2M-KO. The percentage of CD8+ T cells has a trend of increase with anti-PD1 compared to untreated in the MC38 wild type ($p = 0.1$ d12), and a trend of decrease in MC38 B2M-KO ($p = 0.2$ d12), but no change in JAK2-KO tumors ($p = 0.7$ d12). **Conclusions:** JAK1/2 LOF mutations result in insensitivity to IFN induced antitumor effects, but does not impair T cell recognition and cytotoxicity, while B2M LOF results in lack of antigen presentation to T cells and loss of antitumor activity. However both lead to in-vivo resistance to anti-PD-1 therapy, suggesting they do so by independent mechanisms.

3079 Poster Session (Board #174), Mon, 8:00 AM-11:30 AM

Mutually exclusive expression of CD73 and PDL1 in tumors from patients (pt) with NSCLC, gastroesophageal (GE) and urothelial bladder carcinoma (UBC). *First Author: Philip Martin, Medimmune/AstraZeneca, Gaithersburg, MD*

Background: Tumors use multiple means of immune evasion, notably the programmed death-1 (PD1)/PDL1 pathway. Anti-PD1/PDL1 therapy induces anti-tumor activity and has improved pt outcomes. Activation of the immunosuppressive CD39/CD73/adenosine pathway might play a role in pts who do not benefit from anti-PD1/PDL1 therapies. We evaluated expression of CD73 and PDL1 and explored the association between CD73 and intraepithelial (IE) CD8+ cells (TILs) to begin to understand their potential interplay in cancer. **Methods:** Immunohistochemistry for PDL1, CD73 and CD8 was conducted on tumors of non-squamous NSCLC (NSq) (n=42), GE (n=50), and UBC (n=50). PDL1 and CD73 were scored by image analysis with Definiens software. IE CD8+ TILs were scored semi-quantitatively by a pathologist (0-2 = low; 3-4 = high). Using the top tertile of PDL1 and CD73 for high expression levels, a Fisher's meta-analysis was calculated across the three indications. **Results:** Across all tumors, 25% (35/142) were PDL1 high (+), but CD73 low (-) and another 25% (35/142) were CD73+ but PDL1- (p=0.06, see table). This trend for mutually exclusive high expression of PDL1/CD73 was strongest in GE ($p<0.01$). In the PDL1+ group 76% (35/46) had high IE CD8+ TILs whereas in the CD73+ group only 35% (16/46) had high TILs ($p<0.0001$ using a proportions test). In the PDL1+/CD73- pt subset 77% (27/35) were CD8+ high vs only 23% (8/35) in the PDL1-/CD73+ subset. **Conclusions:** The identification of distinct pt subsets based on high PDL1 and/or CD73 expression suggests that tumors have multiple mechanisms of immune evasion. Increased IE CD8+ TILs were associated with PDL1 expression. The finding that PDL1-/ CD73+ tumors have lower IE CD8+ TILs compared to PDL1+/CD73- tumors suggests a role for CD73 in excluding IE TILs. Larger sample sets are needed to confirm these findings and to further explore any relationship with the tumor microenvironment. Our data suggests potential approaches to identify subsets of pts likely to benefit from immunotherapy targeting PDL1 and CD73.

	PDL1-/CD73-	PDL1+/CD73-	PDL1-/CD73+	PDL1+/CD73+
NSq (n=42)	48%	19%	19%	14%
UBC (n=50)	44%	24%	24%	8%
GE (n=50)	38%	30%	30%	2%
Total (n=142)	43%	25%	25%	8%

3080 Poster Session (Board #175), Mon, 8:00 AM-11:30 AM

Characterization of the T-cell receptor repertoire and immune microenvironment in patients with locoregionally advanced squamous cell carcinoma of the head and neck. *First Author: Vassiliki Saloura, University of Chicago Medical Center, Chicago, IL*

Background: Immunotherapy with checkpoint blockade was recently approved for patients with recurrent/metastatic SCCHN, however it has not been investigated in the curative-intent setting yet. In this study, we investigated the T-cell receptor repertoire and the immune microenvironment in tumor tissues of SCCHN patients with locoregionally advanced disease. **Methods:** T-cell receptor sequencing and polymerase chain reaction for immune-related genes of tumor tissues from 44 patients with locoregionally advanced SCCHN prior to treatment with definitive chemoradiotherapy were conducted. T-cell receptor clonality and the mRNA expression levels of immune-related genes were correlated with various clinicopathological parameters. **Results:** In patients with locoregionally advanced SCCHN, tumor infiltrating T-cells clonally expand and*GRZB* mRNA levels were associated significantly with longer progression-free survival (PFS) ($p = 0.003$) independent of HPV status, tumor and nodal stage. The TCR-β DI was significantly lower in HPV-negative compared to HPV-positive tumors ($p = 0.002$), signifying more clonal T-cell expansion in HPV-negative tumors. A higher percentage of HPV-negative tumors expressed HLA-A protein compared to HPV-positive tumors ($p = 0.049$), suggesting that the greater T-cell clonal expansion might be due to more robust antigen presentation by HPV-negative tumors. **Conclusions:** This study suggests the pre-existence of clonally expanded T-cells in patients with locoregionally advanced SCCHN prior to treatment, and provides rationale to introduce immunotherapy in the curative-intent setting. The association of high *GRZB* mRNA levels with favorable PFS independent of HPV-status, tumor and nodal stage supports that the pre-existence of an intrinsically inflamed microenvironment enhances chemoradiotherapy effects. Finally, in HPV-positive tumors, the T-cell infiltrate seemed to be more diverse which could be secondary to virally-induced defective expression of HLA class I molecules.

3081 Poster Session (Board #176), Mon, 8:00 AM-11:30 AM

Ensituximab (E) in patients (pts) with refractory metastatic colorectal cancer (mCRC): Results of a phase I/II clinical trial. *First Author: Richard D. Kim, H. Lee Moffitt Cancer Center, Tampa, FL*

Background: E is an investigational, novel, chimeric monoclonal IgG1 antibody derived from an immunogenic neoantigen with sequence homology to MUC5AC that is preferentially expressed with exquisite specificity to pancreatic cancer and CRC. Its mechanism of action is via antibody-dependent cellular cytotoxicity (ADCC). The efficacy and safety of E was evaluated in a single-arm, open-label, phase 1/2 clinical trial of adult pts with refractory mCRC. **Methods:** Pts were selected based on > 20% expression of tumor antigen, as measured by immunohistochemistry. Based on phase 1 results, E was administered 3 mg/kg IV every 2 weeks until unacceptable toxicity or disease progression. Primary endpoint was overall survival (OS). Serum cytokine levels were analyzed at baseline, day 4, and day 15. E-mediated ADCC of CD16 genotype V/V, V/F, and F/F pt PBMCs was measured with an IN-111 release assay using the E target-expressing ASPC-1 pancreatic cancer cell line. **Results:** Fifty-seven and 63 pts were evaluable for OS and safety, respectively. Median OS was significantly longer than historical control: 6.8 vs 5.0 months (mo); $p = 0.007$; 95% CI: 5.39,8.02. Three pts were alive at end of study (21, 21, and 24 mo); 21 pts survived ≥ 12 mo. Pts had a median of 4 prior therapies (range 2-9); 25% had received regorafenib. Forty-seven pts were evaluable by RECIST, and 20 (43%) had stable disease of target lesions at end of first course (day 57). E was well tolerated, with < 2% grade 3 and no grade 4 toxicities. There were no trends in serum cytokine and chemokine levels. Analysis of 56 samples (8 V/V, 26 V/F, 17 F/F, and 5 undetermined) showed that V/V PBMCs had significantly higher E-mediated ADCC than PBMCs harboring other genotypes. No correlation between CD16 polymorphism and pt outcome was observed. **Conclusions:** E demonstrated excellent tolerability and encouraging OS in this heavily pretreated population. Correlative in vitro data suggest that E can mediate higher levels of ADCC activity in individuals with a V/V versus other genotypes. The lack of correlation between CD16 polymorphism and pt outcomes in this study suggests that other immune-related factors (under investigation) may impact the efficacy of E in vivo. Clinical trial information: NCT01040000.

3082 Poster Session (Board #177), Mon, 8:00 AM-11:30 AM

First-in-human clinical trial with intratumoral BO-112 in solid malignancies: A novel immunotherapy based in double-stranded RNA (dsRNA). *First Author: Ivan Marquez Rodas, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Background: BO-112 is a double stranded synthetic RNA, formulated with the cationic carrier polyethyleneimine that preclinically improves its intracellular delivery and resistance towards nuclease degradation. In melanoma mouse models, systemic administration activates MDA-5 and NOXA, leading to anti-tumoral activity connected to a sustained and extended expression of IFN-response genes. Intratumoral (IT) delivery, seeking a safer and more focused enhancement of local and systemic antitumor effects has been tested in transplanted mouse models. The potential of its IT use as an immune-modulatory treatment, as well as its toxicity profile, is being analyzed in this first in human, proof of concept, clinical trial (NCT02828098). **Methods:** Four patients with malignant solid tumors and palpable cutaneous/subcutaneous or lymph node metastases >1 cm were treated with a single BO-112 dose of 0.6 mg/ml IT. Pre and post treatment biopsies from the injected metastatic lesion were obtained. Pharmacokinetics, serum cytokines and circulating immune cells were sequentially studied in pre and post treatment samples. **Results:** Patients did not experience relevant toxicity with the exception of a single episode of completely reversible grade 4 thrombocytopenia in one patient, attributed to the drug. BO-112 was not detectable in bloodstream following IT delivery. No changes in circulating cytokines were detected. Main immunobiological effects are summarized in the table. **Conclusions:** BO-112 has shown changes in tumoral immune cells in 1/4 patients, while in 3/4 induced both necrosis and changes in circulating immune cells. This ongoing trial will compile more safety data with repeated sequential administrations, escalated to higher doses of BO-112, and will thoroughly characterize its biological effects in humans with solid malignancies amenable to IT injection. Clinical trial information: NCT02828098.

Patient	Tumor	G3-4 AE	CD4/CD8 Infiltrate increase	Necrosis	Increased circulating immune cells
1	Melanoma	Thrombocytopenia	NA	NA	CD8, CD4reg, NK
2	Neuroendocrine	No	+	+	CD8, CD4, CD4reg, monocytes
3	Triple negative breast cancer	No	-	+	CD8, CD4, CD4reg, monocytes
4	Melanoma	No	-	+	CD4reg, monocytes, NK

3083 Poster Session (Board #178), Mon, 8:00 AM-11:30 AM

An open-label, multi-center phase I study of the safety and tolerability of the novel immunomodulatory agent PG545 in subjects with advanced solid tumors. *First Author: Keith Dredge, Zucero Therapeutics Pty. Ltd., Brisbane, Australia*

Background: PG545 (pixatimod, pINN) is a novel immunomodulatory agent which stimulates dendritic cells (DC) via TLR9/IL-12 pathway to activate natural killer (NK) cells. It also inhibits tumour-associated macrophages in cancer models. We report on safety, PK, PD, and antitumor activity of PG545 monotherapy. **Methods:** In this dose escalation (3+3 design) study, eligible pts (ECOG≤1) with advanced solid malignancies who failed standard therapies received PG545 once weekly as a 1-hour i.v. infusion until disease progression or discontinuation due to intolerability. The primary objective was determination of the maximum tolerated dose (MTD). Secondary objectives evaluated safety, antitumor activity based on RECIST (1.1) criteria, PK and PD (plasmacytoid DC & NKp46$^+$NK cells from PBMC, and plasma cytokines/chemokines). **Results:** The study recruited 23 subjects across four cohorts (25, 50, 100 & 150 mg). Three dose limiting toxicities (DLTs) - hypertension (2), epistaxis (1) - occurred in the 150 mg cohort, which was identified as a non-tolerated dose level. No DLTs occurred in the 100 mg cohort, which was identified as the MTD. Six SAEs were reported to be possibly or likely related to PG545 treatment. No RECIST 1.1 objective responses were reported; best response was prolonged stable disease up to 24 weeks (mCRC), with disease control rate in evaluable subjects of 38% (6/16) at eight weeks. Exposure ($AUC_{0\text{-}last}$) was proportional up to 100mg and mean half-life was 144 hours. At 50 and 100mg dose levels, two subjects in each cohort exhibited up to 4-fold increased numbers of NKp46$^+$NK cells, IFN-α-producing pDCs, and increases (up to 25-fold) in plasma IFN-γ, TNF-α, IP-10 and MCP-1. **Conclusions:** PG545 is well tolerated up to 100 mg once-weekly via i.v. infusion. Human exposure data at 50mg and 100mg reach exposures consistent with those required for preclinical efficacy. Preliminary PD data support the proposed mechanism of action, which represents a promising approach to improve the efficacy of existing therapies. These data, and the absence of toxicities associated with chemo- or immunotherapies, support the development of PG545 in combination clinical trials. Clinical trial information: NCT02042781.

3084 Poster Session (Board #179), Mon, 8:00 AM-11:30 AM

PEGylated human IL-10 (AM0010) in combination with pembrolizumab in anti-PD1 and CTLA-4 refractory melanoma. *First Author: Aung Naing, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Melanoma has a high response rate to anti-PD-1 alone. More than 50% of melanoma on anti-PD-1 progress within one year. IL-10 inhibits inflammation and stimulates the cytotoxicity and proliferation of tumor infiltrating CD8+ T cells at higher concentrations. IL-10 receptors and PD1 are induced on activated CD8 T cells, providing a mechanistic rationale for combining AM0010 and anti-PD1. AM0010 alone has established tolerability and anti-tumor activity in a phase 1 study. Objective responses were observed in 4 of 15 pts with RCC, one patient with uveal melanoma and cutaneous T cell lymphoma, each. **Methods:** 25 melanoma pts who had progressed on prior anti-CTLA4 and on prior anti-PD-1 containing regimen were treated with AM0010 (20mg/kg qd, SQ) and pembrolizumab (2mg/kg, q3wk IV). Patients had a median of 3.5 prior therapies (range 2-6) and a median of 2 prior immune therapies (range 1-6). Tumor responses were monitored following irRC. Immune responses were measured by analysis of serum cytokines, activation of blood derived T cells and peripheral T cell clonality. **Results:** AM0010 plus pembrolizumab was well tolerated. All treatment related adverse events (TrAE) were reversible. DLTs and SAEs leading to study discontinuation were not observed. G3/4 TrAEs were observed in 11 of 25 pts and included fatigue (8) thrombocytopenia (6), anemia (4), rash (1) and hypertriglyceridemia (1). There were no objective tumor responses. 9 of 20 evaluable pts had stable disease (DCR = 45%). As of Jan. 31 2017, the mPFS was 2.0 mo. and the mOS was not reached, with a mFU of 15.5 mos (range 10.0-18.4). AM0010 plus pembrolizumab increased Th1 cytokines as well as the number and proliferation of PD1+ Lag3+ activated CD8 T cells in the blood while reducing inflammatory cytokines and TGFb. A de-novo oligoclonal expansion of T cell clones in the blood and an increase of tumor infiltrating Granzyme+ PD1+ CD8+ T cells in tumor biopsies of treated patients was observed. **Conclusions:** AM0010 in combination with anti-PD1 is well-tolerated in refractory melanoma pts. The clinical activity and the observed CD8+ T cell activation may suggest to study AM0010 in combination with an anti-PD-1 in melanoma patients with less prior treatments. Clinical trial information: NCT02009449.

3085 Poster Session (Board #180), Mon, 8:00 AM-11:30 AM

LTX-315, an oncolytic peptide, to convert immunogenically 'cold' tumors to 'hot' in patients with advanced or metastatic tumours: Results from an ongoing phase I study. *First Author: James F. Spicer, King's College London, London, United Kingdom*

Background: Intratumoral LTX-315 disintegrates cytoplasmic organelles with release of tumor antigens in preclinical models accompanied by increase in tumor-infiltrating lymphocytes (TILs). LTX-315 induced complete regression in several rodent models, with systemic immune responses. LTX-315 is strongly synergistic preclinically with immune checkpoint inhibitors (ICI). We are conducting a phase 1 trial to evaluate LTX-315 in combination therapy. **Methods:** Patients with advanced metastatic solid tumours received injections of LTX-315 into a single accessible tumour over 6 weeks. Additional injections could be administered thereafter every 2 weeks. Biopsies of injected lesions were taken at baseline, and on treatment. **Results:** 28 have been enrolled to date, median age is 58 (range 32-80) and median prior treatments 2 (range 1-14). LTX-315 monotherapy was administered at doses of 2-7mg to a median of 1.8 tumour lesions (range 1-6) for a median of 9 weeks (range 1-33). In 24 patients all LTX-315-related adverse events were CTC grade 1 or 2, most commonly local erythema, flushing, pruritis and hypotension, most resolving within minutes of injection. Related grade 3 (3 patients) or 4 (1) allergic/anaphylaxis adverse event occurred and resolved without sequelae. Best response in 44 injected lesions in 20 evaluable patients included 2 complete responses, > 50% reduction in 5 tumours, and 20 stable (injected). Significant increases in TILs occurred in 67% (14 of 21) patients with biopsies of injected tumours available. Regression of distant non-injected tumour has been observed clinically on biopsy (abscopal effect). No irRC response in non-injected tumours has been observed in 16 evaluable patients. Stable disease (median duration 14 weeks) occurred in 50% of patients as best response (melanoma (4), sarcoma (3), breast (1)). **Conclusions:** This phase 1 study demonstrates that intratumoural LTX-315 has a manageable safety profile and induces increases in TILs in pre-treated patients. Partial and complete regression was seen in some injected tumours. Evaluation of LTX-315 in combination with ICIs in breast and melanoma is ongoing. Clinical trial information: NCT01986426.

3086 Poster Session (Board #181), Mon, 8:00 AM-11:30 AM

A phase I study of novel multi-HLA-binding peptides and a new combination of immune adjuvants against solid tumors. *First Author: Hiroto Matsui, Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University, Ube, Japan*

Background: Based on the exploratory analysis of our previous studies of peptide vaccine, we concluded that the combination of adjuvants hLAG-3Ig + Poly-ICLC is essential for controlling negative immune checkpoints and enhancing the induction of CTLs to overcome the traditional peptide studies. Another issue with peptide vaccines is human leukocyte antigen (HLA) restriction. Hence, we developed novel multi-HLA-binding peptides derived from the tumor antigens, HSP70 and GPC3, and confirmed the high expression in many types of cancer. **Methods:** For the identification of peptides, HSP70- and GPC3-derived peptides that have high binding affinity to each of HLA-A2402, 0201, and 0206 were selected as candidate peptides by a binding prediction system (NEC Corporation). We then identified priority candidate peptides by using a peptide-binding assay. Using peripheral mononuclear blood cells from cancer patients, CD8+ T lymphocytes were stimulated with the candidate peptides, and an enzyme-linked immunospot assay was performed. Finally, we identified HSP70- and GPC3-peptide. In this phase I study of a novel peptide cancer vaccine for metastatic solid cancer, primary objective was to evaluate its safety and toxicity. Secondary objective was to examine the immune and clinical response, and also to determine the recommendable dose. This study used a three-tiered dose-escalation strategy with 3 patients' cohorts. In addition to the 3 scheduled cases, 3 more cases were added and 6 cases were enrolled at the recommended dose. **Results:** Twelve HLA-A*24:02-, 02:01-, and 02:06-matched patients (esophagus, 3; colon, 4; liver, 3; pancreas, 1; stomach, 1) were treated in this study. No severe adverse effects related to the treatment were encountered. Peptide-specific CTL induction with HSP70 and GPC3 was observed in 10 and 11 patients, respectively. We observed decreased tumor marker expression in 6 cases, and disease control was observed in f5 patients (4, 3, 8, 2, 2 months, respectively). **Conclusions:** The combination cancer vaccine therapy using multi-HLA-restricted peptides and hLAG-3Ig + Poly-ICLC was safe and effective for treating solid tumors; it therefore warrants further clinical studies. Clinical trial information: UMIN000020440.

3087 Poster Session (Board #182), Mon, 8:00 AM-11:30 AM

Results of a first-in-human phase I study of INVAC-1, an optimized plasmid DNA encoding an inactive form of human telomerase reverse transcriptase (hTERT), in patients with advanced solid tumors. *First Author: Luis Teixeira, Service d'Oncologie Médicale, Hôpital Saint-Louis, APHP, Paris Diderot University, Paris, France*

Background: INVAC-1 is an optimized plasmid encoding an inactive form of human telomerase reverse transcriptase (hTERT). hTERT is a prototype of shared tumor antigen expressed in more than 85% of human tumors. Telomerase activation is associated with maintenance of telomere length and accounts for the unlimited proliferative capacity of cancer cells. In preclinical models, INVAC-1 triggered Th1-polarized hTERT-specific $CD8^+$ and $CD4^+$T-cell immune responses and anti-tumor effects. Here, we report clinical and pharmacodynamics results of the first clinical study with INVAC-1 as a single agent in solid tumors. **Methods:** A 3+3 design phase 1 First in Human study evaluating INVAC-1 given monthly for 3 cycles using electroporation-based intra-dermal (ID) injection was conducted. Primary objectives included safety, tolerability and dose limiting toxicities to identify the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Secondary objectives included immune response and anti-tumor activity. **Results:** 20 patients (pts) with refractory/progressive solid tumors were enrolled in two centers. 3 escalating doses were studied: 100 μg (3 pts), 400 μg (3 pts) and 800 μg (14 pts). At 3-month data cut-off, no dose limiting toxicities or treatment related SAEs have been reported; no MTD was defined. The most common treatment-related adverse events were grade 1 or 2: asthenia and local reaction at injection site. 12 pts experienced stable disease and clinical benefit. For 10 pts, the treatment was extended beyond the per-protocol 3-month duration, up to nine months for 2 pts. IFN-g polarized anti-hTERT immune responses were detected in 55% of pts, in response to INVAC-1 treatment. **Conclusions:** Results from this study indicate that INVAC-1 ID was safe, well tolerated and strongly immunogenic at the doses and schedule tested. Early anti-tumor activity has been observed. The RP2D of INVAC-1 is therefore a monthly ID injection of 800 μg. These results encourage a future evaluation of INVAC-1 is solid tumors, as well as in hematologic malignancies, either as monotherapy or in combination with various immunotherapeutic drugs. Clinical trial information: NCT02301754.

3088 Poster Session (Board #183), Mon, 8:00 AM-11:30 AM

Subgroup efficacy evaluation of the AE37 HER2 vaccine in breast cancer patients in the adjuvant setting. *First Author: Kaitlin M. Peace, San Antonio Military Medical Center, San Antonio, TX*

Background: AE37 is a Ii-Key hybrid of the HER2 peptide AE36 ($HER2_{776\text{-}790}$), which stimulates peptide-specific T cells. We have completed the active phase of a prospective, randomized, multi-center, phase II trial of the AE37 vaccine in the adjuvant setting. The primary analysis, performed after a median follow up (f/u) of 25 months (mo), did not show a significant difference in disease free survival (DFS) between vaccinated and control patients (pts). However, demonstrating the efficacy of cancer vaccines may require more time than other therapies, especially in malignancies with relatively late recurrences like breast cancer. Here, we present updated efficacy data after extended f/u in subgroups of pts stratified by clinicopathologic characteristics. **Methods:** Clinically disease-free, node positive or high-risk node negative pts with any level of HER2 expression were randomized to receive AE37 + GM-CSF (VG) or GM-CSF alone (CG) following standard of care therapy. Pts received 6 monthly intradermal inoculations during the primary vaccine series (PVS) followed by 4 boosters administered every 6 mo. Kaplan Meier and log rank analyses were performed from the time of the first inoculation in pts who completed at least the PVS, according to stage, node status, tumor size, HER2 expression and ER/PR status. **Results:** There were no clinicopathologic differences between groups in the 298 enrolled pts (VG = 153, CG = 145). The vaccine is safe and well tolerated. After a median f/u of 55 mo, there was a trend toward improved DFS in the VG among stage IIB/III pts (VG, n = 73, DFS 82% vs CG, n = 61, 67%, HR = 0.48, p = 0.06) and those with low HER2 expression (HER2 LE, VG, n = 68, 89% vs CG, n = 66, 51%, HR = 0.47, p = 0.1). Improved DFS in the VG was documented in patients with both stage IIB/III disease and HER2 LE (VG, n = 39, 90% vs CG, n = 38, 32%, HR 0.3, p = 0.02) and triple negative (TNBC) pts (VG, n = 21, 89% vs CG, n = 21, 0%, HR 0.26, p = 0.05). **Conclusions:** The AE37 vaccine is safe and well tolerated and has statistically significant efficacy in stage IIB/III pts with HER2 LE and in TNBC pts. This justifies further evaluation in a phase III study enrolling stage IIb/III pts not eligible for trastuzumab treatment and the very high risk TNBC group. Clinical trial information: NCT00524277.

3089 Poster Session (Board #184), Mon, 8:00 AM-11:30 AM

Association of autologous AdHER2 dendritic cell vaccination with antitumor activity and number of circulating tumor cells. *First Author: Lauren Virginia Wood, Vaccine Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: We achieved cure of large established tumors in syngeneic BALB/c mice using an adenoviral vector vaccine expressing rodent HER2 extracellular (EC) and transmembrane (TM) domains mediated by the induction of anti-HER2 antibodies. We report clinical translation utilizing an autologous adenoviral- transduced dendritic cell (DC) vaccine expressing human HER2 EC and TM domains (AdHER2ECTM) in adults with advanced metastatic tumors with 1-3+ HER2 expression. **Methods:** In this two-part phase I study (NCT01730118) subjects with HER2+ metastatic solid tumors naïve to HER2-targeted therapies (Part 1) or HER2+ treatment-experienced breast cancer (Part 2) received 5 doses of vaccine at Weeks 0, 4, 8, 16 and 24. Part 1 dose escalation involved 3 cohorts of 6 patients utilizing $5x10^6$, $10x10^6$ and $20x10^6$ viable DCs per dose, respectively. With no DLTs or evidence of cardiac toxicity, dose escalation to $40x10^6$ viable DCs per dose was allowed in the Part 1 Expansion Cohort and Part 2 treatment was begun at a starting dose of $20x10^6$ viable DCs per vaccine. Adjuvant muscle-invasive bladder cancer patients were allowed to enroll with safety documented out to 12 weeks in > 10 treated patients. Re-staging was assessed using immune-related response criteria (irRC). Remaining study accrual: Part 1 (N = 9), Part 2 (N = 24). **Results:** A total of 27 cancer patients (7 colon, 6 breast, 5 ovarian, 3 bladder, 6 other) have received > 2 vaccine doses (median 4): 19F, 8M, median age 60 yrs, median 3 prior treatment regimens (range 1-11); HER2 IHC 1+ N = 6, 2+ N = 9, 3+ N = 12. Of metastatic patients receiving $10x10^6$viable DCs per dose or higher, 7 of 19 (37%) had evidence of response by irRC: 1 CR (ongoing at 100 weeks), 1 PR (-71% lasting 44 weeks) and 5 SD (median duration 24 weeks, range 8 to 48 weeks). Two adjuvant bladder cancer patients remain without disease at 100 weeks. Adverse events were limited to local injection site reactions < G2. Of patients with paired baseline samples, 40% (8/20), 83% (5/6) and 100% (2/2) exhibited decreases in circulating tumor cells at 12, 28 and 48 weeks, respectively. **Conclusions:** AdHER2 DC vaccination is safe and is associated with evidence of clinical benefit and anti-tumor activity. Clinical trial information: NCT01730118.

3090 Poster Session (Board #185), Mon, 8:00 AM-11:30 AM

Association of CMB305 or LV305-induced and baseline anti-NY-ESO-1 immunity with survival in recurrent cancer patients. *First Author: Seth Pollack, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The correlation of immune response (IR) and clinical benefit in patients (pts) who receive active immunotherapy remains controversial. CMB305 is an active immunotherapy designed to generate and expand anti-NY-ESO-1 T cells, consisting of LV305 (a DC targeting lentiviral vector encoding NY-ESO-1) and a boost (NY-ESO-1 recombinant protein plus GLA-SE, a TLR-4 agonist). Phase 1 studies of LV305 and CMB305 evaluated the IR and survival of pts with NY-ESO-1 positive tumors. **Methods:** 62 pts with recurrent NY-ESO-1 expressing (by IHC) solid tumors were enrolled in 2 Phase 1 trials (31 pts each: 43 sarcomas, 12 ovarian, 4 melanomas, and 3 NSCLC). Peripheral blood was assessed pre and post therapy for anti-NY-ESO-1 T cell responses (IFNγ ELISPOT) and antibodies (Ab) (ELISA) (n = 62), TCR-β CDR3 repertoire and conserved (public) TCR (n = 28), and antigen spreading (ELISA, ELISPOT) (n = 23). Relationship between progression-free survival (PFS), overall survival (OS) and up to 15 biomarkers were analyzed by the Kaplan-Meier method. **Results:** Preexisting anti-NY-ESO-1 T cells and Ab were identified in 34% and 40% of pts. LV305 and CMB305 induced (de novo or increased) anti-NY-ESO-1 T-cells in 51% and 65% pts, and anti-NY-ESO-1 Ab responses in 13% and 68% pts, respectively. LV305 and CMB305 induced antigen spreading in 17% and 36% pts. TCR clonality increased after CMB305 as compared to LV305. The TCRβ-CDR3 amino acid sequences of three NY-ESO-1 specific TCR clones in a patient with a > 2-year response were fully conserved in 20/28 patients. Biomarkers showing the strongest association with OS and PFS were pre-existing anti-NY-ESO-1 T-cell response and Ab, integrated IR (T cells and antibodies), and NY-ESO-1 expression level. Presence of public TCRs was associated with longer survival, particularly in pts with high (> 50%) NY-ESO-1 expression. **Conclusions:** While LV305 and CMB305 are both immunogenic, CMB305 resulted in a stronger and broader integrated IR, including antigen spreading. The three identified survival variables, preexisting and treatment-induced NY-ESO-1 IR and the presence of public TCRs, warrant validation in randomized studies of CMB305.

TPS3091 Poster Session (Board #186a), Mon, 8:00 AM-11:30 AM

A phase I study of the bispecific antibody T-cell engager GBR 1302 in subjects with HER2-positive cancers. *First Author: Martin Wermke, Universitatsklinikum Carl Gustav Carus an der TU Dresden, Dresden, Germany*

Background: GBR 1302, a bispecific antibody based on Glenmark's BEAT platform, is designed to recruit cytotoxic T-cells (independent of their specificity) to HER2-positive cancer cells where they are activated by the CD3e-specific domain of the molecule. Preclinically, GBR 1302 has demonstrated potent killing of HER2-positive human cancer cells (HER2 3+ or 2+ by IHC HercepTest), as well as growth suppression of the trastuzumab-resistant cell line JIMT-1. In contrast, the GBR 1302 concentration required to kill primary cardiomyocytes with normal HER2 levels was up to 1000 times greater than the concentration needed to kill HER2 3+ tumor cell lines. This study will determine safety and tolerability of GBR 1302 monotherapy in subjects with HER2-positive cancers. **Methods:** Part 1 (dose-finding) of this ongoing phase 1 study (NCT02829372) is enrolling adults with progressing HER2-positive solid tumors for which no standard treatment is available. Intravenous GBR 1302 is given every 2 weeks in 28-day cycles at escalating doses (Table). Each of the first 4 cohorts includes a single subject; subsequent cohorts enroll subjects using a standard 3+3 design. Primary endpoints are: maximum tolerated dose (MTD) of GBR 1302; and relationship of GBR 1302 with the incidence, nature, and intensity of adverse events. After Cycle 1, subjects continue GBR 1302 treatment until disease progression or unacceptable toxicity. Part 2 (expansion) will treat subjects at the MTD to further evaluate anti-tumor activity, as well as safety and pharmacokinetics. Due to the known cardiotoxic potential of classic HER2-targeting strategies, this study incorporates a rigorous serological and echocardiographic surveillance schedule. The effects of GBR 1302 on the adaptive immune system will also be studied at cellular and serological levels in translational research. Clinical trial information: NCT02829372.

GBR 1302 dose-escalation schedule.

	Cycle 1 (28 days)		Subsequent Cycles (28 days per cycle)	
Cohort	Day 1 Dose, ng/kg	Day 15 Dose, ng/kg	Day 1 Dose, ng/kg	Day 15 Dose, ng/kg
Single subject				
1	1	3	3	3
2	3	10	10	10
3	10	30	30	30
4	30	60	60	60
3+3 design				
5	60	100	100	100
6	100	200	200	200
7	200	400	400	400
8	400	600	600	600
9	600	800	800	800
10	800	1000	1000	1000

TPS3092 Poster Session (Board #186b), Mon, 8:00 AM-11:30 AM

Phase 1 study of intraperitoneal infusion of autologous monocytes with peginterferon alfa-2b and interferon gamma-1b in women with recurrent or refractory ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. *First Author: Ana Tablante Nunes, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Monocytes can differentiate into classic M1 macrophages inhibiting tumor proliferation and promoting natural killer (NK) cell differentiation. We previously demonstrated that the combination of human monocytes, human interferon alfa-2b (IFNα-2b), and interferon gamma-1b (IFNγ 1b) act synergistically against tumor cells *in vitro* and in mouse models, providing a long and durable response. Additionally, monocytes, IFNα and IFNγ have been individually shown in early phase clinical trials to be safely administered intraperitoneally. As ovarian cancer is largely confined to the peritoneal cavity, it is likely that the administration of IFNs and monocytes intraperitoneally will create a strong anti-tumor environment and can overcome the immunosuppressive environment of epithelial ovarian cancer. We hypothesize that the monocyte and interferon administration will be tolerable to women with relapsed ovarian cancer. **Methods:** A Phase 1 single arm study to determine the maximum tolerated dose of intraperitoneal monocytes and pegylated IFNα-2b and IFNγ-1b is currently enrolling patients with recurrent or refractory ovarian cancer, fallopian tube cancer or primary peritoneal cancer without standard therapy options. Autologous monocytes obtained through apheresis 24 hours prior will be mixed with pegylated IFNα-2b and IFNγ-1b in a 3 + 3 dose escalation and administered intraperitoneally once every 28 days. **Results:** As of February 2017 we are enrolling our first cohort of patients and are evaluating for dose limiting toxicities. **Conclusions:** This is a novel therapy that if successful, may be efficacious alone or used to create a backbone on which to add novel agents such as SMAC mimetics or PD-L1 blockade, in order to increase immune-mediated killing of ovarian cancer. Clinical trial information: NCT 02948426.

TPS3093 Poster Session (Board #187a), Mon, 8:00 AM-11:30 AM

A NKG2D-based CAR-T therapy in a multinational phase I dose escalation and expansion study targeting multiple solid and hematologic tumor types. *First Author: Bikash Verma, Celyad, Boston, MA*

Background: Chimeric Antigen Receptor (CAR)-T therapy has potentially serious limitations related to target antigen loss, toxicity due to pre-conditioning regimen, and lack of activity in many tumor types. To overcome these limitations, we have developed a novel CAR-T, called NKR-2, incorporating the full-length human natural killer receptor NKG2D fused with the human CD3 zeta signaling domain. When expressed in T-cells, the naturally-expressed DAP10 provides co-stimulatory signals to NKR-2 to produce cytokines and selectively target tumor cells upon recognition of up to 8 different stress-induced NKG2D ligands expressed in many solid and hematologic malignancies. In preclinical studies, NKR-2 demonstrated long-term anti-tumor activity towards a breadth of tumor indications, in the absence of pre-conditioning, whilst simultaneously targeting tumor cells and cells from the local tumor neo-vasculature and suppressive immune environment. In our recently completed First-in-Human Phase 1 study (NCT02203825) in hematologic cancers, a single administration of autologous NKR-2 was safe with initial signs of clinical benefit. **Methods:** Exploiting the multiple ligand targeting capability and unique mode of action of NKR-2, the THINK trial (THerapeutic Immunotherapy with NKR-2) is an open-label Phase I study that will assess the safety and clinical activity of multiple infusion NKR-2 treatment (every 2 weeks x 3 infusions) in relapse/refractory patients with metastatic or locally advanced CRC, urothelial carcinoma, TNBC, pancreatic cancer, recurrent epithelial ovarian and fallopian tube carcinoma, AML/MDS and MM, post standard treatment. The study contains two consecutive segments. The dose escalation segment will enroll 18 patients in two separate hematologic and solid malignancy arms, and will evaluate 3 dose levels of NKR-2 ($3x10^8$, $1x10^9$ and $3x10^9$ per injection) following a 3+3 design. The expansion segment will then enroll 96 additional patients in 7 separate cohorts for each indication with 3 steps of statistical analysis (overall futility, cohort futility and final evaluation). The study is open for recruitment in both EU and US. Clinical trial information: NCT03018405.

TPS3094 Poster Session (Board #187b), Mon, 8:00 AM-11:30 AM

A phase I/IIa, open label, clinical trial evaluating the safety and efficacy of autologous T cells expressing enhanced TCRs specific for NY-ESO-1 in patients with recurrent or treatment refractory ovarian cancer (NCT01567891). *First Author: Kunle Odunsi, Roswell Park Cancer Institute, Buffalo, NY*

Background: Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (~80%) and is the leading cause of death from gynecologic cancer in the US. Due to lack of effective screening strategies, the majority (63%) of patients are diagnosed with ovarian cancer at advanced stages. New therapies are needed to address the unmet medical need of patients with ovarian cancer. 11-40% of ovarian cancers express NY-ESO-1 cancer testis/antigen. This study is evaluating affinity enhanced autologous NY-ESO-1^{c259}T cells recognizing an NY-ESO-1 derived peptide complexed with HLA-A*02 in ovarian cancer. **Methods:** This single arm, open label clinical trial is evaluating safety and tolerability, antitumor activity (response rate by RECIST v1.1, progression free survival, overall survival, duration of response), and translational research endpoints. The study evaluates two lymphodepleting regimens: cyclophosphamide (enrolment completed; n = 7) and cyclophosphamide plus fludarabine (at least 10 subjects to be enrolled). Subjects must be ≥ 18 years old; HLA-A*02:01, *02:05, or *02:06 positive; have recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma with refractory or platinum-resistant disease expressing NY-ESO-1 by IHC; have measurable disease; have ECOG status 0 or 1; and have adequate organ function. Following apheresis, the T cells are isolated and expanded with CD3/CD28 beads, transduced with a lentiviral vector containing the NY-ESO-1^{c259} TCR, and $1 - 6 \times 10^9$ transduced T cells are infused intravenously on Day 0 after lymphodepletion with fludarabine 30 mg/m^2/day and cyclophosphamide 600 mg/m^2/day on days -7 to -5. Response is assessed at weeks 4, 8, 12 and 24, and then every 3 months until confirmation of disease progression. Clinical trial information: NCT01567891.

TPS3095 Poster Session (Board #188a), Mon, 8:00 AM-11:30 AM

A phase 1b/2 study of CD30-specific chimeric antigen receptor T-cell (CAR-T) therapy in combination with bendamustine in patients with CD30+ Hodgkin and non-Hodgkin lymphoma. *First Author: Steven I. Park, Levine Cancer Institute, Charlotte, NC*

Background: CAR-T therapy has emerged as one of the most promising therapeutic approaches for lymphoma. CD30 antigen is expressed on virtually all Hodgkin (HL) and various subtypes of non-Hodgkin lymphoma (NHL). HL and NHL are both sensitive to the cellular immune response and antibody-directed therapy, which makes CD30 an excellent target for CAR-Ts. In the "first-in-human" clinical trial of CD30.CAR-Ts, the dose of 2×10^8 CD30.CAR-Ts/m^2 was found to be safe; however, no conditioning therapy was given prior to CD30.CAR-T infusion and the expansion of CAR-Ts was thus limited. In the current study, we have further developed the CD30.CAR-T-based therapy by combining it with bendamustine. We hypothesized that bendamustine may improve therapeutic efficacy of CD30.CAR-Ts by causing sufficient depletion of endogenous immune cells to facilitate the expansion and persistence of CAR-Ts *in vivo*. **Methods:** In this phase 1b/2 clinical study, patients with CD30+ HL or NHL receive bendamustine followed by CD30.CAR-Ts (NCT02690545). The primary objective is to establish the safety of CD30.CAR-Ts in combination with bendamustine. Secondary objectives include estimation of 2-year overall and progression-free survival rates. Patients receive bendamustine (90 mg/m^2 on days 1 and 2) followed by CD30.CAR-Ts within 1 to 4 days of lymphodepletion. The maximal tolerated dose is determined based on 3 + 3 design for dose escalation starting at 1×10^8 CD30.CAR-Ts/m^2. If the first 3 enrolled subjects do not experience a DLT within 6 weeks of the cell infusion, the number of cells for the infusion is increased to 2 x 10^8/m^2. Once the number of cells for infusion is established, up to 25 subjects will be enrolled in the Phase 2 portion of the study to further establish the safety and efficacy of this treatment regimen. Response will be assessed at 6 weeks after CD30.CAR-Ts infusion, and a second CD30.CAR-Ts infusion equal to or lower than the dose may be administered to patients with partial response or stable disease. Patient's peripheral blood samples will be evaluated at various time points to monitor safety, function, and persistence of transduced T-cells. Clinical trial information: NCT02690545.

TPS3096 Poster Session (Board #188b), Mon, 8:00 AM-11:30 AM

Two phase I/II open label clinical trials evaluating the safety and efficacy of autologous T cells expressing enhanced TCRs specific for NY-ESO-1 or MAGE-A10 in subjects with stage IIIb or stage IV non-small cell lung cancer (NCT02588612/NCT02592577). *First Author: Ben C. Creelan, Moffitt Cancer Center, Tampa, FL*

Background: Non-small cell lung cancer (NSCLC) accounts for 84% of lung cancer. Survival has recently been impacted by molecularly targeted therapies and checkpoint inhibitors (CPI), and the promising CPI results implicate a role for the immune system in NSCLC. 10-40% of NSCLC express NY-ESO-1 or MAGE-A10 cancer/testis antigens. These studies will evaluate the safety and antitumor activity of genetically engineered affinity enhanced TCRs (NY-ESO-1^{c259}T or MAGE-$A10^{c796}$T) directed towards a NYESO-1 or MAGE-A10 derived peptides complexed with HLA-A*02. In addition, correlative studies to evaluate persistence, phenotype, functionality of engineered T cells, mechanisms of resistance and antigen spreading will be performed. **Methods:** Patients (pt) are screened (NCT02636855) to identify those who have the relevant HLA-A*02 alleles and NY-ESO-1 or MAGE-A10 tumor expression. For entry into either treatment protocol, pt must have Stage IIIb or IV NSCLC, have failed at least one platinum-containing regimen (may have received CPIs), have measurable disease, ECOG 0-1, adequate organ function, and be without brain metastases, history of severe autoimmune disease or current uncontrolled illness. Following apheresis, T cells are isolated and expanded with CD3/CD28 beads, transduced with a lentiviral vector containing the NY-ESO-1^{c259}T or MAGE-$A10^{c795}$ TCR, and infused into the pt following lymphodepleting chemotherapy with fludarabine and cyclophosphamide. The NY-ESO-1^{c259}T study is a 10 pt study utilizing a dose of 1-6 x 10^9 transduced T cells. The MAGE-$A10^{c796}$T first-in-human study is a modified 3+3 design in up to 28 pt with escalating doses of 0.1, 1.0 and 1-6 x 10^9 transduced T cells, with staggered treatments to allow for safety review; dose escalation will be guided by the DLT observed and by safety review committee guidance. Response to treatment will be assessed by RECIST v1.1 at weeks 4, 8, 16, 24, every 3 months (for 2 yr) and every 6 months until disease progression. Clinical trial information: NCT02588612/NCT02592577.

TPS3097 Poster Session (Board #189a), Mon, 8:00 AM-11:30 AM

A pilot study of NY-ESO-1^{c259} T cells in subjects with advanced myxoid/round cell liposarcoma (NCT02992743). *First Author: Sandra P. D'Angelo, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Myxoid/round cell liposarcomas (MRCLS) account for 6-10% of soft tissue sarcomas. Although a chemosensitive tumor, metastatic MRCLS has a poor prognosis and is inevitably fatal. More effective, durable and less toxic therapies are needed. NY-ESO-1 is a cancer/testis antigen that is expressed in 80-90% of MRCLS tumors. This study will evaluate the safety and efficacy of genetically engineered affinity enhanced autologous NY-ESO-1^{c259}T cells recognizing an NY-ESO-1 derived peptide complexed with HLA-A*02 in MRCLS. **Methods:** This open label phase I/II non-randomized pilot study will evaluate efficacy (overall response rate by RECIST v1.1, time to response, duration of response, progression free survival, overall survival), safety, and translational research endpoints. Patients must meet these criteria: ≥ 18 yrs old; HLA-A*02:01, *02:05 or *02:06 positive; have advanced (metastatic or inoperable) MRCLS expressing NY-ESO-1 at 2+/3+ intensity in ≥30% of tumor cells by IHC; measurable disease; prior systemic anthracycline therapy; have ECOG status 0 or 1; and adequate organ function. Initially, ten patients are planned to be enrolled, with potential to enroll an additional 5 patients. Patients who do not receive the minimum cell dose or who do not receive the T-cell infusion may be replaced. Following apheresis, the T cells are isolated and expanded with CD3/CD28 beads, transduced with a lentiviral vector containing the NY-ESO-1c259 TCR, and 1– 8 $\times$ 10^9 transduced T-cells are infused intravenously on Day 1 after lymphodepletion with fludarabine 30 mg/m^2/day and cyclophosphamide 600 mg/m^2/day on days -7 to -5. Response is assessed at 4, 8, 12 and 24 weeks, and then every 3 months until confirmation of progression of disease. On study tumor biopsies and blood samples will be evaluated to compare the pre- and post-T cell infusion immune profile for association with treatment outcome. Clinical trial information: NCT02992743.

TPS3098 Poster Session (Board #189b), Mon, 8:00 AM-11:30 AM

A phase I single arm, open label clinical trial evaluating safety of MAGE-$A10^{c796}$T in subjects with advanced or metastatic head and neck, melanoma, or urothelial tumors (NCT02989064). *First Author: David S. Hong, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MAGE-A10 is a cancer/testis antigen that has been identified in 42, 26 and 17% of urothelial, melanoma and head and neck tumors, respectively. This study will evaluate the safety and antitumor activity of genetically engineered affinity enhanced autologous MAGE-$A10^{c796}$T cells directed towards a MAGE-A10 peptide expressed on tumors in the context of HLA *02:01 and/or *02:06. **Methods:** This first-in-human T cell dose escalation study utilizes a modified 3+3 design to evaluate safety, including dose limiting toxicities (DLT). Secondary objectives include anti-tumor activity (overall response, duration of response, time to response, PFS, OS) and translational research assessments. Patients are screened under a separate protocol (NCT02636855). Those who are HLA*02:01 and/or *02:06 positive and have inoperable or metastatic (advanced) urothelial cancer, melanoma, or squamous cell head and neck tumors with MAGE-A10 expression and meet all other entry criteria are eligible for treatment. Patients must have received standard of care therapies and have progressive disease. Following apheresis, the T cells are isolated and expanded with CD3/CD28 beads, transduced with a lentiviral vector containing the MAGE-$A10^{c796}$ TCR, and infused into the subject (Day 1) after receiving lymphodepleting chemotherapy (fludarabine 30 mg/m^2/day and cyclophosphamide 600 mg/m^2/day, on days -7, -6 and -5). The DLT observation period will be during the first 30 days following the infusion of MAGE-$A10^{c796}$T for each patient in all groups. Up to 10 patients will be enrolled at the target dose. Disease assessments will be conducted at week 6, 12, 18 and 24, and then every 3 months until confirmation of disease progression. On study tumor biopsies and blood samples will be evaluated to compare the pre- and post-T cell infusion immune profile for association with treatment outcome. Clinical trial information: NCT02989064.

Group	Number of Subjects	Transduced cells
1	3-6	$0.1x10^9$ (±20%) transduced cells
2	3 - 6	$1x10^9$ (±20%) transduced cells
3	3 -6	$5x10^9$ (range: >1.2 - $6x10^9$) transduced cells

TPS3099 Poster Session (Board #190a), Mon, 8:00 AM-11:30 AM

Phase 1 trial of CA-170, a novel oral small molecule dual inhibitor of immune checkpoints PD-1 and VISTA, in patients (pts) with advanced solid tumor or lymphomas. *First Author: James J. Lee, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: Programmed-death 1 (PD-1) and V-domain Ig suppressor of T-cell activation (VISTA) are independent immune checkpoints that negatively regulate T-cell function and are implicated in various malignancies. Preclinical studies have demonstrated that dual blockade of these pathways is synergistic. CA-170 is a first-in-class oral small molecule that directly targets both PD-1/PD-L1 and VISTA pathways and has shown anti-tumor activity in multiple preclinical models. **Methods:** The dose escalation phase has a target enrollment of 50 pts with advanced solid tumors or lymphomas onto escalating doses; the first four single-pt cohorts are accelerated titration but then switch to 3+3 design. The dose expansion phase has a target enrollment of 250 pts with select tumor types known to be responsive to anti-PD-1/L1 inhibitors and/or known to express PD-L1 or VISTA. Key eligibility criteria include: age $\geq$ 18 years, ECOG $\leq$1, adequate organ function, and ineligible for/did not respond to standard therapy including anti-PD-1/L1 inhibitors, where available. Primary objectives of this first-in-human study: safety, maximum tolerated dose, and recommended phase 2 dose. Secondary objectives: pharmacokinetics (PK) and anti-tumor activity. Exploratory endpoints: biomarkers and pharmacodynamic (PD) effects, which include changes in immune cell and peripheral cytokine populations in tumor (IHC/mRNA) and blood (flow cytometry/mRNA). Oral CA-170 is administered once daily in 21-day cycles. Response will be evaluated every other cycle per RECIST (v1.1) and Immune-related Response Criteria or by Cheson criteria (2007). Patients who discontinue treatment for reasons other than progressive disease will be followed for progression-free survival. Serial plasma, blood, and tumor samples will be collected for PK and PD evaluation. Clinical trial identifier: Clinical trial information: NCT02812875.

TPS3100 Poster Session (Board #190b), Mon, 8:00 AM-11:30 AM

A phase 1 study to evaluate the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and antitumor activity of the OX40 agonist MEDI0562 in combination with tremelimumab or durvalumab in adult aubjects with advanced solid tumors. *First Author: Brendan D. Curti, Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR*

Background: Recent advances in treatment of solid tumors include single or combined use of monoclonal antibodies (mAbs) against the immune checkpoints CTLA-4 or PD-1/PD-L1 that can reactivate antitumor cytotoxic tumor-infiltrating lymphocytes (TILs) and significantly improve OS (Menon S, et al. *Cancers (Basel).* 2016;8:E106.) (Antonia S, et al. Lancet Oncol. 2016; 17:299-308). Activation of TILs via the costimulatory OX40 (CD134) molecule, may offer an alternative and non-redundant pathway for increasing antitumor immunity. OX40 costimulation promotes effector T cell expansion and longevity, overcomes regulatory T cell suppression and provides survival benefit in animal models of tumor challenge (Linch SN, et al. *Front Oncol.* 2015;5:34). MEDI0562 is an investigational, humanized IgG1κ anti-OX40 mAb that triggers OX40 signaling. Coadministration of an OX40 agonist and either a CTLA-4 or PD-1/PD-L1 pathway inhibitor may promote synergistic effects against certain solid tumors and may be tolerable administered in combination. **Methods:** A Phase 1, multicenter, open-label study (NCT02705482) is underway to evaluate safety (primary endpoint), pharmacokinetics, pharmacodynamics, immunogenicity and antitumor activity (secondary endpoints) of MEDI0562 in combination with either anti-PD-L1 mAb durvalumab or anti-CTLA-4 mAb tremelimumab in adult subjects with previously treated advanced solid tumors. Subjects with primary CNS tumors and hematologic malignancies are excluded. The study includes a dose escalation and expansion phase, with 2 treatment arms in each: MEDI0562/durvalumab combination (Arm A) and MEDI0562/tremelimumab combination (Arm B). Safety assessments include AEs, serious AEs, dose-limiting toxicities, abnormal laboratory parameters, vital signs, and electrocardiogram results. Antitumor efficacy will be assessed as OR, disease control, duration of response, PFS, and OS using RECIST Version 1.1. Subjects will remain on treatment until unacceptable toxicity, progressive disease or other reasons for discontinuation. Clinical trial information: NCT02705482.

TPS3101 Poster Session (Board #191a), Mon, 8:00 AM-11:30 AM

A phase 1 dose-escalation trial of intratumoral TTI-621, a novel immune checkpoint inhibitor targeting CD47, in subjects with relapsed or refractory percutaneously-accessible solid tumors and mycosis fungoides. *First Author: John A. Thompson, University of Washington Seattle Cancer Care Alliance, Seattle, WA*

Background: CD47 is an immune checkpoint that binds to signal regulatory protein alpha (SIRPα) and delivers a "do not eat" signal to suppress macrophage phagocytosis. Tumor cells frequently overexpress CD47 and exploit this pathway to evade macrophage-mediated destruction. CD47 blockade promotes both innate (macrophage phagocytosis) and adaptive immunity (T cell responses). TTI-621 (SIRPαFc) is an immune checkpoint inhibitor designed to bind human CD47 and block the "do not eat" signal. The IgG1 region of TTI-621 engages Fcγ receptors on macrophages, converting the inhibitory signal to one that activates, thereby enhancing phagocytosis, and antitumor activity. A Phase 1 study is ongoing to evaluate the safety/tolerability and preliminary efficacy of IV administered TTI-621 in subjects with relapsed/refractory hematologic malignancies. It is hypothesized that employing direct intratumoral injections will result in very high local target engagement, promoting the development of innate and adaptive immune responses. **Methods:** A Phase 1 multicenter, open-label study was initiated to characterize the safety and tolerability of delivering TTI-621 directly into cancer lesions to achieve high local CD47 engagement to increase phagocytosis of tumor cells (NCT02890368). Subjects are being enrolled in sequential cohorts that gradually increase in dose and dosing frequency to characterize the feasibility of intratumoral TTI-621 injections and their safety, PK, pharmacodynamics, and preliminary antitumor activity. Eligible subjects are adults with relapsed or refractory percutaneously-accessible solid tumors or mycosis fungoides (MF), which have progressed on standard anticancer therapy or for which no other approved therapy exists. TTI-621 is delivered by intratumoral injection at protocol-defined doses and dosing regimens starting at 1 mg/injection. Serial biopsies are being collected to characterize local anti-tumor responses and assess the impact of TTI-621 on the tumor microenvironment. Clinical trial information: NCT02890368.

TPS3102 Poster Session (Board #191b), Mon, 8:00 AM-11:30 AM

Nivolumab in combination with daratumumab, with or without pomalidomide and dexamethasone, for relapsed/refractory multiple myeloma: 2 cohorts of the phase 1 CheckMate 039 safety study. *First Author: Alexander M. Lesokhin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Multiple myeloma (MM) is largely incurable despite available therapies, including immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies (mAbs). As most MM patients (pts) eventually have relapsed/refractory (RR) disease, there is an unmet need. Myeloma cells upregulate PD-L1 [Liu et al, 2007]. Nivolumab (nivo), an immuno-oncology mAb, binds PD-1 on T cells and natural killer cells and inhibits signaling by PD-L1–expressing tumor cells, thus augmenting antitumor immunity. Nivo monotherapy has shown acceptable safety and modest clinical activity in RRMM [Lesokhin et al 2016]. Daratumumab (dara) is a cytolytic mAb that targets CD38+ myeloma cells, inducing antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis, and may have an immunomodulatory role via depletion of CD38+ immune-suppressor cells [Dimopoulos et al 2016]. Dara is approved as monotherapy (US: after $\geq$3 prior lines of therapy; EU: after a prior PI and IMiD and progression on last therapy), and with lenalidomide/dexamethasone (dex) or bortezomib/dex (US: after $\geq$1 prior line of therapy for both combinations). Combining PD-1 and CD38 mAbs, immunotherapies with different mechanisms of action, may overcome resistance and improve outcomes. This phase 1 safety study (NCT01592370) includes multiple cohorts of nivo as monotherapy or in combination regimens across RR hematologic malignancies; 2 MM cohorts will evaluate nivo plus dara, with or without pomalidomide and dex. **Methods:** Eligible pts are aged $\geq$18 y, with RRMM after $\geq$2 prior therapies. Pts are RR to their last regimen, RR to prior IMiD and PI therapy, and agreed to bone marrow aspiration. Primary outcome of safety/tolerability will be measured by incidence of drug-related adverse events (AEs), serious AEs, and laboratory test abnormalities. Secondary endpoints include minimal residual disease, overall response rates and duration of response, and progression-free survival. Study funding: BMS. Writing support: C Tomas, Caudex, funded by BMS. Clinical trial information: NCT01592370.

TPS3103 Poster Session (Board #192a), Mon, 8:00 AM-11:30 AM

Phase II study for the evaluation of efficacy of pembrolizumab (MK-3475) in patients with cancer of unknown primary. *First Author: Gauri R. Varadhachary, The University of Texas MD Anderson Cancer Center, Department of Gastrointestinal Medical Oncology, Houston, TX*

Background: Cancer of unknown primary is a biopsy proven malignancy for which an anatomic primary remains unidentified after a focused search. It accounts for 3-4 % of all solid cancers and most investigators limit it to epithelial and undifferentiated cancers. Patients with metastatic melanoma and sarcoma are excluded. Sophisticated imaging, robust pathologic evaluation including immunostains, and genomic and proteomic characterization of these cancers have challenged the management of CUP. The paradigm has shifted from empiric platinum based combination doublets to a personalized approach. Nevertheless, without an anatomic primary, clinical trial opportunities are limited. There remains an unmet research need to evaluate the role of immunotherapy, specifically checkpoint blockade drugs in specific subsets of CUP patients. **Methods:** Adult Patients ≥ 18 years of age with ECOG PS 0-1, must meet the definition of a CUP cancer. Patients must be intolerant and/or refractory to at least one line of established therapy known to provide clinical benefit for their condition within the last 6 months (often, a platinum based therapy for carcinomas). Patients must have either measurable (RECIST 1.1) or evaluable disease. Although not limited to subtypes, there is a signficant interest in enrolling patients with isolated disseminated lymphadenopathy, HPV (+) CUP and those who have an IHC profile of those known cancers for which anti-PD therapy has been approved (lung, renal, others) The primary objective of this trial is to evaluate efficacy by evaluation of non-progression rate (NPR) at 27 weeks (9 cycles) as defined as the percentage of CUP patients who are alive and progression-free at 27 weeks (9 cycles) as assessed by RECIST 1.1. Secondary objectives include evaluating safety and tolerability of pembrolizumab (MK-3475); correlating efficacy, non-progression rate (NPR) at 27 weeks (9 cycles), objective response (CR or PR), progression-free survival (PFS), overall survival (OS) and duration of response (DOR) to PD-L1 status; and identifying imaging characteristics associated with immunological changes in tumor following treatment with pembrolizumab. Enrollment is ongoing. Clinical trial information: NCT02721732.

TPS3104 Poster Session (Board #192b), Mon, 8:00 AM-11:30 AM

A phase 1b study to evaluate TAK-659 in combination with nivolumab in patients (pts) with advanced solid tumors. *First Author: Dejan Juric, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: TAK-659 is an investigational, reversible, potent dual inhibitor of SYK and FLT-3. In ongoing early-phase studies (NCT02000934; NCT02323113), TAK-659 demonstrated an acceptable pharmacokinetic and safety profile, with evidence of preliminary activity in pts with DLBCL, follicular lymphoma, CLL, and AML (Kaplan et al. Blood 2016;128:624/2834). In preclinical studies, TAK-659 in combination with nivolumab, an anti-PD-1 checkpoint inhibitor, resulted in loss of myeloid suppressor cells (MDSCs), increased T-cell activation, and complete tumor growth suppression (Kannan et al. Eur J Cancer 2016;69:S92). This first-in-human combination study will investigate the efficacy and safety of TAK-659 and nivolumab in pts with advanced solid tumors. **Methods:** This open-label, multicenter, phase 1b study (NCT02834247) will include dose-escalation and expansion phases. Pts with advanced solid tumors who have failed ≥1 prior lines of therapy and have no effective therapeutic options available by investigator assessment will be eligible for the dose-escalation phase. Pts will receive oral TAK-659 at doses of 60–100 mg QD in a standard 3+3 schema, plus nivolumab 3 mg IV on days 1 and 15 of 28-day cycles. The expansion phase at the recommended phase 2 dose (RP2D) will include 3 cohorts of pts with relapsed/refractory metastatic triple-negative breast cancer, locally advanced/metastatic NSCLC, or locally advanced/metastatic head and neck squamous cell carcinoma (n = 30 response-evaluable pts in each cohort; 24 naïve, 6 relapsed/refractory to prior anti-PD-1/PD-L1 therapy). Ten pts in each cohort will receive 2 weeks of single-agent TAK-659 before starting combination therapy; the other 20 pts will receive combination therapy throughout. The primary endpoints are maximum tolerated dose/RP2D (dose-escalation phase) and overall response rate by investigator per RECIST v1.1 (expansion phase). Secondary endpoints include adverse events, disease control rate, duration of response, progression-free survival, overall survival, and TAK-659 pharmacokinetics. There are currently 7 pts enrolled; recruitment to the 100 mg dose-escalation cohort is ongoing. Clinical trial information: NCT02834247.

TPS3105 Poster Session (Board #193a), Mon, 8:00 AM-11:30 AM

A multicenter, open-label, phase II study of PGG beta-glucan and pembrolizumab in patients (pts) with advanced melanoma (MEL) following progression on treatment with checkpoint inhibitors (CPI) or triple negative breast cancer (TNBC) failing front-line chemotherapy for metastatic disease. *First Author: Jose Luis Iglesias, Apobiologix, Toronto, ON, Canada*

Background: Imprime PGG (Imprime) is a *P*athogen-*A*ssociated *M*olecular *P*attern that enhances innate immune cell killing, counteracts immune suppression and triggers activation and maturation of antigen presenting cells. Imprime's ability to trigger a coordinated innate and adaptive immune response is critical for enhancing the efficacy of CPIs in several pre-clinical tumor models. We are now exploring the combination of PGG beta-glucan and Pembrolizumab, a humanized mAb against programmed death receptor-1 (PD-1) in the clinic. In previous trials, Pembro yielded a 33% ORR and 23 mo mOS in 655 pts with advanced MEL and an 18.5% ORR and 11.2 mo mOS in 27 evaluable pts with metastatic/recurrent TNBC (Ribas et al., 2016; Nanda et al., 2016). Pre-treatment levels of anti-beta glucan antibodies (ABA) are correlated with pt response to Imprime. **Methods:** This Phase 2 study is enrolling ABA positive pts with advanced MEL following progression on treatment with a CPI or metastatic TNBC failing front-line chemotherapy. The study is a Simon optimal 2-stage design with sample size of 12 pts of each tumor type in Stage 1. If response and AE criteria (≤ 4 [or ≤ 33%] pts with grade 3/4 in Cycle 1) for each tumor type are met, an additional 17 pts with MEL and 30 pts with TNBC will be enrolled in Stage 2. Primary endpoints of the study are ORR (based on RECIST 1.1) and safety. Secondary endpoints include TTR, CRR, DoR, PFS, and OS. PK data will be profiled. Exploratory endpoints include ORR and PFS based on irRECIST, analysis of an ABA biomarker, immune cell activation markers, and changes in the tumor immune microenvironment. Screening and enrollment are underway in the US. Biothera Pharmaceuticals, Inc. is sponsoring the trial (ClinicalTrials.gov NCT02981303) under a collaborative agreement with Merck. Clinical trial information: NCT02981303.

TPS3106 Poster Session (Board #193b), Mon, 8:00 AM-11:30 AM

Phase 1/2 study of in situ vaccination with tremelimumab + intravenous (IV) durvalumab + poly-ICLC in patients with select relapsed, advanced cancers with measurable, biopsy-accessible tumors. *First Author: Craig L. Slingluff, University of Virginia School of Medicine, Charlottesville, VA*

Background: Immunotherapy has demonstrated promising antitumor activity in various advanced cancers. Combined tumor targeting from multiple drugs with unique mechanisms may provide further improved outcomes. Tremelimumab (TRE) is a CTLA-4 antibody and durvalumab (DUR) blocks PD-L1. Poly-ICLC is a toll-like receptor 3 agonist. Intratumoral (intra-T) injection of poly-ICLC directly alters the tumor microenvironment (TME), and by creating an in situ vaccination, may trigger a clinically effective systemic anti-tumor response when also combined with DUR and TRE. **Methods:** This is an ongoing Phase 1/2, open-label, multicenter study (NCT02643303). The study evaluates the use of intra-T administration of TRE and IV DUR + poly-ICLC (intra-T and intramuscular [IM]) to determine the safety, preliminary efficacy and immune activity of this regimen in patients with advanced, measurable, biopsy-accessible tumors: head and neck squamous cell carcinoma, breast cancer, sarcoma, merkel cell carcinoma, cutaneous T-cell lymphoma, melanoma, genitourinary cancer, and other solid tumors. Phase 1 determines the recommended combination dosing (RCD) for the regimen with dose de-escalation based on dose limiting toxicities (DLTs) and standard 3 + 3 rules. Starting doses are: DUR, 1500 mg IV; TRE, 75 mg IV; TRE, 10 mg intra-T; poly-ICLC, 1 mg intra-T/IM. Phase 1 starts with Cohort 1A (DUR + poly-ICLC). Upon demonstration of tolerability, enrollment proceeds with Cohort 1B (DUR + IV TRE + poly-ICLC) and Cohort 1C (DUR + intra-T TRE + poly-ICLC). The RCD is the highest dose at which < 2/6 patients have DLTs. In Phase 2, up to 66 evaluable patients are treated using the RCD regimen, with enrollment of 6 patients per tumor type initially, and enrollment of 6 additional patients per 3 tumor types contingent upon at least 1 response among the initial 6 patients. Study endpoints are RCD and safety, objective response rate, progression-free survival, and overall survival. Exploratory endpoints are biological activity, including effects on the TME and immunological responses. Enrollment opened on 28 Dec 2016. Clinical trial information: NCT02643303.

TPS3107 Poster Session (Board #194a), Mon, 8:00 AM-11:30 AM

PROCLAIM-001: A first-in-human trial to assess tolerability of the protease-activatable anti-PD-L1 Probody CX-072 in solid tumors and lymphomas. *First Author: Alexander I. Spira, Virginia Cancer Specialists Research Institute and Oncology Research, Fairfax, VA*

Background: CX-072 is a novel Probody therapeutic (PbTx) targeting PD-L1. PbTx s are fully recombinant antibody prodrugs designed to be converted to active antibodies by tumor-associated proteases that are highly expressed malignant tissue; the PbTx remains largely inactive in normal tissues. In pre-clinical tumor models, a PD-L1-directed PbTx provided comparable anti-tumor efficacy to its parental anti-PD-L1 antibody, but displayed reduced auto-immunity in a model of Type 1 diabetes. Based on these pre-clinical data, CX-072 has the potential to enable combination therapies that are otherwise poorly tolerated. This Phase 1/2 study (PROCLAIM-001 (PRObody CLinical Assessment In Man) assesses the tolerability and antitumor activity of CX-072 in humans with an emphasis on immune-related adverse events, particularly in combinations. CX-072 will be administered as monotherapy (Part A), in combination with 2 schedules of ipilimumab (Parts B1 and B2) and in combination with vemurafenib (Part C). The expansion cohort (Part D) will include CX-072 monotherapy in PD-L1 responsive tumor types. **Methods:** Key eligibility criteria are as follows: Parts A and B1: checkpoint inhibitor-naive patients with advanced, refractory solid tumor or lymphoma (unmeasurable disease allowed) for whom approved PD agents are not available. Part B2: advanced, refractory solid tumors or lymphomas with measurable disease who have progressed on a previous treatment with a PD-(L)1 inhibitor, but did not discontinue due to toxicity. Part C: checkpoint inhibitor, BRAF-inhibitor and MEK-inhibitor-naïve metastatic V600E BRAF-mutated melanoma. Patients without an active autoimmune disease, ongoing infection, and ECOG PS 0-1 may be eligible to participate in the study. Dose escalation follows the 3+3 design in all arms. Ipilimumab (Parts B1 and B2) is dosed at the approved 3 mg/kg every 3 weeks x 4. The dose of vemurafenib (Part C) is 960 mg/kg twice daily. Exploratory biomarkers are used to characterize tumor protease activity, inflammatory changes within the tumor, and CX-072 activation in tumor versus peripheral blood. Clinical trial information: NCT03013491.

TPS3108 Poster Session (Board #194b), Mon, 8:00 AM-11:30 AM

Keynote-200 phase 1b: A novel combination study of intravenously delivered coxsackievirus A21 and pembrolizumab in advanced cancer patients. *First Author: Hardev S. Pandha, University of Surrey, Surrey, United Kingdom*

Background: Coxsackievirus A21 (CVA21, CAVATAK) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. Pembrolizumab is a human programmed death receptor-1 (PD-1) blocking antibody that has yielded significant solid tumor responses via reversal of tumor induced T-cell suppression. Intravenous (i.v.) CVA21 mono-therapy is generally well tolerated, with low toxicity and can successfully target tumors in patients with melanoma, NSCLC and bladder cancer as confirmed by detection of CVA21 viral RNA in post-treatment tumor biopsies *(Pandha et al., 2016).* Intratumoral CVA21 replication has the potential to up-regulate numerous key immune checkpoint molecules, including PD-L1 *(Andtbacka et al., 2016).* The combination of i.v. CVA21+pembrolizumab may translate to a potential enhanced benefit in the clinic. **Methods:** The Phase Ib KEYNOTE-200 (NCT02043665) *Treatment:* Primary objectives are to assess dose-limiting toxicities (DLT) of CVA21 in combination with pembrolizumab. Secondary objectives are to assess ORR by irRECIST 1.1 criteria, PFS, and OS. Patients (pts) are infused with CVA21 in 100 mL saline + pembrolizumab. In Cohort 1 (n = 3), CVA21 is administered at a dose of 1 x 10^8 $TCID_{50}$, in Cohort 2 (n = 3) at a dose of 3 x 10^8 $TCID_{50}$ and in Cohort 3 (n = ~80) at a dose of 1 x 10^9 $TCID_{50}$ on study days 1,3,5,8,29,and Q3W for 6 additional infusions. Pembrolizumab is given in all cohorts at 200 mg IV Q3W from Day 8 for up to 2 years. Treatment (tx) with CVA21 + pembrolizumab will continue until confirmed CR or PD (whichever comes first) per irRECIST 1.1 or DLT.To date the combination of intravenous CVA21 and pembrolizumab has been generally well-tolerated. At present one gr 3 CVA21-related hyponatremia with no DLT for the combination of CVA21 and pembrolizumab being observed. Enrolment in Cohorts 1 and 2 is complete with tx of pts in Cohort 3 currently underway. *Key eligibility:* Pts with advanced disease considered appropriate tx with CVA21 + pembrolizumab, lesion(s) accessible for core biopsy, ECOG PS 0-1, no active cerebral metastases, no autoimmunity/immunosuppression. Clinical trial information: NCT02043665.

TPS3109 Poster Session (Board #195a), Mon, 8:00 AM-11:30 AM

Phase 1-2 study of TI-061 alone and in combination with other anti-cancer agents in patients with advanced malignancies. *First Author: T.R. Jeffry Evans, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom*

Background: The cell surface protein CD47 is expressed or over-expressed on many tumor types. CD47 binds to signal regulatory protein alpha (SIRPα) on macrophages resulting in a "don't eat me" signal that blocks host cell phagocytosis of the tumor cells, thus allowing them to escape removal by the innate immune system. Recent data indicate that anti-CD47 antibodies also contribute to an effective anti-tumor T cell response in immune-competent mice. Therefore, anti-CD47 antibodies are a new class of immune checkpoint inhibitors that modulate both the innate and adaptive immune systems. Ti-061 is a novel IgG4 humanized monoclonal antibody that specifically binds to CD47 with Kd values range from 100 – 500 pM. Ti-061 exhibits cross-species binding to cynomolgus monkey, mouse and rat CD47, enabling efficacy and toxicity testing across species. Ti-061 binds to CD47 on RBCs; however, it does not cause agglutination of RBCs in vitro from any of the species tested. Ti-061 exhibits anti-tumor activity in several in vivo mouse tumor models. This ongoing Phase 1-2 study will assess the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of Ti-061 alone and in combination with other anti-cancer agents in patients with advanced malignancies. **Methods:** Part A is an open-label, dose-escalation study of Ti-061 administered as a weekly 1-hour IV infusion at doses ranging from 1 to 20 mg/kg. Once the MTD/RP2D or "active dose" is determined, patients with specific solid tumors and high CD47 expression will be enrolled in 4 or more expansion cohorts. Up to 160 patients with histologically confirmed solid tumors, ECOG PS 0-1, adequate blood counts (Hb≥ 10 g/dL), organ function, and archival or fresh tumor tissue will be enrolled in Part A, and will be treated until disease progression, unacceptable toxicity, or withdrawal. Primary endpoint is safety, which will be assessed using NCI-CTCAE v4.03. Secondary endpoints include PK, PD, objective response rate (ORR) and progression-free survival (PFS), which will be assessed using RECIST v1.1. The results of this study will support further development of Ti-061 in combination with checkpoint inhibitors (Part B) and other anti-cancer agents.

TPS3110 Poster Session (Board #195b), Mon, 8:00 AM-11:30 AM

A phase 1b/2 study of ARRY-382, an oral inhibitor of colony stimulating factor 1 receptor (CSF1R), in combination with pembrolizumab (Pembro) for the treatment of patients (Pts) with advanced solid tumors. *First Author: Wael A. Harb, Horizon Oncology Center, Lafayette, IN*

Background: CSF1, which signals via CSF1R, regulates tumor-associated macrophages and myeloid-derived suppressor cells, both critical drivers of immune escape in the tumor microenvironment. ARRY-382 is a highly selective, oral inhibitor of the CSF1R intracellular tyrosine kinase. The first-in-human study of ARRY-382 monotherapy identified the maximum tolerated dose (MTD) of 400 mg QD, with biologic activity at doses ≥200 mg QD (Bendell JC et al. *Mol Cancer Ther.* 2013;12:A252). Preclinical data supports combining a PD-1 inhibitor with a CSF1R inhibitor (Zhu Y et al. *Cancer Res.* 2014;74:5057-69). This study is designed to evaluate ARRY-382 in combination with pembro, a potent and highly selective humanized monoclonal antibody that targets PD-1. **Methods:** This is an open-label, multicenter, phase 1b/2 study (NCT02880371) to determine the MTD and/or recommended phase 2 dose (RP2D) of ARRY-382 + pembro and to evaluate the activity of the combination in select indications. In phase 1b (Part A), the primary objective is to identify the MTD/RP2D. Up to 18 pts with select advanced solid tumors (Part A) will be enrolled in 2 successive cohorts evaluating ARRY-382 at doses of 200 mg QD and 400 mg QD, respectively, in combination with pembro 2 mg/kg Q3W. Once the MTD/RP2D has been determined in phase 1b, phase 2 will concurrently evaluate the combination in up to 20 pts with advanced unresectable/metastatic melanoma (Part B) and in up to 33 pts with PD-L1-positive (tumor proportion score ≥50) non-small cell lung cancer (NSCLC) (Part C). The primary objective of Part B is to assess the pharmacodynamics and antitumor activity of ARRY-382 + pembro in pts with advanced unresectable/metastatic melanoma, and the endpoints include effects of treatment on circulating growth factors and cytokines, markers of bone resorption, and objective response rate (ORR). The primary objective of Part C is to assess the efficacy of ARRY-382 + pembro in pts with PD-L1–positive NSCLC (Part C). The primary endpoint is ORR. Immune-related response rate and safety will be evaluated in all pts in the study. Clinical trial information: NCT02880371.

TPS3111 Poster Session (Board #196a), Mon, 8:00 AM-11:30 AM

A phase I trial of ALKS 4230, an engineered cytokine activator of NK and effector T cells, in patients with advanced solid tumors. *First Author: Ulka N. Vaishampayan, Wayne State University, Detroit, MI*

Background: ALKS 4230 is an engineered fusion protein comprised of a circularly permuted interleukin-2 (IL-2) and IL-2 Receptor (IL-2R) α designed to selectively activate the intermediate-affinity (ia) IL-2R, comprised of IL-2Rβ and γ_c. The iaIL-2R is expressed predominantly on effector lymphocytes, which play an important role in driving antitumor immune responses. In contrast, unmodified IL-2 activates high-affinity (ha) IL-2R, driving the expansion of haIL-2R-expressing cell types including immunosuppressive $CD4^+$ regulatory T (T_{reg}) cells at concentrations below those at which iaIL-2R bearing effector cells are activated. Also, the haIL-2R is expressed on endothelial cells and may contribute to IL-2 mediated toxicity via capillary leak syndrome. Thus, selective activation of the iaIL-2R by ALKS 4230 has the potential to provide enhanced tumor killing as well as improved tolerability. **Methods:** ALKS 4230 is being studied in a phase 1 first-in-human trial in patients with advanced solid tumors. Key study objectives are to determine a recommended phase 2 dose and characterize the safety profile, pharmacokinetics (PK), pharmacodynamics (PD) and evidence of antitumor activity. A dose-escalation phase in patients with refractory solid tumors (Part A) will be followed by expansion cohorts in defined populations (Part B). ALKS 4230 is administered as a 30-minute intravenous infusion once daily for five days each cycle. Eligibility requires age 18, ECOG PS 0-1 and adequate bone marrow, liver and kidney function. The dose will be escalated until reaching MTD or an Optimal Biologic Dose. The first two dose cohorts will use a 3+3 design. Subsequent cohorts in Part A will enroll a minimum of 6 subjects. In Part B up to 21 patients will be enrolled into each of four tumor-specific cohorts. Peripheral blood samples will be collected for PK, immunogenicity and PD assessments. The primary PD endpoint is change-from-baseline in $CD8^+$ T, NK and T_{reg} cell counts. Other PD measures include serum concentrations of multiple proinflammatory cytokines and immunohistochemical assessment of markers of immune activation in tumor tissue from selected patients. Recruitment for Part A is ongoing. Clinical trial information: NCT02799095.

TPS3112 Poster Session (Board #196b), Mon, 8:00 AM-11:30 AM

A phase I dose escalation (DE) and cohort expansion (CE) study of ERY974, an anti-glypican 3 (GPC3)/CD3 bispecific antibody, in patients with advanced solid tumors. *First Author: Kenji Hashimoto, Chugai Pharma Europe Ltd., London, United Kingdom*

Background: Bispecific antibodies to facilitate T-cell directed cytotoxicity (TDCC) is a proven therapy strategy in cancer. ERY974 is a humanized IgG4 bispecific antibody designed to simultaneously bind to cytotoxic T-cell CD3 receptors and GPC3 (a glycoprotein expressed on cell surface of several tumors) to elicit T-cell activation and TDCC. The objectives of this multi-country, phase 1 study of ERY974 is to determine the maximum tolerated dose (MTD) and to perform a preliminary assessment of anti-tumor activity in patients with solid tumors expressing GPC3. **Methods:** ERY974 is dosed IV weekly. All patients receive premedication with dexamethasone (DEX) prior to 1^{st} and 2^{nd} ERY974 dose. DE uses an accelerated titration design (ATD), then a modified continual reassessment method (mCRM) described by one-parameter logistic model, to determine MTD, where DLT occurrence rate is 0.25. Combining ATD and mCRM is to permit rapid dose escalation whilst minimizing patient numbers exposed to sub-therapeutic doses, and to accurately determine MTD. Once grade 2 (G2) cytokine release syndrome (CRS) is observed, DEX is increased. If $\geq$G2 CRS is again observed, then at all subsequent doses the 1^{st} dose of ERY974 is fixed at the last dose level when $<$ G2 CRS was not seen, DE proceeds with the 2^{nd} dose. ATD commences with n = 1, increasing to n = 3 once drug-related $\geq$G2 toxicity is seen. mCRM starts after 1^{st} dose limiting toxicity (DLT), with the modifications of at least 3 patients required to dose escalate and up to 1.5x increment to minimize risk of toxicity. CE has 3 arms: GPC3+ gastric/gastroesophageal junction adenocarcinoma; GPC3+ squamous esophageal cancer; and other GPC3+ tumors. A 2-stage design is used to allow CE to stop early for futility. Subjects are adults with histologically confirmed, measurable malignant solid tumors and/or metastatic disease not amenable to standard therapy, and life expectancy $\geq$3 months. Patients with $>$ 1cm or $>$ 1 brain metastasis, current/previous interstitial lung disease, and acute/chronic infection are excluded. 3 cohorts have been completed without DLT. Cohort 4 began in January 2017. Clinical trial information: NCT02748837.

TPS3113 Poster Session (Board #197a), Mon, 8:00 AM-11:30 AM

INDUCE-1: A phase I open-label study of GSK3359609, an ICOS agonist antibody, administered alone and in combination with pembrolizumab in patients with advanced solid tumors. *First Author: Eric Angevin, Institut Gustave Roussy, Villejuif, France*

Background: Inducible T cell Co-Stimulator (ICOS), a member of the CD28/B7/CTLA-4 receptor superfamily expressed on T cells after engagement with cognate antigen and activation, provides a co-stimulatory signal augmenting T cell proliferation, survival and cytokine production. GSK3359609 is a humanized IgG4 antibody selected for its potent agonist activity against human ICOS. The unique mechanistic profile of an ICOS agonist antibody, such as GSK3359609, offers an opportunity to investigate the antitumor potential of targeting a T cell co-stimulator alone and in combination with other cancer immunotherapies such as pembrolizumab. **Methods:** INDUCE-1 is a first- in-human study evaluating safety, pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary antitumor activity of GSK3359609 administered as an intravenous (IV) infusion once every 3 weeks (Q3W) alone (Part 1) and in combination with 200 mg pembrolizumab (Q3W IV infusion) or other immunotherapy (Part 2) in approximately 304 adult patients. In dose escalation, eligible patients are required to have selected relapsed/refractory solid tumors. Primary objective is to determine safety, tolerability, and maximum tolerated or administered dose. Modified toxicity probability interval method will inform dose escalation decisions (minimum 3 patients per dose level [DL]). In expansion, cohorts may be defined by factors such as tumor histology, biomarker features, or prior treatment. More than one GSK3359609 DL may be evaluated in an expansion cohort by random assignment. Blood immunophenotyping is monitored in all patients; tumor biopsies (before and on-treatment) are optional in escalation and required in expansion to provide biomarker data that may inform on optimal dose selection as well as mechanistic understanding of GSK3359609. Efficacy measures are every 9 weeks and are according to immune-related RECIST. As of 7 Feb 2017, the first 3 monotherapy DL cohorts completed without dose limiting toxicities; DL 4 enrollment is ongoing. Study is funded by GlaxoSmithKline and is in collaboration with Merck & Co., Inc. Clinical trial information: NCT02723955.

TPS3114 Poster Session (Board #197b), Mon, 8:00 AM-11:30 AM

A phase I study of the safety and immunogenicity of a multipeptide personalized genomic vaccine in the adjuvant treatment of solid cancers. *First Author: Chrisann Kyi, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Mutation-derived tumor antigens (MTAs) arise as a direct result of somatic variations, including nucleotide substitutions, insertions, and deletions that occur during carcinogenesis. These somatic variations can be characterized via genetic sequencing and used to identify MTAs. We propose a platform for a fully-personalized MTA-based vaccine in the adjuvant treatment of solid tumors. **Methods:** This clinical trial is a single-arm, open label, proof-of-concept phase I study designed to test the safety and immunogenicity of the Personalized Genomic Vaccine 001 (PGV001). The single-center study will enroll 20 eligible subjects with histological diagnosis of the following tumor types: (a) head and neck squamous cell cancer, (b) non-small cell lung cancer, (c) ductal or lobular breast cancer, (d) serous carcinoma of the ovary, uterine adnexa, (e) urothelial carcinoma of renal pelvis or bladder, (f) cutaneous squamous cell cancer. Subjects must have no measurable disease at time of first vaccine administration, and 5-year disease recurrence risk of $>$ 30%. Patients will receive 10 doses of PGV001 as well as 10 doses of poly-ICLC (toll-like receptor-3 agonist, vaccine adjuvant), administered 1 day after PGV001 vaccination. Toxicity (endpoint 1) will be defined by Common Terminology Criteria for Adverse Events v5.0. Blood samples will be collected at various time points for immune response monitoring of MTA-specific humoral and cellular immune responses. For each patient, immunogenicity (endpoint 2) will be defined as an epitope-specific T cell response, detectable in peripheral blood samples after PGV001 vaccination. The change in the frequency of vaccine-induced epitope-specific T lymphocyte populations post-vaccination relative to baseline will be determined using mixed effects linear regression modeling. **Conclusions:** Our clinical trial will test for the first time the safety and immunogenicity of PGV001 in patients with multiple solid cancers. The information learned from this clinical trial will instruct the next generation of MTA-based vaccines, future development of immunotherapeutic approaches and rational combinations. Clinical trial information: NCT02721043.

TPS3115 Poster Session (Board #198a), Mon, 8:00 AM-11:30 AM

A phase I study of enadenotucirev (EnAd), an oncolytic Ad11/Ad3 chimeric group B adenovirus, in combination with nivolumab in tumors of epithelial origin. *First Author: Wael A. Harb, Horizon Oncology Center, Lafayette, IN*

Background: EnAd is a tumor-selective chimeric Ad11/Ad3 group B oncolytic adenovirus developed using directed evolution. Phase I clinical studies have identified a well-tolerated systemic dose and regimen for EnAd monotherapy. EnAd shows a high level of selective replication and cell killing for a broad range of carcinoma cell lines with little replication in normal and non-carcinoma cells. Previous studies have shown that after systemic administration there is significant uptake and replication of EnAd in various carcinomas associated with improved CD8+ T-cell tumor infiltration. These data provide the rationale for combination of EnAd with the checkpoint inhibitor (CPI), nivolumab (anti-PD-1 antibody) to potentially enhance the response to nivolumab. This is a phase I study in subjects with metastatic or advanced carcinoma. The study design has a dose escalation stage, followed by a dose expansion stage which will evaluate the ability to improve responses in tumors normally non-responsive to CPI and also to evaluate the ability to detect meaningful responses in PDL1 negative tumors that are less responsive to CPI. **Methods:** The dose escalation phase consists of 5 cohorts of patients with metastatic or advanced epithelial tumors in a standard "3 + 3" design. Subjects will receive increasing dose levels and/or cycles of EnAd followed by a q3w regimen of nivolumab (360mg). EnAd treatment cycles comprise 3 intravenous (IV) infusions on Days 1, 3 and 5. Nivolumab is administered as an IV infusion given every 3 weeks starting on Day 15 and continuing for up to 8 treatment cycles. The Dose Expansion phase will investigate the combination of EnAd and nivolumab in expanded cohorts of colorectal cancer, urothelial cell carcinoma, squamous cell carcinoma of the head & neck, and non-small cell lung cancer patients. The primary objectives are to establish the MTD of EnAd and nivolumab combination, to evaluate the safety and to recommend doses for future studies. Secondary endpoints include overall response, duration of response and progression free survival, assessed according to RECIST Version 1.1 and irRECIST Version 1. Enrollment to cohorts 3 & 4 began in January 2017. Clinical trial information: NCT02636036.

TPS3116 Poster Session (Board #198b), Mon, 8:00 AM-11:30 AM

An open-label, phase Ib study of NEO-PV-01 + adjuvant with nivolumab in patients with melanoma, non-small cell lung carcinoma, or transitional cell carcinoma of the bladder. *First Author: Aung Naing, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cancer cells contain unique DNA mutations that result in altered amino acid sequences known as neoantigens. Growing evidence supports a central role for neoantigens as targets for tumor directed immune responses. Tumor mutational burden as well as neoantigen load have been associated with anti-tumor activity of checkpoint inhibitors. Vaccines targeting neoantigens offer a highly specific way to induce de novo T cell reactivity and to expand existing T cell responses against neoantigens. Here, we describe NEO-PV-01, a personalized, neoantigen vaccine designed specifically for the molecular profile of each individual's tumor. **Methods:** NT-001 is a single-arm, phase IB study designed to evaluate the safety of administering NEO-PV-01 + adjuvant (Poly-ICLC) with nivolumab in patients with advanced melanoma, smoking-associated non-small cell lung carcinoma, or transitional cell carcinoma of the bladder who have received no more than one prior systemic treatment. Patients undergo a baseline tumor biopsy and HLA typing. DNA and RNA sequencing is performed on the tumors as well as peripheral blood to serve as normal DNA controls. On Day 1, patients begin treatment with nivolumab at a dose of 240 mg IV while their customized vaccine is being generated. Each vaccine is custom designed for the individual patient and contains up to 20 peptides 14-35 amino acids in length. The peptides are pooled into four groups and mixed with Poly-ICLC at the time of administration. Beginning at Week 12, patients receive five priming immunizations over a three-week period followed by booster vaccinations at Weeks 19 and 23. The primary endpoint is safety. Secondary endpoints are ORR, CBR, PFS, and assessment of response conversion between Week 12 and Week 24. Exploratory endpoints include extensive immune monitoring. Clinical trial information: NCT02897765.

3500 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Three versus six months adjuvant oxaliplatin-based chemotherapy for patients with stage III colon cancer: The French participation to the International Duration Evaluation of Adjuvant chemotherapy (IDEA) project. *First Author: Thierry Andre, Department of Medical Oncology, Hopital Saint-Antoine, APHP, Paris, France*

Background: The IDEA international collaboration was established to combine data from 6 randomized trials to assess whether a 3-month (3M) of oxaliplatin/fluoropyrimidines-based adjuvant chemotherapy (CT) is non-inferior to the 6-month (6M) for 3-year disease free survival (DFS) in stage III colon cancer (CC). **Methods:** French IDEA randomized patients (pts) between 3M and 6M of CT with mFOLFOX6 or XELOX (physician/pts choice). DFS was estimated using the Kaplan–Meier method and described using 3 years DFS rate. **Results:** Among 2022 randomized pts between May 2009 and May 2014, 2010 (99.4%) received CT and were enrolled in the mITT population: 49.9 and 50.1% in 3M and 6M, respectively. 99.5% of the mITT pts had stage III (N1: 74.9%; N2: 25.2%); median age 63.9 years; mFOLFOX6: 90% and XELOX 10% of pts. DFS median follow-up is 50.2 months. There were 578 DFS events (314 in 3M and 264 in 6M arm) leading to a 3-year DFS rate of 72.1% in the 3M vs. 75.7% in the 6M (HR=1.24; 95%CI 1.05–1.46, p=0.0112). For pts receiving mFOLFOX6, 3-year DFS rate was 72.0% in the 3M vs. 76.3% in the 6M (HR=1.27; 95% CI 1.07–1.51 p=0.0069). 94.2% and 78.0% of pts completed 3 and 6 months of CT, respectively. Median oxaliplatin doses intensity were 96.9% in 3M and 72.1% in 6M (495.0 and 735.1 mg/m2). By considering the neuropathy grade with 15375 neuropathy longitudinal measurements the overall maximal neuropathy grade 0-1/2/3-4 was 63.6/28.5/7.9% in 3M and 33.4/41.3/25.3% in 6M; p<0.0001. At last follow-up assessment, with a median of 43.1 months, final residual grade 2/3-4 neuropathy was 2.1/0.4% in 3M and 5.4/1.3% in 6M; p<0.0001. **Conclusions:** The IDEA France study, with 90% of patients treated with mFOLFOX6 regimen has shown that 6 months adjuvant treatment is superior to 3 months treatment. IDEA France study results should be considered in line with the international IDEA project that will also be presented at ASCO 2017. Clinical trial information: 2009-010384-16.

3501 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

FOLFOX4/XELOX in stage II–III colon cancer: Efficacy results of the Italian three or six colon adjuvant (TOSCA) trial. *First Author: Alberto F. Sobrero, IRCCS A.O.U. San Martino IST, Genoa, Italy*

Background: Six months of oxaliplatin-based treatment has been the standard of care as adjuvant therapy for stage III colon cancer and an accepted option for high-risk stage II. Given the cumulative neurotoxicity associated to oxaliplatin, a shorter duration of therapy, if equally efficacious, would be advantageous for patients and health-care systems. **Methods:** TOSCA was an open-label, phase III, multicenter, non-inferiority trial randomizing patients with high-risk stage II or stage III radically resected colon cancer to receive 3 months or 6 months of FOLFOX4/XELOX. Primary end-point was relapse-free survival. **Results:** From June 2007 to March 2013, 3759 patients were accrued from 130 Italian sites, 64% receiving FOLFOX4 and 36% XELOX in either arm. Two thirds were stage III. At the cut-off time for analysis the median time of follow-up was 62 months and 772 relapses or deaths have been observed. The RFS rate at 8 years is 75%. This analysis was done when 82% of the planned number of events was reached, with a power of 72% instead of 80%. The decision to anticipate the analysis was based on the participation to the IDEA joint collaborative analysis of studies sharing this clinical question. The Hazard Ratio of the 3months vs 6 months for relapse/death was 1.14 (95%CI 0.99-1.31, p for non inferiority = 0.253) and the confidence interval crossed the non inferiority limit of 1.20. **Conclusions:** TOSCA was not able to demonstrate that 3 months of oxaliplatin-based adjuvant treatment is as efficacious as 6 months. Nevertheless , because the absolute difference in RFS between the two treatment durations is small (less than 3 % at 5 years), the decision to complete the whole 6-month program should be individualized based on toxicity and patients' attitude. This study is registered with ClinicalTrials.gov Registration Number: NCT00646607. It was supported by a grant from AIFA (Agenzia Italiana del Farmaco) Grant Code FARM5RWTWZ. Clinical trial information: NCT00646607.

3502 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Final DFS results of the SCOT study: An international phase III randomised (1:1) non-inferiority trial comparing 3 versus 6 months of oxaliplatin based adjuvant chemotherapy for colorectal cancer. *First Author: Timothy Iveson, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom*

Background: Six months of oxaliplatin-based treatment has been the mainstay of adjuvant chemotherapy for colorectal cancer for the last 13 years. Neurotoxicity from oxaliplatin is cumulative, dose limiting, and potentially irreversible. A shorter duration of treatment would save patients significant toxicity/time and substantially reduce the costs of the drug, its administration, and treatment of adverse effects. **Methods:** SCOT is a non-inferiority randomised study designed to determine whether 3 months of adjuvant chemotherapy with OxMdG or Xelox (physician/patient choice) in Stage III/high risk Stage II colorectal cancer is as effective as 6 months treatment. Non-inferiority was determined to be a maximum 2.5% fall in 3-year disease-free survival (DFS) on the 3 month arm (from 78% on the 6 month arm) corresponding to a hazard ratio upper limit of 1.13. The study was designed with 90% power at the 2.5% 1-sided level of statistical significance and aimed to recruit 9500 patients to observe 2,750 DFS events (relapses/deaths/new colorectal cancers). Analysis used a Cox model adjusted for study minimisation factors. **Results:** 6088 patients (60% male, median age 65) with Stage III/high risk Stage II cancers of the colon or rectum were randomised between 27th March 2008 and 29th November 2013. The arms were balanced for clinical and pathological factors. Intended treatment was OxMdG for 1981 and Xelox for 4107 patients. There were 1469 DFS events (734 in 3 month arm and 735 in 6 month arm) giving the study 66% power. 3 year DFS was 76.8% (se = .8%) for the 3 month arm and 77.4% (se = .8%) for the 6 month arm (HR 1.008, 95% CI 0.910-1.117, test for non-inferiority p = 0.014). Non-inferiority appeared stronger for Xelox than OxMdG (test for heterogeneity, p = .059). Results will be shown broken down by stage, site, age, gender and achieved duration of treatment. **Conclusions:** The SCOT study has shown that 3 months adjuvant treatment is not inferior to 6 months treatment. However the SCOT study is part of the IDEA consortium and the results from the 6 studies in the IDEA consortium addressing the same duration question will also be presented at ASCO 2017. Clinical trial information: ISRCTN59757862.

3503 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Primary (1°) tumor location as an independent prognostic marker from molecular features for overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB / SWOG 80405 (Alliance). *First Author: Alan P. Venook, University of California, San Francisco, San Francisco, CA*

Background: 80405 found no OS or Progression Free Survival (PFS) difference when bevacizumab (BV) or cetuximab (Cet) was added to 1st-line FOLFOX or FOLFIRI in All *RAS* wild type (wt) mCRC pts. There was a significant 1° side by biologic interaction (P int: OS = 0.008, PFS = 0.001) favoring pts with left-sided (L) 1°. Analyses of 1° tumors beyond All *RAS* includes Consensus Molecular Subtype (CMS), *BRAF* and MSI. (CMS results - see Lenz et al; *BRAF* -see Innocenti et al) We asked whether 1° tumor location - L vs right (R) - is an independent prognostic marker when these other molecular features are considered. **Methods:** We used a Cox proportional hazard model stratified by prior XRT and +/- adjuvant chemo; adjusted for age, gender, synchronous vs metachronous, CMS, MSI and *BRAF* status. Pts with transverse (T) tumors were excluded in this analysis. **Results:** Sidedness was determined in 782 pts (L - 472; R - 256; T -54). Molecular data from 728 pts (with L - and R-sided 1°s) was available as follows: *KRAS* – 291, *NRAS* -393, *BRAF* - 393, MSI - 378, CMS - 533. L vs R mOS: 32.9 v 19.6 months (mo) (p < 0.0001). See Table for OS results in All *RAS* / *BRAF* wt and *BRAF* mutant (mut) pts. Sidedness (R vs L) is an independent prognostic marker even after adjusting for all these molecular features: HR = 1.392 (1.032, 1.878), p = 0.031. **Conclusions:** Primary tumor location is an independent prognostic factor when adjusted for age, gender, synchronous/metachronous, CMS, MSI and *BRAF* status. We are exploring clinical variables such as tumor burden, metastatic sites and measurability of disease in an attempt to explain the impact of sidedness. *Support: U10CA188021, U10CA180882. Eli Lilly and Co, Genentech/ Roche, Pfizer, Sanofi.* Clinical trial information: NCT002655850.

Population	Median OS (95% CI) L-sided R-sided	Log-rank p-value	Adjusted HR (95%, CI)
80405 (N = 728)	32.9 (30.7, 35.3) 19.6 (7.0, 23.6)	< 0.0001	1.39 (1.03, 1.88)
All *RAS* /*BRAF* wt (N = 225)			
BV (N = 91)	38.7 (34.3, 42.3) 34.4 (23.6, 82.0)	0.918	0.62 (0.32, 1.23)
Cet (N = 96)	40.3 (34.0, 48.3) 18.4 (14.2, 30.1)	0.003	1.68 (0.85, 3.34)
***BRAF* mut (N = 48)**			
BV (N = 23)	12.0 (4.8, 14.5) 23.7 (7.9, 36.9)	0.035	
Cet (N = 16)	9.6 (8.6, NE) 5.8 (1.9, 11.7)	0.508	

3504 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Somatic DNA mutations, MSI status, mutational load (ML): Association with overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC) of CALGB/SWOG 80405 (Alliance). *First Author: Federico Innocenti, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: CALGB 80405 was a randomized phase III trial that found no difference in OS in first-line mCRC pts treated with either bevacizumab (Bev) or cetuximab (Cet). Primary tumor DNA from 361 pts, including KRAS mutant (mut) pts, has been profiled for somatic gene mutations/ML/MSI to discover molecular markers of OS. **Methods:** Mutations in 11 genes were determined by PCR, MSI by microsatellite analysis, and ML by next-generation sequencing (FoundationOne). Cox proportional hazard models are used, stratified by prior XRT and +/- adjuvant chemotherapy; adjusted by age, race, gender, synchronous vs. metachronous, liver metastases, sidedness, all RAS. **Results:** BRAF: Mut pts had shorter OS than wild-type (wt) pts (HR 1.92, 95% CI 1.34,2.75; p<0.001); HR 1.65 (1.09,2.50) after adjusting for sidedness (p 0.022). In mut pts longer OS is observed in Bev arm vs. Cet arm (p 0.041); in wt pts no arm difference is observed (p 0.291, table). MSI: OS does not differ between MSI-H and MSI-S pts (HR 0.78 [0.40, 1.52], p 0.450). In MSI-H pts longer OS is observed in Bev arm vs. Cet arm (p 0.002); in MSI-S pts no difference is observed (p 0.305, table). ML: Hypermutated MSI-H pts are excluded. In a subset of 205 pts, pts with ML>5 (N=93) have longer OS than pts with ML≤5 (N=112) (HR 0.65 [0.42,1.00], p 0.048). In Bev arm higher ML confers longer OS than lower ML (HR 0.85 [0.80,0.96], p 0.004); in Cet arm no difference is observed (HR 0.99 [0.90,1.09], p 0.862). **Conclusions:** BRAF is a strong negative prognostic factor in mCRC, even when sidedness is taken into account. ML is a novel marker for further evaluation. The effect of Bev and Cet in either BRAF mut or MSI-H pts should be tested in larger datasets. Updated results from more screened samples will be presented.

	Median OS 95% CI (months)	HR_{adj} (95% CI)
BRAF mut (N=51)		
Bev	17.4 (12.4,32.6)	0.49 (0.25,0.97)
Cet	10.9 (5.6,19.0)	REF
BRAF wt (N=310)		
Bev	35.1 (30.3,38.8)	0.86 (0.66,1.13)
Cet	30.1 (25.6,34.6)	REF
MSI-H (N=21)		
Bev	30.0 (10.9, NE)	0.13 (0.04,0.46)
Cet	11.2 (4.9,24.6)	REF
MSI-S (N=320)		
Bev	32.6 (26.3,36.0)	0.86 (0.64,1.15)
Cet	30.1 (24.7,34.2)	REF

Support: U10CA180821, U10CA180882, Genentech, Eli Lilly, Sanofi.

3505 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). *First Author: Scott Kopetz, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Metastatic colorectal cancer (mCRC) patients (pts) with *$BRAF^{V600}$* mutations have poor outcomes with standard of care chemotherapy and rarely respond to the BRAF inhibitor vemurafenib. In preclinical models, blockade of $BRAF^{V600}$ by vemurafenib (V) causes feedback upregulation of EGFR, whose signaling activities can be impeded by cetuximab (C) with anti-tumor activity augmented by irinotecan (I). **Methods:** Pts with *$BRAF^{V600}$* mutated and extended *RAS* wild-type mCRC were randomized to irinotecan (180 mg/m^2 IV every 14 days) and cetuximab (500 mg/m^2 IV every 14 days) with or without vemurafenib (960 mg PO twice daily). Eligible pts had ECOG PS ≤1, and had received 1 or 2 prior regimens with no prior anti-EGFR agents. Randomization was stratified for prior irinotecan. Crossover from the control arm (IC) to the experimental arm (VIC) was allowed after documented progression. The primary endpoint was progression-free survival (PFS, investigator assessed), with 90% power to detect a HR of 0.5, with two-sided type 1 error of 5%. **Results:** 106 pts were enrolled (99 eligible, 49 in the experimental arm) from 12/2014 to 4/2016, with median age 62 years, 59% female, and 39% with prior irinotecan therapy. PFS was improved with the addition of vemurafenib (HR 0.42, 95% confidence interval [CI] 0.26 to 0.66, P < 0.001) with median PFS of 4.4 (95% CI 3.6 – 5.7) mos vs 2.0 (95% CI 1.8 – 2.1) months. Response rate was 16% vs 4% (P = 0.08), with disease control rate of 67% vs 22%. In pts with no prior irinotecan, median PFS was 5.7 (95% CI 3.0-6.1) months in the VIC arm vs 1.9 (95% CI 1.7 – 2.1) months in the IC arm. Grade 3/4 adverse events higher in the VIC arm included neutropenia (28% vs 7%), anemia (13% vs 0%), and nausea (15% vs 0%). There was no increase in skin toxicity or fatigue. 23 pts (46%) in the IC arm crossed over at the time of progression, with median PFS from crossover of 6.0 months (95% CI 3.7 – 7.4). Overall survival (OS) data will be mature for ASCO 2017. **Conclusions:** These results demonstrate the clinical benefits of the VIC triplet (vemurafenib, cetuximab, and irinotecan) in pts with treatment-refractory $BRAF^{V600}$ mutated mCRC, and support VIC as a potential new treatment option in this molecular subset. Clinical trial information: NCT02164916.

3506 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

SUNSHINE: Randomized double-blind phase II trial of vitamin D supplementation in patients with previously untreated metastatic colorectal cancer. *First Author: Kimmie Ng, Dana-Farber Cancer Institute, Boston, MA*

Background: In prospective observational studies of mCRC patients, higher plasma levels of 25-hydroxyvitamin D have been associated with improved progression-free (PFS) and overall survival (OS), but the role of vitamin D supplementation in the treatment of mCRC is unknown. **Methods:** SUNSHINE was a multi-center double-blind phase II randomized controlled trial in previously untreated mCRC patients. Patients were eligible if they had histologically confirmed mCRC, no prior therapy for metastatic disease, ECOG PS 0-1, and were not taking vitamin D >2,000 IU/day x 1 year. All subjects received standard treatment with mFOLFOX6 + bevacizumab with 1:1 randomization to concurrent: HiVitD (vitamin D3 po 8,000 IU/d x 2 wks as loading dose followed by 4,000 IU/d) or LowVitD (standard vitamin D3 400 IU/d) until disease progression, intolerable toxicity, or withdrawal of consent. The primary endpoint was PFS, with the sample size designed to provide 80% power to detect a HR of 0.66 for PFS at a 1-sided alpha=0.2. **Results:** From April 2012 to November 2016, 139 patients were randomized. Median age was 54 yrs (range 24-82), 57% were male, 77% were white, and 7% had received prior adjuvant chemo. Baseline characteristics were balanced between arms except ECOG PS = 0 was 42% vs. 60% in HiVitD vs. LowVitD. Median follow-up was 16.1 mos (range 0-45.9) and median compliance with VitD capsules was 98%. Patients randomized to HiVitD experienced longer PFS than those receiving LowVitD (median PFS, 12.4 vs. 10.7 mos, respectively; log rank *P*=0.03). After multivariate adjustment for prognostic variables, HR was 0.66 (95% CI, 0.45-0.99, 2-sided *P*=0.04). Comparing HiVitD vs LowVitD, RR was 58% vs. 63% (*P*=0.54) and disease control rate was 100% vs. 94% (*P*=0.05). The most common grade 3-4 toxicities were as expected for FOLFOX-bevacizumab, and none were related to vitamin D. Currently, 14 patients are still actively receiving treatment, and OS data are not yet mature. **Conclusion:** SUNSHINE met its prespecified primary endpoint, with patients randomized to HiVitD experiencing longer PFS compared to those randomized to LowVitD. A larger confirmatory phase III randomized trial appears warranted. Clinical trial information: NCT01516216.

3507 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer. *First Author: Ricky A. Sharma, Oxford Institute for Radiation Oncology, University of Oxford, Oxford, United Kingdom*

Background: The FOXFIRE, SIRFLOX and FOXFIRE-Global (FF-SF-FFG) randomized studies evaluated the efficacy of combining first-line chemotherapy for metastatic colorectal cancer (mCRC) with selective internal radiotherapy (SIRT) using yttrium-90 resin microspheres in patients with liver metastases. The studies were designed for prospective, combined analysis of overall survival (OS). **Methods:** FF-SF-FFG randomized (1:1) chemotherapy-naïve mCRC patients (performance status 0/1) with liver metastases not suitable for curative resection/ablation. Arm A was oxaliplatin-based chemotherapy (mFOLFOX6/ OxMdG) ± investigator-chosen biologically targeted agent. Arm B was the same systemic therapy (oxaliplatin dose modification) + single treatment SIRT with cycle 1/2 of chemotherapy. Primary tumor in situ and/or limited extra-hepatic metastases were permitted. Minimum sample size was 1075 patients (HR 0.8, 80% power, two-sided 5% significance). Secondary outcomes included PFS, liver-specific PFS and response rate. Apart from safety, outcomes were analysed on intention-to-treat population using meta-analytic methods of pooled individual patient data. **Results:** Between 2006 and 2014, 1103 patients were randomized in 14 countries. Median age was 63 years (range 23-89); median follow-up 43.3 months. There were 844 deaths. There was no difference in OS (HR 1.04; 95% CI 0.90-1.19, *p*= 0.609) or PFS (HR 0.90, CI 0.79-1.02, *p*= 0.108) between Arms. Objective response rate (*p*= 0.001) and liver-specific progression (HR 0.51, CI 0.43-0.62, *p*< 0.001) were significantly more favorable in Arm B. Patients in Arm B had higher risk of non-liver progression as first event (HR 1.98, CI 1.53-2.58, *p*< 0.001). Grade 3-5 adverse events were more common in Arm B (74.0%) than A (66.5%), *p*= 0.009. In health status questionnaires, EQ-5D utility scores were not significantly different between Arms at 6, 12 or 24 months. **Conclusion:** Despite higher response rates and improved liver-specific PFS, the addition of SIRT to first-line oxaliplatin-fluorouracil chemotherapy for patients with liver-only and liver-dominant mCRC did not improve OS or PFS. Clinical trial information: 83867919.

3508 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

A randomized, double-blind, placebo-controlled, multi-centered phase 3 trial comparing fruquintinib versus placebo plus best supportive care in Chinese patients with metastatic colorectal cancer (FRESCO). *First Author: Jin Li, Fudan University Shanghai Cancer Center, Shanghai Medical College, Shanghai, China*

Background: Treatment options for third-line metastatic colorectal cancer (mCRC) patients remain limited in China. Fruquintinib, an oral kinase inhibitor selectively targeting vascular endothelial growth factor receptors, in a phase II study was found to significantly improve progression free survival ("PFS") in patients with mCRC as compared to placebo (ESMO abs#2111). Based on these results, a Phase III registration trial, FRESCO, was carried out to confirm fruquintinib's efficacy and safety in third-line mCRC patients (clinicaltrials.gov # NCT02314819). **Methods:** This is a randomized, double-blind, placebo-controlled, multi-center phase III trial. Patients with mCRC who have failed at least 2 lines of systemic chemotherapy were enrolled from 28 centers in China. Patients were stratified based on prior anti-VEGF therapy and K-ras status and randomized to a fruquintinib or placebo arm in a 2:1 ratio. The primary endpoint was overall survival ("OS") which was analyzed in the intent-to-treat population. **Results:** Between December 12, 2014 and May 13, 2016, 416 patients were randomized. Protocol predefined number of OS events for final analysis was reached on January 17, 2017. Fruquintinib significantly improved OS comparing to placebo with a hazard ratio of 0.65 (95% CI: 0.51-0.83; two sided $p<0.001$). Median OS was 9.30 months [95% CI 8.18-10.45] in the fruquintinib group versus 6.57 months [95% CI 5.88-8.11] in the placebo group. Statistically significant benefits were also seen with fruquintinib in all secondary endpoints, such as PFS, objective response rate and disease control rate. The most frequent fruquintinib-related ≥ Grade 3 treatment emerged adverse events included hypertension (21.6%), hand-foot skin reaction (10.8%), proteinuria (3.2%) and diarrhea (3.2%). **Conclusion:** In this phase III confirmatory trial, fruquintinib demonstrated a statistically significant and clinically meaningful OS benefit as compared with placebo in mCRC patients in China. Fruquintinib was well tolerated with a safety profile that is consistent with what was reported previously. Clinical trial information: NCT02314819.

3509 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM

Clinical utility of colon cancer molecular subtypes: Validation of two main colorectal molecular classifications on the PETACC-8 phase III trial cohort. *First Author: Laetitia Marisa, Ligue Nationale Contre le Cancer, Paris, France*

Background: The molecular subtyping of colon cancers (CC) has been the subject of several recent publications, leading to an international consensus. The clinical relevance of these molecular classifications remains to be evaluated on large prospective patient cohorts using a tool that can be widely used on formalin-fixed paraffin-embedded (FFPE) samples. **Methods:** We aimed to evaluate the clinical relevance of two molecular subtyping systems, CMS (Guinney et al. 2015) and CCMST (Marisa et al. 2013), on the PETACC-8 cohort, a randomized phase III trial comparing adjuvant FOLFOX with or without cetuximab in patients with stage III CC. For each of these two classification systems, a predictor tool was developed and adapted to FFPE samples. The NanoString nCounter platform was used to screen 196 genes. Predictors were built from 249 frozen tumor samples previously used to build our classification system and 61 new paired FFPE/frozen samples. Both predictors were then applied to 1781 PETACC-8 FFPE samples. Subtypes associations to clinical and molecular features were analyzed. **Results:** The CMS predictor assigned 297 samples to CMS1 (17%), 585 to CMS2 (34%), 68 to CMS3 (4%) and 770 to CMS4 (45%). CMS were significantly associated with several molecular and clinical features, including MSI status (49% in CMS1, $p < 0.001$), CIMP status (47% in CMS1, $p < 0.001$), KRAS mutation (75% in CMS3, $p < 0.001$), BRAF mutation (34% in CMS1, $p < 0.001$), tumor location (less proximal tumors in CMS2, $p < 0.001$), validating the predictor tool developed. The classification was significantly associated to prognosis in multivariate analysis, CMS4 subtype having a shorter overall survival (hazard ratio = 1.7, $p = 0.021$). A deleterious effect of cetuximab was observed in CMS1 ($p < 0.05$). Similar results were obtained with the CCMST classification. **Conclusions:** We validated molecular CC subtyping predictors for both CMS and CCMST classifications on PETACC-8 FFPE samples. The prognostic value of CMS and CCMST classifications was confirmed, stem-like tumors being associated with a poor prognosis. These results pave the avenue for widely use of the CC molecular classification in clinical routine.

3510 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM

Consensus molecular subgroups (CMS) of colorectal cancer (CRC) and first-line efficacy of FOLFIRI plus cetuximab or bevacizumab in the FIRE3 (AIO KRK-0306) trial. *First Author: Sebastian Stintzing, Department of Hematology and Oncology, Klinikum Grosshadern and Comprehensive Cancer Center, University Hospital Grosshadern, LMU Munich, Munich, Germany*

Background: FIRE-3 compared 1st-line therapy with FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS exon 2 wt mCRC patients. CMS is grouping CRCs according to their gene-signature in 4 different types. Relevance of CMS for the treatment of mCRC remains unclear. **Methods:** Patients were grouped according to tumor CRC-CMSs. Using ALMAC's Xcel tissue array, gene signatures of FIRE-3 tumor samples were analyzed. Survival was compared using Kaplan-Meier estimation and log-rank tests. Hazard ratios (HR) were estimated according to the Cox proportional hazard method. **Results:** CMS classification could be determined in 385 specimens available from the ITT population (n = 592). In this KRAS exon 2 wt population (n = 385), frequencies were: CMS1 (10.4%), CMS2 (36.6%), CMS3 (11.7%), CMS4 (29.1%), non-consensus (12.2%). In RAS wt (n = 315), frequencies were: CMS1 (11.1%), CMS2 (38.1%), CMS3 (9.5%), CMS4 (29.5%), non-consensus (11.7%). Independent of the treatment, CMS was a strong prognosticator for ORR ($p = 0.023$), PFS ($p < 0.001$) and OS ($p < 0.001$). For data on CMS and treatment efficacy in the RAS wt population see the following table. **Conclusions:** CMS classification is prognostic for mCRC. The survival benefit in RAS wt previously observed for FOLFIRI cetuximab vs. FOLFIRI bevacizumab is not significantly different across CMS groups, although there are trends when comparing OS HR between categories with CMS4 showing the best HR.

	Median PFS (months)					Median OS (months)				
	events	All	FOLFIRI Cetuximab	FOLFIRI Bevacizumab	p* HR	events	All	FOLFIRI Cetuximab	FOLFIRI Bevacizumab	p* HR
CMS 1	33/35	6.1 (3.2-9.1)	5.1 (0.2-10.1)	6.7 (3.9-9.4)	0.83 1.08	32/35	13.1 (6.7-19.4)	20.3 (8.4-32.3)	11.0 (5.1-16.8)	0.28 0.68
CMS 2	93/117	12.3 (10.9-13.7)	12.2 (9.5-14.9)	12.4 (10.9-13.8)	0.54 1.14	64/117	31.9 (25.1-38.8)	38.3 (27.5-49.2)	30.8 (26.7-34.8)	0.40 0.80
CMS 3	27/30	7.6 (4.0-11.2)	7.3 (6.2-8.4)	10.0 (4.2-15.7)	0.76 0.90	20/30	18.7 (11.9-25.4)	16.6 (NE-41.2)	18.7 (12.7-25.6)	0.60 0.77
CMS 4	81/93	9.9 (9.0-10.9)	10.5 (6.9-14.1)	9.7 (8.8-10.6)	0.07 0.67	56/93	25.3 (19.8-30.3)	41.3 (19.2-63.4)	22.3 (15.9-28.8)	0.016 0.53

*p = logrank test , HR = Hazard ratio

3511 Clinical Science Symposium, Tue, 9:45 AM-11:15 AM

Impact of consensus molecular subtyping (CMS) on overall survival (OS) and progression free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *First Author: Heinz-Josef Lenz, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: CALGB 80405 was a randomized Ph3 trial showing no OS or PFS difference in mCRC pts treated with Bevacizumab (BV) or Cetuximab (Cet) in the first line. A Nanostring platform was used to determine the CMS classification of 392 KRAS wt (codon 12 and 13) primary tumors and correlated it with OS and PFS in patients enrolled in 80405. **Methods:** CMS for 392 of 431tumors were defined using a custom CRC Nanostring panel (39 CMS classification not possible). Stratified Cox proportional hazard model was used to evaluate the effect of CMS classification stratified by prior radiation, prior chemotherapy, adjusting for age, sex, race, primary in place, liver met only, and sidedness. **Results:** We found CMS1 (14%), CMS2 (47%), CMS3 (2%), CMS4 (29%), NonConsensus (8%). Results are shown in Table 1. Patients with CMS1 who received BV had significantly longer OS than those who received Cet (HR 0.47, 95% CI [0.24, 0.92]). Patients with CMS2 who received BV tended to have shorter OS than those who received Cet (HR 1.41, CI [0.95, 2.08]). **Conclusions:** Our data suggest that CMS is associated with OS and PFS in first line therapy in mCRC patients. Preliminary data suggest that certain CMS may be associated with efficacy of Bev and Cet based chemotherapy. CMS classification should be explored as a stratification factor in future trials. Support: U10CA180821, U10CA180830, U10CA180882 Clinical trial information: NCT00265850.

	OS (mths)				PFS (mths)			
	Overall		BV	Cet	Overall		BV	Cet
CMS Classification	Events/N	Median (95% C.I.)	Median (95% C.I.)	Median (95% C.I.)	Events/N	Median (95% C.I.)	Median (95% C.I.)	Median (95% C.I.)
CMS 1	40/55	17.0 (11.3-27.8)	20.4 (11.3-NE)	11.7 (10.6-27.8)	45/55	6.5 (5.4-10.6)	7.0 (5.7-15.9)	6.0 (3.9-14.4)
CMS 2	131/183	39.7 (35.3-43.1)	36.8 (33.6-43.1)	41.2 (37.2-54.4)	169/183	13.3 (12.4-14.9)	12.9 (10.2-14.8)	14.9 (12.9-19.4)
CMS 4	92/114	23.7 (18.8-29.5)	26.7 (19.3-36.9)	20.0 (16.4-31.0)	106/114	9.6 (8.4-11.1)	9.9 (9.0-11.6)	9.5 (7.6-11.8)
Logrank P-Value		0.003	0.115	<0.001		<0.001	0.113	0.003
Adjusted P-Value		0.022	0.596	0.005		0.011	0.228	0.005
P-Value for interaction (between CMS and BV/Cet)		0.042	—	—		0.224	—	—

3513 Poster Discussion Session; Displayed in Poster Session (Board #136), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A phase III trial (ZJBIO009): CMAB009 plus irinotecan versus irinotecan alone as second-line treatment after fluoropyrimidine and oxaliplatin failure in wild-type *K-ras* metastatic colorectal cancer patients. *First Author: Yuankai Shi, National Cancer Center /Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing Key Laboratory of Chinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: More efficient second line treatment regimen for mCRC is urgently needed. CMAB009, a recombinant human/mouse chimeric monoclonal antibody, is specifically targeting human epidermal growth factor receptor. This study aimed to determine clinical efficacy and safety of CMAB009 plus irinotecan compared with irinotecan alone in wild-type *K-ras* mCRC patients (pts). **Methods:** This is a open-label, randomized, phase 3 trial. Patients had histologically confirmed wild-type *K-ras* mCRC, who previous failure of 5-fuorouracil plus oxaliplatin more than 1 month of the last-dose enrolled in study. Pts were randomly assigned on a 2:1 to receive CMAB009 (initial 400mg/m^2 on day 1, and then 250 mg/m^2 weekly) plus irinotecan (180mg/m^2, every 2 weeks) (A arm) or irinotecan alone (B arm). B arm pts could switch to CMAB009 sequential treatment (C arm) on diseas progression. The primary end point was overall response rate (ORR). The secondary endpoints were PFS, OS, DCR, and DOR (NCT01550055). **Results:** From May 2009 to December 2012, 512 pts were assigned from 38 sites. Efficacy evaluation could be in 501 pts, ORR were 33.2% (112/337) and 12.8% (21/164) in A arm and B arm ($p < 0.0001$). C arm had 115 pts, DCR was 63.5% (73/115). DOR in A arm and B arm were 210 days and 109 days (p=0.001). In C arm, DOR was 148 days. Median PFS was significantly longer in A arm than B arm (169 days *vs* 95 days; $p < 0.0001$). In C arm, median PFS was 84 days. Median OS was 425 days in A arm and 401 days in B arm (p=0.94). 96.2% (484/503) pts experienced at least one adverse event (AE). 55.3%(187/338) and 37.6%(62/165) patients in A arm and B arm had at least one grade ≥3 AE respectively. The most common AE included diarrhea, emesis, leucopenia, neutropenia and fatigue. Adding CMAB009 to irinotecan increased the risk of rash (66.6% *vs* 5.5%, $p < 0.001$) and paronychia (9.8% *vs* 0,$p < 0.001$). **Conclusions:** CMAB009 plus irinotecan significantly increased ORR and prolonged PFS compared with irinotecan alone. CMAB009 plus Irinotecan were efficient and well tolerated, which could be considered as a standard second-line treatment choice in wild-type *K-ras* mCRC pts. Clinical trial information: NCT01550055.

3514 Poster Discussion Session; Displayed in Poster Session (Board #137), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Tumor sidedness and intrinsic subtypes in patients with stage II/III colon cancer: Analysis of NSABP C-07 (NRG Oncology). *First Author: S. Rim Kim, NSABP/NRG Oncology, Pittsburgh, PA*

Background: The predictive value of tumor sidedness in colorectal cancer is currently of interest especially in metastatic setting for anti-EGFR therapy response. We tested whether intrinsic molecular subtype classification predictive of treatment benefit in stage II/III colon cancer is an independent novel marker in association with tumor sidedness. **Methods:** All available cases included in the NSABP/NRG C-07 trial for which we had both gene expression data and anatomical data (n=1603) were used to determine the molecular subtypes using the following classifiers; the Colorectal Cancer Assigner (CRCA), the Colon Cancer Subtypes (CCS) and the Consensus Molecular Subtypes (CMS). Frequency of tumor sidedness in each subtype and recurrence-free survival were analyzed. **Results:** Intrinsic subtypes were differentially distributed in right- and left-colon tumors with the exception of the stem-like or CMS4 (mesenchymal) subtype (Table 1). Sidedness was not associated with prognosis (p=0.82, HR: 1.022 [CI: 0.851-1.227]) or prediction of patients with greater benefit from oxaliplatin when combined with 5-Fu+LV (interaction p=0.484). **Conclusions:** Although tumor sidedness is associated with distribution of intrinsic subtypes in stage II/III colon cancer, it is not predictive of survival benefit from oxaliplatin in C-07. Support: -180868, -180822, U24-CA196067; HI13C2162; PA DOH; Sanofi-Synthelabo Clinical trial information: NCT00004931.

Classifier	Subtype	Right Colon	Left Colon	Unknown Location	Total
CRCA					
	Enterocyte	70 (9.8%)	114 (13%)	0 (0%)	184
	Goblet-like	84 (11.8%)	58 (6.6%)	0 (0%)	142
	Inflammatory	242 (34%)	157 (17.9%)	6 (42.9%)	405
	Stem-like	220 (30.9%)	255 (29%)	3 (21.4%)	478
	TA	95 (13.4%)	294 (33.5%)	5 (35.7%)	394
	Subtotal	711 (100%)	878 (100%)	14 (100%)	1603
CCS					
	CCS1	148 (20.8%)	396 (45.1%)	5 (35.7%)	549
	CCS2	256 (36%)	155 (17.7%)	6 (42.9%)	417
	CCS3	307 (43.2%)	327 (37.2%)	3 (21.4%)	637
	Subtotal	711 (100%)	878 (100%)	14 (100%)	1603
Consensus					
	CMS1 (MSI immune)	232 (32.6%)	134 (15.3%)	6 (42.9%)	372
	CMS2 (canonical)	118 (16.6%)	387 (44.1%)	5 (35.7%)	510
	CMS3 (metabolic)	78 (11%)	45 (5.1%)	0 (0%)	123
	CMS4 (mesenchymal)	197 (27.7%)	233 (26.5%)	1 (7.1%)	431
	Unknown	86 (12.1%)	79 (9%)	2 (14.3%)	167
	Subtotal	711 (100%)	878 (100%)	14 (100%)	1603

3515 Poster Discussion Session; Displayed in Poster Session (Board #138), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Association of prognostic value of primary tumor location in stage III colon cancer with RAS and BRAF mutational status. *First Author: Julien Taieb, Hopital Européen Georges Pompidou, Paris, France*

Background: Recent data suggest that the anatomic site of colon primary tumor may be an important factor in the interpretation of molecular markers with clinical outcome in metastatic colon cancer (CC) patients (pts). We assessed here the prognostic value of primary location in fully resected stage III CC pts and its relationship to MSI, *RAS* and *BRAF* mutational status. **Methods:** Pts enrolled in the PETACC-8 trial were analyzed. We categorized tumor site as located proximal (left-sided) or distal (right-sided) to the splenic flexure. The association between tumor location and disease free survival (DFS), survival after relapse (SAR) and overall survival (OS) were assessed by Cox models and adjusted for clinical and pathological features, MSI, *BRAF* and *RAS*mutation status. The outcome of pts receiving FOLFOX or FOLFOX and cetuximab in the adjuvant setting were also determined according to tumor site. **Results:** Among the 1869 pts with full molecular data available, 755 (40%) had a right-sided tumor, 164 (10%) were MSI, 942 (50%) were mutated for *RAS* and 212 (11%) were mutated for *BRAF*. Right-sided tumor was not prognostic for DFS in the whole population but was associated to a shorter SAR (HR: 1.54 [1.23 - 1.93], p = 0.001) and OS (HR: 1.25 [1.02 - 1.54], p = 0.03). Same results were observed for MSS and for MSI pts. However, when looking at pts mutated for *RAS* or *BRAF*(MUT) and those double wild type (DWT) for those mutations, we found that right-sided tumors, when compared to left-sided tumors, was associated with a worst DFS in DWT patients (HR:1.39[1.01-1.92], p = 0.04) and a better DFS in MUT patients (HR:0.77[0.63-0.95], p = 0.01). These results were found independently of the treatment received and no beneficial effect of cetuximab on DFS or OS was observed in left-sided tumors. **Conclusions:** In the whole study population of stage III CC pts, though right-sided tumor location influences OS as previously reported, it does not seem to influence DFS but only SAR, when disease becomes metastatic. Interestingly, sidedness seems to influence DFS when splitting the population in MUT or DWT for *RAS* and *BRAF,* with a worst DFS for right-sided tumors in DWT and a worst DFS for left-sided tumors in *RAS* or *BRAF* mutants. Clinical trial information: 2005-003463-23.

3516 Poster Discussion Session; Displayed in Poster Session (Board #139), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Analysis of serum vitamin D levels and prognosis in stage III colon carcinoma patients treated with adjuvant FOLFOX+/- cetuximab chemotherapy: NCCTG N0147 (Alliance). *First Author: Frank A. Sinicrope, Mayo Clinic Cancer Center, Rochester, MN*

Background: Epidemiological data suggest a protective effect of vitamin D on CC risk. However, association of serum vitamin D level with clinical outcome in pts with surgically resected CC remains unknown. We analyzed total circulating 25-hydroxyvitamin D [25(OH)D)] with clinical outcome in pts with resected stage III CC treated with FOLFOX +/- cetuximab in a phase III trial. **Methods:** Association of pre-treatment level of plasma 25(OH)D with disease-free survival (DFS) and time-to-recurrence (TTR) was analyzed with 25(OH)D as a continuous variable by a relative risk model with splines and as a binary variable (vitamin D deficient [<30 ng/mL]) using multivariable Cox regression. **Results:** Overall, 49% (291/600) of pts were vitamin D deficient. Prevalence of vitamin D deficiency was significantly higher in women vs men (52% vs. 48%, p=0.030) and in blacks vs whites (74% vs. 45%, p=0.0003). The continuous 25(OH)D level and pt sex were associated by the interaction test ($p_{interaction}$=0.044). There were no statistically significant associations with DFS/TTR for either continuous 25(OH)D level (DFS, p=0.22; TTR, p=0.26) nor for vitamin D deficiency (DFS, adjusted hazard ratio [HR_{adj}]=1.01, 95% CI, 0.74-1.38; p_{adj}=0.94; TTR, HR_{adj}=1.00; CI, 0.72-1.38; p_{adj}=0.99. A comparison of the highest vs lowest tertile showed a significant association between the highest 25(OH)D level and better outcomes in men (DFS, $HR_{adj.}$=0.18, CI, 0.04-0.76, p_{adj}=0.020; TTR, $HR_{adj.}$=0.12, CI, 0.02-0.64, p_{adj}=0.014), but not in women (DFS, $p_{interaction}$=0.039; TTR, $p_{interaction}$=0.033). **Conclusions:** Nearly one-half of pts in the clinical trial cohort were vitamin D deficient with lowest 25(OH)D levels found in women and blacks. While vitamin D deficiency was not associated with adverse outcome, high levels of vitamin D in men, but not women, were associated with longer survival. Support: U10CA180821, U10CA180882, U10CA180820, U10CA180863, U10CA180888, U10CA077202, CCSRI 021039. ClinicalTrials.gov Identifier: NCT00079274.

3517 Poster Discussion Session; Displayed in Poster Session (Board #140), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Nut consumption and survival in stage III colon cancer patients: Results from CALGB 89803 (Alliance). *First Author: Temidayo Fadelu, Dana-Farber Cancer Institute, Boston, MA*

Background: Recent prospective cohort studies suggest states of energy excess and hyperinsulinemia, including type 2 diabetes (T2D), obesity, sedentary lifestyle, Western pattern diet, increased dietary glycemic load, high intake of sugar-sweetened beverages, and elevated plasma C-peptide are each associated with an increased risk of colon cancer (CC) recurrence and mortality. Conversely, observational studies indicate that increasing nut intake is associated with lower risk of T2D, metabolic syndrome and insulin resistance. However, the effect of nut intake on CC recurrence and survival is unknown. **Methods:** We conducted a prospective, observational study of 826 patients with stage III CC who reported dietary intake with food frequency questionnaires while enrolled in a randomized adjuvant chemotherapy trial. Using Cox proportional hazards regression, we assessed associations of nut intake with cancer recurrence and mortality. The primary endpoint was disease-free survival (DFS) defined as time from completion of dietary questionnaire following adjuvant therapy to cancer recurrence, death or last follow-up. **Results:** Compared to patients who abstained from nuts, those who consumed ≥ 2 servings of nuts per week had an adjusted hazard ratio (HR) of 0.58 (95% CI, 0.37 to 0.92; $P_{trend} = 0.03$) for DFS and 0.43 (95% CI, 0.25 to 0.74; $P_{trend} = 0.01$) for overall survival (OS). On subgroup analysis, the significant association was confined to tree-nut intake: HR = 0.54 (95% CI, 0.34 to 0.85; $P_{trend} = 0.04$) for DFS and HR = 0.47 (95% CI, 0.27 to 0.82; $P_{trend} = 0.04$) for OS. There was no significant association between intake of peanut or peanut butter and patient outcome. Association of total nut intake with improved outcomes was maintained across other known or suspected predictors of recurrence and mortality, including across common genomic alterations (microsatellite instability, KRAS mutation, BRAF mutation, and PIK3CA mutation). **Conclusions:** Higher consumption of nuts may be associated with significantly reduced cancer recurrence and death in patients with stage III CC. Support: U10CA180821, U10CA180882, Pfizer. Clinical trial information: NCT00003835.

3518 Poster Discussion Session; Displayed in Poster Session (Board #141), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Comparison of long-term survival outcomes between laparoscopic and open surgery for mid or low rectal cancer treated with preoperative chemoradiotherapy: 7-year follow-up of COREAN trial. *First Author: Ji Won Park, Department of Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea*

Background: Laparoscopic surgery for rectal cancer has been used widely. However, recent two randomized trials raised concerns about short-term oncologic safety of laparoscopic surgery for rectal cancer. The aim of this study was to evaluate the long-term oncologic safety of laparoscopic surgery for rectal cancer based on 7-year data from the Comparison of Open versus laparoscopic surgery for mid or low REctal cancer After Neoadjuvant chemoradiotherapy (COREAN) trial. **Methods:** COREAN trial was a non-inferiority, randomized controlled trial. Between April, 2006, and Aug, 2009, eligible participants with mid or low rectal cancer treated with preoperative chemoradiotherapy were randomly assigned (1:1) to laparoscopic (n = 170) or open surgery (n = 170). Seven-year outcomes included overall and disease-free survival, and local recurrence. Log-rank test and stratified Cox regression analysis were used for survival analysis. Analysis was by intention to treat. **Results:** The median follow-up times were 84 months (IQR: 61.5-97.0). No differences were found between laparoscopic and open surgery group in terms of overall and disease-free survival, and local recurrence (7-year overall survival: 83.2% [laparoscopic] vs 77.3% [open], p = 0.48; 7-year disease-free survival: 71.6% [laparoscopic] vs 64.3% [open], p = 0.20; 7-year local recurrence: 3.3% [laparoscopic] vs 7.9% [open], p = 0.08). Stratified Cox regression analysis adjusted for ypT, ypN and tumor regression grade showed no significant difference between groups in terms of overall and disease-free survival, and local recurrence. The hazard ratios for overall survival, disease-free survival and local recurrence (open *vs* laparoscopic surgery) were 0.96 (95% CI = 0.58-1.57), 1.03 (95% CI = 0.70-1.53), and 2.28 (95% CI = 0.82-7.16), respectively. **Conclusions:** The 7-year analysis confirm the long-term oncological safety of laparoscopic surgery for rectal cancer treated with preoperative chemoradiotherapy. The use of laparoscopic surgery does not compromise the long-term survival outcomes in rectal cancer. Clinical trial information: NCT00470951.

3519 Poster Discussion Session; Displayed in Poster Session (Board #142), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Total neoadjuvant chemotherapy to facilitate delivery and tolerance of systemic chemotherapy and response in locally advanced rectal cancer. *First Author: Andrea Cercek, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The most common therapy for locally advanced (T3/4 or N+) rectal cancer (LARC) consists of preoperative chemoradiotherapy (chemoRT) followed by surgery and adjuvant chemotherapy. Recently, use of total neoadjuvant therapy (TNT) with preoperative chemotherapy in addition to chemoRT prior to resection has been accepted as an alternative. **Methods:** Of 811 consecutive patients (pts) who presented with LARC at our cancer center in 2009-2015, 320 received chemoRT with planned adjuvant chemotherapy, and 308 received TNT (induction FOLFOX/CAPOX chemotherapy followed by chemoRT). Treatment and outcome data for those two cohorts were compared. **Results:** Pts in the TNT cohort received greater percentages of the planned oxaliplatin and fluorouracil prescribed dose than those in the chemoRT with planned adjuvant chemotherapy cohort ($p < 0{\cdot}005$ and $p < 0{\cdot}001$, respectively). The complete response (CR) rate, which includes pathological CR (pCR) and clinical CR (cCR) at 6 months post-treatment, was 21% in the chemoRT with planned adjuvant chemotherapy cohort and 36% in the TNT cohort. The median follow-up was 40 months in the chemoRT with planned adjuvant chemotherapy cohort and 23 months in the TNT cohort. Fewer distant recurrences were seen in patients who had T downstaging ($p < 0{\cdot}001$), N downstaging ($p < 0{\cdot}005$), a cCR ($p = 0{\cdot}005$), or a pCR ($p < 0{\cdot}005$). There was no statistically significant difference in distant-recurrence-free survival between the two cohorts. **Conclusions:** Our findings provide additional support for the National Comprehensive Cancer Network (NCCN) guidelines for rectal cancer treatment, which categorizes TNT as a viable treatment strategy that facilitates superior compliance and delivery of systemic therapy. Given its high CR rate, TNT may be beneficial as part of a nonoperative treatment strategy aimed at organ preservation.

3520 Poster Discussion Session; Displayed in Poster Session (Board #143), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Colorectal cancer (CRC) patients surveyed by ^{18}FDGPET-CT (PET-CT): An open-label multicenter randomized trial (NCT 00624260). *First Author: Iradj Sobhani, Departement of Gastroenterology and Oncology Hopital Henri Mondor, Creteil, France*

Background: Curative surgery is the best therapy of CRC and recurrences. We assessed whether adding semi-annual PET-CT to the usual surveillance would be cost-effective in high risk recurrent CRC patients. **Methods:** CRC patients (stage II tumor perforated, stages III and IV) in remission after curative surgery were randomly assigned (1:1) to trimester usual surveillance (control) or usual surveillance + semi-annual course PET-CT (intervention) for a 3-yr follow up period. Every 3 months, multidisciplinary committee decided about recurrence by yes/no/doubtful. If yes, curative surgery alone (when relevant), or chemotherapy alone (unresecable recurrence) were conducted; additional exams could be performed if doubtful. Primary composite endpoint (failure) comprised unresectable recurrence & death. The economic assessments according to standards (CHEERS) were performed and costs were compared between groups. Statistical tests for calculation of the relative risk (RR) were used and survival was analyzed using Kaplan-Meier method, Log-Rang test and Cox models. **Results:** Baseline characteristics of 239 patients (120/119) enrolled in 12 centers were balanced. The failure rate was 29.2% (31 unresectable recurrences & 4 deaths) and 23.5% (27 & 1) in Interventional vs Control, respectively with no significant difference (RR = 1.24, 95% CI: 0.81-1.90; $P = .32$). Similar results were observed in multivariate analysis (Cox models) adjusted for stage and tumor differentiation (HR = 1.33, 95% CI: 0.8-2.19, $P = .27$). Period until the unresectable recurrence was significantly shorter in Interventional (median = 7; IQR: 3-20 months) than in Control group (14.3; 7.3-27; $P = 0.016$). This was consistent with lower elevation (median; IQR) of tumour marker in interventional (3.8; 2.8-19) than in control group (10; 5.2-28.6) at the first recurrence time as compared to the baseline (p = 0.007). Overall (mean; SD) cost (euros)/patient was higher in the PET-Scan (9385; 11658) than in the control group (7027; 7656). **Conclusions:** Although recurrences were detected earlier in PET-CT group, the strategy was less effective, more expensive. This exam should not be advised routinely. Clinical trial information: NCT 00624260.

3521 Poster Discussion Session; Displayed in Poster Session (Board #144), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

The potential of circulating tumor DNA (ctDNA) to guide adjuvant chemotherapy decision making in locally advanced rectal cancer (LARC). *First Author: Jeanne Tie, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia*

Background: The optimal approach to adjuvant chemotherapy for rectal cancer is keenly debated. Routine practice and clinical guidelines vary widely. After pre-operative chemoradiation (CRT), a pathologic complete response (pCR) or nodal involvement (pN+) are prognostic markers that can guide clinical decision-making, but markers that better define the patients (pts) that are likely or unlikely to benefit from chemotherapy are urgently needed. We investigated the potential role of ctDNA as a biomarker to guide therapy. **Methods:** We conducted a prospective, multi-centre study in pts with LARC (T3/T4 and/or N+) planned for CRT and curative resection. Serial plasma samples were collected pre-CRT, post-CRT, and 4-10 weeks after surgery. Somatic mutations in individual pts' tumor were identified via sequencing of 15 genes commonly mutated in colorectal cancers. We then designed personalized assays to quantify ctDNA in plasma samples. Pts received adjuvant therapy at clinician discretion. **Results:** 200 pts were enrolled between Apr-2012 and Dec-2015. Median age was 62 years (range 28-86), 67% were male and 159 pts had pre-CRT and post-op ctDNA samples available for analysis. Of these, 122 (77%) pts had detectable ctDNA prior to therapy. After surgery, 19 pts had detectable ctDNA and 11 of these 19 (58%) have recurred during a median follow up of 22 months. Recurrence occurred in only 12 of 140 (8.6%) with negative ctDNA (HR 12, $p < 0.001$). One hundred and two (64%) pts received adjuvant chemotherapy. Post-op ctDNA detection was predictive of recurrence irrespective of adjuvant chemotherapy (chemo: HR 10, $p < 0.001$; no chemo: HR 16, $p < 0.001$). Thirty-four pts (21%) achieved a pCR, 43 (27%) had pN+ disease. pCR (vs non-pCR) was associated with a trend for lower recurrence risk (HR 0.31, $p = 0.089$) and pN+ (vs pN0) with a higher recurrence risk (HR 4.2, $p < 0.001$). ctDNA detection remained predictive of recurrence among pts with a pCR (HR 14, $p = 0.014$) or with pN+ disease (HR 11, $p < 0.001$). **Conclusions:** Post-op ctDNA analysis stratifies pts with LARC into very high and low risk groups. ctDNA analysis remains strongly predictive of recurrence among pts with both lower risk (pCR) and higher risk (pN+) disease.

3522 Poster Discussion Session; Displayed in Poster Session (Board #145), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Circulating tumor DNA (ctDNA) utilizing a high-sensitivity panel to detect minimal residual disease post liver hepatectomy and predict disease recurrence. *First Author: Michael J. Overman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Preliminary data suggests that ctDNA can serve as a marker of minimal residual disease following colorectal cancer (CRC) tumor resection. Applicability of current ctDNA testing is limited by the requirement of sequencing known individual tumor mutations. We explored the applicability of a multi-gene panel ctDNA detection technology in CRC. **Methods:** Plasma was prospectively collected from CRC patients (pts) undergoing hepatic resections with curative intent between 1/2013 to 9/2016. In a blinded manner 5ml of preoperative (preop) and immediate post-operative (postop) plasma were tested using a novel 30kb ctDNA digital sequencing panel (Guardant Health) covering SNVs in 21 genes and indels in 9 genes based on the landscape of genomic alterations in ctDNA from over 10,000 advanced cancer pts with a high theoretical sensitivity (96%) for CRC. Median unique molecule coverage for this study is 9000 for cfDNA inputs ranging from 10 – 150 ng (media input preop = 27 ng, median input postop = 49 ng) with 120,000X sequencing depth on an IIlumina HiSeq2500. **Results:** A total of 54 pts underwent liver metastectomies with curative intent with a median follow-up of 33 months. Preop blood was a median of 49 days from last systemic chemotherapy and 3 days prior to surgery; postop blood was a median of 17 days after resection. Tumor mutations from standard of care hotspot multigene panel testing (at MDACC) were identified in 46 of 54 pts (85%). Preop ctDNA mutation detection rate was 80% (43/54) and 44% (24/54) in postop setting, with postop median allele frequency of 0.16% (range 0.01% to 20%). In pts with a minimum of 1 year follow up, sensitivity of postop ctDNA for residual disease was 58% (95%CI; 41%-74%), and specificity was 100% (66%-100%). In 43 patients who underwent successful resection of all visible disease, postop detection of ctDNA significantly correlated with RFS ($P = 0.002$, HR 3.1; 95% CI 1.7-9.1) with 2-year RFS of 0% vs. 47%. Recurrence was detected in ctDNA a median of 5.1 months prior to radiographic recurrence. **Conclusions:** The detection of postop ctDNA using an NGS panel-based approach is feasible and is associated with a very high rate of disease recurrence.

3523 Poster Discussion Session; Displayed in Poster Session (Board #146), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Profiling circulating tumor (ct)DNA mutations after panitumumab treatment in patients with refractory metastatic colorectal cancer (mCRC) from the phase III ASPECCT study. *First Author: Michael Boedigheimer, Amgen Inc., Thousand Oaks, CA*

Background: ASPECCT was a clinical trial performed in the chemotherapy-refractory third-line mCRC setting (N = 1010). This biomarker analysis explores the mutational landscape in panitumumab monotherapy subjects. Analysis of plasma ctDNA at baseline and post-treatment (PT) by next-generation sequencing provides a snapshot of the main changes in key genes before and after therapy. **Methods:** CtDNA collected at baseline and PT was analyzed for mutations using the Plasma*Select*-R™ 63-gene panel (0.1% limit of detection). Gain or loss of mutation was defined at the amino acid level. Net change is the sum of mutations gained minus the sum of mutations lost. A single individual could have both net gain and/or net loss of mutations within a single gene. **Results:** Significant tumor clonal diversification was observed during therapy. In 238 subjects with paired plasma samples,29% of subjects had multiple mutations in the same gene at baseline and 41% of subjects had multiple mutations in the same gene PT. At least 10% of subjects demonstrated an on-therapy acquired mutation in at least one of the following genes: *APC*, *EGFR*, *ALK*, *HER4*, *TP53*, *AR*, *KRAS*, *BRAF*, *PDGFRA*, *STK11, ESR1, FBXWT*, and *KIT* (ordered by frequency). New mutations were noted both inside and outside the EGFR pathway. Unexpectedly, patients with a large decrease in mutant DNA burden after anti-EGFR treatment were also seen. EGFR pathway genes with significant net gain were: *KRAS*, *EGFR*, *NRAS*, *BRAF*, *MAP2K1*, *PIK3CA*, and *AKT1*. Non-EGFR pathway mutations gained included: *APC*, *CDK6*, *SMARCB1*, *FBXW7*, *TERT*, *RB1*, *CTNNB1*, and *IDH1*. **Conclusions:** This 63-gene plasma analysis suggests that there are significant dynamic changes in clonal mutational fraction under anti-EGFR selection. Our analysis reveals that increasing global tumor heterogeneity is associated with poorer overall survival. A subset of patients demonstrated an overall decrease in tumor heterogeneity on panitumumab therapy (28%), indicating that under anti-EGFR selective pressure mutational heterogeneity can also decrease. Clinical trial information: NCT01001377.

3525 Poster Session (Board #148), Sat, 8:00 AM-11:30 AM

Primary tumor location and efficacy of second-line therapy after initial treatment with FOLFIRI in combination with cetuximab or bevacizumab in patients with metastatic colorectal cancer- FIRE-3 (AIOKRK0306). *First Author: Dominik Paul Modest, Department of Hematology and Oncology, Klinikum Grosshadern, University of Munich, Munich, Germany*

Background: FIRE3 compared 1st-line therapy with FOLFIRI plus either cetuximab (arm A) or bevacizumab (arm B) in 592 patients (pts) with KRAS exon 2 wild-type metastatic colorectal cancer (mCRC). Second-line therapies appeared more successful in arm A compared to arm B. The impact of primary tumor location on this observation is unclear. **Methods:** Pts. were stratified for primary tumor site (left- vs. right-sided). Duration of 2nd-line therapy was calculated as time from first to last application. Progression-free survival (PFS2nd) and overall survival (OS2nd) of second-line therapy) were evaluated by Kaplan-Meier method and compared by log rank test as well as Cox regression. All analyses were performed in the RAS wild-type population of the trial and reported according to drug sequences. **Results:** 272 of 400 pts. (68%) received 2nd-line therapy, of those 206 (109 in arm A, 97 in arm B) pts. presented left-sided, whereas 66 (26 in arm A, 40 in arm B) pts. presented right-sided primaries. PFS2nd was markedly longer in pts. with left-sided as compared to right-sided primary tumors (6.0 (95% CI: 5.5-6.7) vs. 3.4 (95% CI: 3.0-5.8) months, hazard ratio (HR): 0.64 (95% CI: 0.47-0.87), $P = 0.005$). Differences in PFS2nd between study-arms were evident in pts. with left-sided primaries (arm A: 7.3 (95% CI: 6.4-7.7) vs. arm B: 5.3 (95% CI: 4.3-5.9) months, HR: 0.61 (95% CI: 0.44-0.84), $P = 0.002$), but not in pts. with right-sided primaries (arm A: 4.0 (95% CI: 3.0-6.3) vs. arm B: 3.3 (95% CI: 2.6-5.8) months, HR: 1.09 (95% CI: 0.62-1.90). Consistent observations were also made for treatment duration and OS2nd. **Conclusions:** This retrospective analysis indicates that treatment duration and efficacy of second-line therapy are associated with primary tumor location. Efficacy of second-line therapy was significantly greater in pts. with left-sided tumors as compared to right sided tumors. This difference was driven by superior activity of second-line regimens of arm A compared to arm B in left-sided tumors. Our observations confirm the strong prognostic value of primary tumor location in mCRC across treatment lines. Clinical trial information: NCT00433927.

3528 Poster Session (Board #151), Sat, 8:00 AM-11:30 AM

Statistical modeling of CALGB 80405 (Alliance) to identify influential factors in metastatic colorectal cancer (CRC) dependent on primary (1o) tumor side. *First Author: Leon Furchtgott, GNS Healthcare, Cambridge, MA*

Background: CALGB 80405 is a phase III clinical trial of FOLFOX and FOLFIRI w/ randomly assigned cetuximab or bevacizumab. Novel machine learning approaches to the study dataset provide valuable insights into CRC prognosis and management of CRC progression. **Methods:** Using a Monte Carlo Bayesian Generalized Linear Model analytical platform, we built an ensemble of models for overall survival (OS). We used 99 baseline and demographic variables, including 1904 patients w/ 1^o side and 949 w/ KRAS wild-type status. Building an ensemble of predictive models reduces risk of overfitting, estimates model uncertainty and identifies key variables by model consensus as measured by ensemble frequency (freq). We fit gender and 1^o side (L vs R) stratum-specific models to examine differences in drivers of disease in those strata. **Results:** 1^o side (avg Cox hazard ratio = 0.89, R side reference), ECOG performance status (1.30, reference level 0), AST concentration (1.01), peripheral neutrophil percentage (1.01) and local primary and abdominal site of disease indicators (1.22; 1.26) were key variables predictive of OS ($>$ 75% freq). In 1^o side stratum-specific models, urine protein level (1.61), treatment intent (0.75, nonpalliative as reference) and hemoglobin concentration (0.85) were more associated w/ L side progression (freq $>$ 85% in L stratum model, $<$ 20% in R), while liver and lung sites of disease (2.3; 1.09) were more associated w/ R side progression (freq $>$ 65% in R stratum model, $<$ 20% in L). Predictors of 1^o left-sidedness included age (avg log odds ratio = 0.02), hemoglobin (0.41), and abdominal (3.79) and liver (0.68) sites of disease. Modest differences in disease prognostic factors existed between genders: women more influenced by metastatic status, age, liver site of disease and creatinine level; men more influenced by urine protein level and prior diabetes. **Conclusions:** 1^o side plays a central role in potentially explaining both variation in OS and differences in drivers of OS. Availability of these measures at baseline enables better sense of disease course at initiation of treatment. Support: U10CA180821, U10CA180882, Eli Lilly & Co., Genentech, Pfizer Clinical trial information: NCT00265850.

3529 Poster Session (Board #152), Sat, 8:00 AM-11:30 AM

Phase 1b/II study of cancer stemness inhibitor napabucasin (BBI-608) in combination with FOLFIRI +/- bevacizumab (bev) in metastatic colorectal cancer (mCRC) patients (pts). *First Author: Johanna C. Bendell, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: Cancer stem cells are considered to be fundamentally important for resistance, recurrence and metastasis. Napabucasin is a first-in-class cancer stemness inhibitor in development identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells (Li et al, PNAS 112(6):1839, 2015). Preclinically, napabucasin sensitizes cancer cells to chemotherapy and targeted agents. **Methods:** A phase Ib/II multi-center study in mCRC pts was done to confirm the RP2D and signs of anti-cancer activity of napabucasin in combination with FOLFIRI +/- Bev. Pts received napabucasin 240 mg PO BID with bi-weekly FOLFIRI IV +/- Bev 5 mg/kg until disease progression or other discontinuation criterion. **Results:** 82 pretreated mCRC pts were enrolled (ITT); including 32 (39%) previously treated with FOLFIRI +/- bev. Of the 82 pts, 48 received FOLFIRI and 34 FOLFIRI plus bev in combination with napabucasin. There was no dose-limiting or unexpected toxicity or significant PK interactions. Most common adverse events (AEs) included grade 1/2 diarrhea, cramping, nausea, vomiting, fatigue and anorexia with grade 4 diarrhea in 1 pt and 27 pts with grade 3 AEs including: diarrhea (15), fatigue (5), dehydration (1), electrolyte imbalance (4), abdominal pain (1), vomiting (1) and weight loss (1), which resolved with dose reduction and supportive care. Disease control (CR+PR+SD) was observed in 55 of 66 pts who received RECIST evaluation (83%), with 1 CR (1.5%), 13 PR (20%) (33-100% regression) and 27 SD with tumor regression (41%). **Conclusions:** This phase Ib/II study confirmed that napabucasin can be safely combined with FOLFIRI +/- bev, and shows encouraging signs of efficacy in pretreated mCRC pts, including pts previously treated with FOLFIRI +/- bev. Clinical trial information: NCT02024607.

	DCR %		ORR %	
Subset	**Evaluable**	**ITT**	**Evaluable**	**ITT**
All	83 (55/66)	67 (55/82)	21 (14/66)	17 (14/82)
>/=2nd Line FOLFIRI-naïve	85 (33/39)	66 (33/50)	21 (8/39)	16 (8/50)
>/=2nd Line FOLFIRI-exposed	81 (22/27)	69 (22/32)	22 (6/27)	19 (6/32)
GERCOR (Tournigand et al. 2004) 2nd Line FOLFIRI-naive	41 (24/59)	35 (24/69)	5 (3/59)	4 (3/69)

3530 Poster Session (Board #153), Sat, 8:00 AM-11:30 AM

MABp1 to improve clinical outcomes of patients with symptomatic refractory metastatic colorectal cancer patients: Per-protocol population analysis of phase III study (PT026). *First Author: Lucjan Wyrwicz, Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland*

Background: Refractory metastatic colorectal cancer (mCRC) patients derive minimal benefit from further exposure to toxic agents. MABp1 is an anti-interleukin 1 alpha antibody that is shown to prolong survival (NCT01767857) and improves outcomes when assessed with a primary endpoint based on a constellation of objective and patient self-reported measures (NCT02138422) (Hickish T. et al Lancet Oncology 2017). In the latter study, clinically advanced patients were enrolled (symptomatic, ECOG 1,2), and 18% of patients progressed prior to reaching the endpoint assessments. Here we present the outcomes in per-protocol population (PP), those patients completing week 8 assessments. **Methods:** 309 patients randomized 2:1 to receive MABp1 versus placebo. Patients were ECOG 1-2, with mCRC refractory to chemotherapy, any degree of weight loss, and cancer-associated symptoms. The composite primary endpoint assessed the rate of patients achieving stabilization or improvement in lean body mass (LBM) and two of three symptom measures (pain, fatigue, appetite loss) from screening to the week 8 assessment. The study was designed for placebo cross-over, thus OS analysis for MABp1 vs placebo was not possible. **Results:** 57 patients (38 MABp1 [18%] and 19 placebo [19%]) discontinued study prior to the week 8 assessment due to disease progression, including 17 (8%) and 11 (11%) deaths in MABp1 and placebo respectively. 62% of placebo patients received MABp1 after 8 weeks. 252 patients, 40% in MABp1 (68/169) vs 23% in placebo (19/83) met the primary endpoint ($p = 0.003$). 139 patients were available for PP survival analysis (90 MABp1 vs 49 Placebo). Median OS of those achieving the primary endpoint was 11.7 months vs 5.7 months for those that did not (HR 0.39; $p < 0.0001$). Radiographic stable disease was improved (42% vs 12%; $p < 0.001$) and incidence of SAEs (6% vs 15%; $p = 0.11$) reduced in those achieving the primary endpoint. **Conclusions:** Achieving the primary endpoint was associated with improvement in outcomes, RECIST stabilization, SAEs and survival. Further study should confirm the effect of MABp1 on survival in this population. Clinical trial information: NCT02138422.

3531 Poster Session (Board #154), Sat, 8:00 AM-11:30 AM

Combination of nivolumab (nivo) + ipilimumab (ipi) in the treatment of patients (pts) with deficient DNA mismatch repair (dMMR)/high microsatellite instability (MSI-H) metastatic colorectal cancer (mCRC): CheckMate 142 study. *First Author: Thierry Andre, Hopital Saint Antoine, Paris, France*

Background: Nivo, a fully human anti-PD-1 mAb, provided an ORR of 31%, durable responses (median DOR not reached), and a 12-mo OS rate of 73.8% in pts with dMMR/MSI-H mCRC (Overman M, et al. 2017). Preliminary analysis of nivo + ipi, a humanized anti-CTLA-4 mAb, demonstrated manageable safety and promising efficacy in pts with dMMR/MSI-H mCRC (Overman M, et al. 2016). Here we report interim safety and efficacy of nivo + ipi in this pt population from the Checkmate 142 study (NCT02060188). **Methods:** Pts with dMMR/MSI-H mCRC who progressed on or were intolerant of $\geq$1 prior line of therapy received nivo 3 mg/kg + ipi 1 mg/kg q3w $\times$ 4 doses followed by nivo 3 mg/kg q2w until discontinuation due to disease progression or other reason. Primary endpoint was investigator-reported ORR by RECIST 1.1. Other endpoints included DOR, PFS, OS, safety, and tolerability. **Results:** 27 pts with dMMR/MSI-H mCRC treated with nivo + ipi received the first dose $\geq$6 mo prior to the database lock (DBL; Sept 2016). Of these pts, 93% received $\geq$2 prior lines of therapy. At the time of DBL, 44% of pts remained on treatment, and 14 pts had discontinued therapy due to disease progression (n=8) or TRAEs (n=6). ORR was 41% and disease control rate (DCR) was 78% (Table). The median time to response was 2.7 mo, and 82% of responses (9/11) were ongoing at 6 mo. The medians for DOR, PFS and OS had not been reached. Grade 3–4 TRAEs occurred in 10 pts (37%).TRAEs leading to discontinuation included acute kidney injury, increased transaminases, necrotizing myositis, sarcoidosis, dyspnea, and thrombocytopenia (1 each). No deaths were attributed to therapy. **Conclusions:** Initial analysis ofnivo + ipi in pts with $\geq$6-mo follow-up demonstrated a manageable safety profile and clinical activity characterized by a high DCR and encouraging survival benefit. This study is ongoing, and updated efficacy and biomarker analyses of $\approx$80 pts with $\geq$6-mo follow-up will be presented. Clinical trial information: NCT02060188.

	Nivo + Ipi (n=27)
ORR, n (%)	11 (41)
CR	1 (4)
PR	10 (37)
SD	14 (52)
PD	2 (7)
DCR[a], n (%)	21 (78)
Median DOR (95% CI), mo	NR (8.8–NE)

[a]CR+PR+SD for $\geq$12 weeks.

3532 Poster Session (Board #155), Sat, 8:00 AM-11:30 AM

REsect: Blinded assessment of amenability to potentially curative treatment of previously unresectable colorectal cancer liver metastases (CRC LM) after chemotherapy ± RadioEmbolization (SIRT) in the randomized SIRFLOX trial. *First Author: Benjamin Garlipp, Otto-von-Guericke-University Hospital, Magdeburg, Germany*

Background: Secondary resection and radiofrequency ablation (RFA) of primarily unresectable LM from CRC can prolong survival and cure some patients (pts). Effective downsizing treatments are needed but their impact on secondary amenability to surgery/RFA is difficult to evaluate objectively. The added value of SIRT is not well established. **Methods:** Baseline (BL) and follow-up (FU) imaging at best response for CRC pts treated with FOLFOX chemotherapy±bevacizumab (bev) (CT) *vs.* CT+SIRT in the phase III SIRFLOX RCT were reviewed by 3−5 expert HPB surgeons (from a panel of 15) for resectability of LM. Reviewers were blinded to each other and to all clinical information incl. time of imaging (BL/FU). Resectability was defined as ≥60% of reviewers assessing a pt as resectable. For non-resectable cases, surgeons indicated whether a combination of surgery and RFA could completely remove all LM. Lesions deemed suitable for RFA by a surgeon needed to be confirmed by an interventional radiologist. Pts were defined as "clearable" if ≥60% of reviewers assessed them as amenable to complete removal of LM by surgery alone or surgery+RFA. **Results:** 472 pts were evaluable (CT, n = 228; CT+SIRT, n = 244). There was no significant difference in LM resectability at BL (CT, n = 25, 10.96%; CT+SIRT, n = 29, 11.89%; p = 0.77). At FU, significantly more pts in the SIRT arm had resectable LM (CT, n = 66, 28.95%; CT+SIRT, n = 93, 38.11%; p < 0.0001). Of 203 pts in the CT arm and 215 pts in the CT+SIRT arm deemed unresectable at BL, 46 (22.66%) and 67 (31.16%), respectively, were converted to resectability (p < 0.0001). Assessing "clearability" using surgery and RFA, again no difference was noted at BL (CT, n = 31, 13.60%; CT+SIRT, n = 42, 17.21%; p = 0.309). At FU, a trend in favor of CT+SIRT was seen (CT, n = 79, 34.65%; CT+SIRT, n = 102, 41.80%; p = 0.1296). **Conclusions:** The addition of SIRT to FOLFOX(±bev) based CT significantly increased the gain in resectability of primarily unresectable CRC LM compared with CT alone. For amenability to the combination of surgery+RFA, this effect was still seen, albeit attenuated. Subgroup analyses are ongoing. Clinical trial information: NCT00724503.

3533 Poster Session (Board #156), Sat, 8:00 AM-11:30 AM

"CHARTA": FOLFOX/Bevacizumab vs. FOLFOXIRI/Bevacizumab in advanced colorectal cancer—Final results, prognostic and potentially predictive factors from the randomized Phase II trial of the AIO. *First Author: Hans-Joachim Schmoll, Martin Luther University, Division Clinical Oncology, University Hospital, Halle, Germany*

Background: FOLFOXIRI/Bevacizumab (Bev) is superior to FOLFIRI/Bev in the TRIBE trial (F Loupakis, NEJM 2014). The CHARTA trial was developed parallel to TRIBE with the same 4-drug-protocol but vs. FOLFOX/B ev as control arm. **Methods:** From 7/11 to 12/14 250 patients were randomized, including ECOG 0-2, ≥ 1 measurable lesion > 1cm, stratified by ESMO-Group 1,2,3 (HJ Schmoll, Ann Oncol 2012). Induction: 6 months, maintenance Capecitabine+Bev until progression or max.12 months, at P reinduction by investigators decision. 25% dose reduction was allowed in cycle 1 + 2 on the investigator's discretion. Primary EP: significant improvement of PFS-rate @ 9 months (p<0.1, 2-sided Fisher's-exact test); secondary EP: RR, PFS, OS, toxicity. **Results:** 241 pts. (1 not elig., 8 prot. violation) are evaluable after a follow up of 31.4 (0.1-51) months. m/f: 65%/35%, age 61y (21-82), ECOG 0-1/2: 96%/4%. The *Primary Endpoint* was met: PFS @ 9 months 56% vs. 68%, p= 0.086. PFS was improved: 9.8 vs. 12.0 months, HR 0.7 (ns.), identical to TRIBE with 9.7 vs. 12.1 months. Response rate (A/B): CR: 5%/5%, CR/PR 60%/70%, SD 25%/21%, PD 14%/9%. Final OS will be available at the meeting. Toxicity was low to moderate without major differences except ° $^{3}/_{4}$ diarrhea (12%/16%) and neutrophils (14%/20%). Clinical/molecular prognostic or predictive factors are equally distributed (stratification by ESMO groups) (see table). There are major, but mostly not significant differences in RR/ PFS in most subgroups, however, not strong enough to safely identify patients with high potential to benefit from the 4-drug combination. Therefore, a multivariate analysis to model a common prognostic and predictive risk score is ongoing and will be presented at the meeting. **Conclusion:** "CHARTA" supports the superiority of FOLFOXIRI/Bev. A combined prognostic and predictive classification is required to better select those patients with most potential benefit from the 4-drug combination. Clinical trial information: NCT01321957.

PFS by clinical and molecular subgroups.

Factors	all	% pts 241	Arm A 9.8	Arm B 12.0	HR 0.80	p-value 0.097
Risk Score [(1)]	low	9%	9.6	12.7	0.83	0.71
	intermed	74%	11.1	11.7	0.81	0.21
	high	17%	7.0	11.9	0.66	0.23
ESMO Group	1	29%	10.4	12.9	0.74	0.25
	2	55%	9.6	11.5	0.89	0.53
	3	16%	10.4	15.8	0.62	0.18
RAS	wt	42%	9.6	13.1	0.70	0.12
	mut	58%	10.4	12.3	0.82	0.32
BRAF	mut	6%	7.8	10.1	0.72	0.61
Location	left	73%	10.4	12.2	0.73	**0.051**
	right	27%	8.3	10.9	0.81	0.44

[(1)]Köhne et al. Ann Oncol 2003

3534 Poster Session (Board #157), Sat, 8:00 AM-11:30 AM

Variability in genomic alterations between right- and left-sided microsatellite stable (MSS) metastatic colorectal cancer and impact on survival. *First Author: Rona Yaeger, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Metastatic colorectal cancers (mCRCs) with a right-sided primary site are associated with shorter survival and insensitivity to EGFR inhibitors compared to those originating in the left side of the colon or rectum. **Methods:** We performed targeted gene sequencing of 928 consecutive MSS mCRCs. Primary tumor site was divided into right-sided for cecum to distal transverse colon (n = 242), left-sided for splenic flexure to rectum (n = 673), or unknown colonic location (n = 13). Histologic subtypes were conventional (adenocarcinoma not otherwise specified), conventional with mucinous features (< 50% mucinous), mucinous, signet ring, and poorly differentiated. To evaluate receptor tyrosine kinase (RTK) signaling, we analyzed ligand mRNA expression in TCGA. **Results:** Overall survival from time of metastasis was shorter for right-sided than left-sided primary site (survival at 5 years: 45% v 67%, p < 0.001). Right-sided tumors had more mutations (5.60 v 4.62 per MB, p < 0.001) but fewer copy-number changes (0.18 v 0.22 fraction genome altered, p = 0.001) compared to left-sided tumors. Alterations of KRAS, BRAF, PIK3CA, PTEN, AKT1, RNF43, and SMAD4 were significantly enriched in right-sided tumors, and of APC and TP53 in left-sided tumors. In a multivariate model, APC (HR = 0.7, p = 0.03), BRAF (HR = 3.7, p < 0.001), and KRAS (HR = 1.7, p < 0.01) alterations predicted for survival, but primary site did not (HR = 0.74, p = 0.07). Amphiregulin, epiregulin, neuregulin, and HGF expression was significantly higher in left-sided tumors. We found a higher proportion of conventional histology (83% v 63%) and moderate differentiation (82% v 69%) for left versus right-sided cases. **Conclusions:** We find that within MSS mCRC there are significantly more oncogenic mutations in right-sided tumors, and the difference in survival between right- and left-sided mCRC is primarily driven by differences in mutations. Left-sided tumors more commonly exhibit a "simpler" conventional histology that is lower grade and may rely on native RTK signaling, such as EGFR, for growth, providing a potential mechanism for the differential sensitivity to EGFR inhibitors seen by primary tumor site.

3535 Poster Session (Board #158), Sat, 8:00 AM-11:30 AM

Heterogeneity in early lesion changes on treatment as a marker of poor prognosis in patients (pts) with metastatic colorectal cancer (mCRC) treated with first line systemic chemotherapy ± biologic: Findings from 9,092 pts in the ARCAD database. *First Author: Fang-Shu Ou, Mayo Clinic Cancer Center, Rochester, MN*

Background: CRC is known to be a heterogeneous disease. This study quantifies within pt heterogeneity in early lesion change rate (LCR) in the era of targeted agents compared to chemo alone and its potential impact on survival. **Methods:** Pts with 2-10 lesions measured at baseline were included. For each lesion, the early LCR was defined as the change in size (shrinking or growing) from baseline to 12 weeks on treatment. Within pt heterogeneity in early LCR among lesions was estimated by standard deviation (STD). A larger value of STD indicates larger variation of LCR per pt. Stratified multivariate Cox models were used to assess the associations between LCR STD with overall survival (OS). Adjusted hazard ratios (HR_{adj}) and 95% confidence intervals (CIs) are reported. **Results:** Data were available on 9,092 mCRC pts (median age 61; 60% male, 55% ECOG PS 0; 61% 2+ metastatic sites) enrolled in 16 1st-line randomized trials, with 44%, 42%, and 10% of pts received chemo alone, + a VEGF inhibitor (VEGFi) or an EGFR inhibitor (EGFRi), respectively. LCR heterogeneity is the highest among pts received EGFRi but lowest among pts received VEGFi (Table). Overall, higher heterogeneity is associated with worst OS (HR_{adj}1.22, 95% CI (1.16, 1.27)). The effect is most pronounced in pts received VEGFi (interaction p=0.0012). **Conclusions:** There was heterogeneity observed in lesion size changes within pts. Its magnitude varies across treatment approaches, and was associated with poor survival. This preliminary result reveals the great potentials to define novel response endpoint and refine treatment decision-making by incorporating heterogeneities in lesion changes.

	No. of pts[&] (%)	LGR STD Median (Q1, Q3)	$HR_{adj\#}$ (CI)
Overall	9092	0.51 (0.26, 0.89)	1.22 (1.16, 1.27)
VEGFi	3857 (42)	0.47 (0.25, 0.81)	1.31 (1.18, 1.46)
EGFRi	870 (10)	0.60 (0.31, 1.01)	1.16 (1.03, 1.31)
Chemo alone	4016 (44)	0.55 (0.27, 0.95)	1.25 (1.16, 1.35)
		p-value* <0.0001	

* compares LGR STD across different treatment. # adjusted for age, gender, PS, lesion baseline sum, min and median of LCR. [&] 349 pts received EGFRi+VGFRi were not included

3536 Poster Session (Board #159), Sat, 8:00 AM-11:30 AM

A large multicenter study evaluating prognosis and chemosensitivity of metastatic colorectal cancers with microsatellite instability. *First Author: David Tougeron, Gastroenterology Department, Poitiers University Hospital, Poitiers, France*

Background: Deficient Mismatch Repair (dMMR) in colorectal cancers (CRC) represent 12% of all tumors. In non-metastatic CRC setting, dMMR are associated with good prognosis but also with resistance to adjuvant 5-FU chemotherapy. In metastatic CRC (mCRC) setting, dMMR is found in less than 5% and its influence on prognosis and treatment response is little known. **Methods:** This multicenter retrospective study included all consecutive patients with dMMR mCRC treated between 2005 and 2015 in 17 centers. The Kaplan-Meier method was used to calculate overall survival (OS) and progression-free survival (PFS). Prognostic variables were evaluated in univariate analysis using the Log rank test and in multivariate analysis using the Cox regression model. **Results:** A total of 198 patients with dMMR mCRC were included (median age 64.6 years). dMMR mCRC were mostly diagnosed with synchronous metastases (59%) and frequent peritoneal carcinosis (43%). Lynch syndrome was found in 34% of cases and 36% of tumors had a *BRAF*^{V600E} mutation. Median OS was 20.6 months. A low risk Kohne's prognostic index (HR = 0.40 [0.22-0.72], p = 0.02) and absence of peritoneal carcinosis (HR = 0.51 [0.29-0.90], p = 0.02) were associated with better OS in multivariate analysis. Main first-line regimens were 5FU-based (n = 20), oxaliplatin-based (n = 75) or irinotecan-based (n = 46) chemotherapy. Median PFS on first-line treatment was 5.9 months. The objective response rate (ORR) was 0%, 19% and 36% for 5FU-based, oxaliplatin-based and irinotecan-based chemotherapies, respectively (p = 0.02). A trend for a longer PFS (3.3, 5.5 and 10.2 months, respectively, p = 0.06) and OS (17.7, 21.1 and 34.2 months, respectively, p = 0.05) was also observed for irinotecan-based chemotherapy. The addition of bevacizumab to chemotherapy was associated with a significant increase of ORR (p = 0.01) and PFS (p = 0.04) as compared to the addition of an anti-EGFR therapy. **Conclusions:** This study suggests that dMMR mCRC are associated with poor prognosis and chemoresistance, especially to 5FU-based chemotherapy. Efficacy of irinotecan and bevacizumab should be evaluated in a prospective trial in combination with immune checkpoint inhibitors.

3537 Poster Session (Board #160), Sat, 8:00 AM-11:30 AM

Neoadjuvant radiotherapy vs. surgery alone for stage II/III mid-low rectal cancer with or without high risk factors: A multicenter randomized trial. *First Author: Ziqiang Wang, West China Hospital Sichuan University, Chengdu, China*

Background: Neoadjuvant (chemo)radiotherapy (NRT) is the standard treatment for locally advanced rectal cancer (RC),which reducing local recurrence (LR) without survival benefit. There are also reports claiming similar local control achieved by surgery alone in selected patients, that raising the issue of omitting NRT in low risk patients. The aim of this study was to clarify the benefit of NRT in stage II/III RC with or without high risk factors. **Methods:** Eligible participants with mid-low cT3-4aN$\pm$ RC were included and classified as high risk patients and low risk patients according to the clinical staging. High risk was defined as T3 tumor with extramural spread $>$ 5mm, T4a or lymph node $>$ 8mm. High and low risk patients were both randomized into two groups: high risk radiotherapy (HRR) or high risk surgery (HRS), low risk radiotherapy (LRR) or low risk surgery (LRS) separately. Patients in HRR and LRR received short term NRT (5*5Gy) + TME, while patients in HRS and LRS underwent surgery alone. The primary endpoint was 3-y LR. The secondary endpoints were OS, DFS, quality of surgery and safety. **Results:** From Jun. 2011 to Dec. 2015,401 consecutive patients were analyzed (LRS 99, LRR 97, HRS 102, HRR 103). As for primary endpoint, 3-y LR was obviously lower in low risk patients (3% vs. 9%, p = 0.026), but comparable in LRR vs. LRS (3% vs. 2%, p = 0.32) and HRR vs. HRS (11% vs. 7%, p = 0.42). Concerning secondary endpoints, low risk patients were favorable in 3-y OS ($p < 0.001$), DFS ($p < 0.001$), and distant metastasis (p = 0.001), compared to the high risk. And 3-y OS in HRR was higher than that in HRS (82% vs. 70%, p = 0.032). NRT caused 1.5% grade 3/4°radiation-related complications with a higher rate of late leakage (4.5% vs 0.0%, p = 0.004). Besides, positive CRM was higher in HRS (HRS 14.7% vs. HRR 4.9%, p = 0.017). **Conclusions:** Depth of extramural spread and lymph node status are favorable predictors for LR and survival. NRT may improve OS for high-risk RC. Low-risk RC has very low LR, suggesting against routine use of NRT. Relatively high LR and better OS in high risk patients justify use of NRT or NCR. Short-term radiation is safe for Asian patients, given caution be paid to more late leakage. Clinical trial information: NCT01437514.

3538 Poster Session (Board #161), Sat, 8:00 AM-11:30 AM

Velour trial biomarkers update: Impact of RAS, BRAF, and sidedness on aflibercept activity. *First Author: Pratyaksha Wirapati, Swiss Institute of Bioinformatics, Lausanne, Switzerland*

Background: Addition of (ziv)-aflibercept (A) to FOLFIRI in second-line therapy for metastatic colorectal cancer (CRC) has been shown to be beneficial in phase III VELOUR trial (NCT00561470). A follow-up study (NCT01754272) was undertaken to acquire tumor samples for biomarker analyses and identify subgroups of patients with differential treatment effects. The primary results assessing efficacy according to well-established CRC subgroups defined by RAS, BRAF status and sidedness are reported here. **Methods:** Tissue specimens were collected for 666 patients from 1226 ITT pts. Suitable specimens were assayed for somatic mutation using NGS targeting extended RAS and BRAF genes. NGS assays with no missing values were obtained for 482 pts. Affymetrix gene chip technology was used for whole-transcriptome profiling; sidedness was extracted from available pathological reports. Differences between subgroups were assessed by interaction analysis. **Results:** The treatment effects on overall survival (OS) for the 482 pts is still significant HR=0.80 (CI 0.65-0.99), and similar to the ITT (n=1226) results (HR=0.82, CI 0.71-0.93). Two established ways of defining mutations (traditional KRAS exon 2 and extended RAS using NGS) show a trend for a differential effect across mutation groups.(see table for OS). Interestingly, BRAF mutants (which are all RAS wild type) show a trend for better outcome Same is seen for PFS and RR. Sidedness did not affect efficacy (HR: 0.83 (0.63- 1.1) for left and HR: 0.83 (0.54-1.3) for right. **Conclusions:** None of the mutations subgroup results shows significant interaction, although the ratios of treatment HR favor RAS wild types. Similar trends were observed in published trials with bevacizumab or ramucirumab. *Sanofi supported this ISS.* Clinical trial information: NCT01754272.

Mutation	Status	N	Med OS FOLFIRI+Placebo	Med OS FOLFIRI + A	HR 95% CI	Interaction (ratio of HR, 95% CI, p-value)
KRASex2	wt	281	11.6	14.9	0.74 (0.56-0.99)	1.21 (0.79 - 1.86)
	mut	201	10.6	12.6	0.90 (0.65-1.24)	p = 0.38
ExtRas	wt	218	11.7	16.0	0.70 (0.50-0.97)	1.39 (0.90 - 2.13)
	mut	264	11.2	12.6	0.93 (0.70-1.23)	p = 0.13
BRAF	wt	446	12.4	13.0	0.84 (0.67-1.05)	0.49 (0.22 - 1.09)
	mut	36	5.5	10.3	0.42 (0.16-1.09)	p = 0.08

3539 Poster Session (Board #162), Sat, 8:00 AM-11:30 AM

Final results of the McCAVE trial: A double-blind, randomized phase 2 study of vanucizumab (VAN) plus FOLFOX vs. bevacizumab (BEV) plus FOLFOX in patients (pts) with previously untreated metastatic colorectal carcinoma (mCRC). *First Author: Johanna C. Bendell, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: VEGF-A and ANG-2 have complementary roles in regulation of tumor angiogenesis. Targeting VEGF-A with BEV in combination chemotherapy (CT) in mCRC has proven to increase PFS and OS. ANG-2 is overexpressed and associated with poor outcome of mCRC pts receiving BEVcontaining treatment. Hence, dual blockade of VEGF-A and ANG-2 by the bispecific mAb VAN with standard CT may improve clinical activity in mCRC. **Methods:** All pts received mFOLFOX-6 and were randomized 1:1 to also receive intravenous VAN 2000 mg every other week (Q2W) (Arm A) or BEV 5 mg/kg Q2W (Arm B). The primary end point was investigator assessed progression-free survival (PFS). Key eligibility criteria included pts with non-resectable mCRC, no prior therapy for advanced disease, PS 0-1, adequate organ functions, and no history of GI fistula/perforation or intraabdominal abscess within the last 6 months. **Results:** 192 pts were randomized (Arms A/B, n = 95/97) by 39 sites in 7 countries, between Oct 2014 and May 2016. Median follow-up was 17.6 months (range 2.8 – 20.7). In the ITT population (n = 189; Arms A/B, n = 94/95), median PFS in Arms A and B was 11.3 and 11.0 months (stratified hazard ratio (HR) 1.00 (95%CI 0.64-1.58; p = 0.985)), respectively. Objective response rate was 52.1% vs 57.9%. Relevant prognostic factors incl. RAS/BRAF status and tumor sidedness were balanced between arms and did not significantly influence outcome. Baseline plasma ANG-2 levels were prognostic in both arms but not predictive for response to VAN. The overall incidence of adverse events (AEs) grade $\geq$ 3 was similar (Arms A/B, 83.9%/82.1%); AEs grade $\geq$ 3 attributed to the mode of action of VAN/BEV included hypertension (37.6%/18.9%), hemorrhage (2.2%/1.1%), thromboembolic events (venous 6.5%/2.1%; arterial 1.1%/3.2%) and GI perforations incl. GI fistula & abdominal abscess (10.6%/8.4%). **Conclusions:** The combination of VAN and FOLFOX did not improve PFS and was associated with a marked increase in hypertension compared with BEV plus FOLFOX. Our results strongly suggest that ANG-2 is not a relevant therapeutic target in the setting of first line mCRC. Clinical trial information: NCT02141295.

3540 Poster Session (Board #163), Sat, 8:00 AM-11:30 AM

Regorafenib (REG) versus trifluridine/tipiracil (TAS-102) as salvage-line in patients with metastatic colorectal cancer refractory to standard chemotherapies (REGOTAS): A propensity score analysis from a JSCCR multicenter observational study. *First Author: Shota Fukuoka, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital, Chiba, Japan*

Background: It is unclear which drug of REG or TAS-102 should be used earlier for the patients with metastatic colorectal cancer (mCRC) who have access to both drugs. This study investigated the comparison of the efficacy between REG and TAS-102 in patients with refractory to standard chemotherapies. **Methods:** The clinical data of patients who were treated with REG or TAS-102 among these drugs naive mCRC patients between Jun 2014 and Sep 2015 were retrospectively delivered from 24 institutions of Japanese Society for Cancer of the Colon and Rectum (JSCCR). The primary endpoint was overall survival (OS). Propensity score (PS) was calculated with a logistic regression, in which using baseline parameters were included. Two methods, adjusted and matched analysis, to take propensity score were used. The clinical outcomes were evaluated with Kaplan-Meier method and Cox models based on PS adjustment and matching. **Results:** Total of 589 patients were enrolled and 550 patients (223 patients in the REG group and 327 patients in the TAS-102 group) met criteria for inclusion in the analysis. The results from PS adjusted analyses showed that OS was similar between the two groups (HR of TAS-102 to REG, 0.96; 95% confidence interval, 0.78–1.18). There were also no statistically significant differences between two groups for progression-free survival (HR 0.94) and time to ECOG Performance status≥2 (HR 1.00), expect for time to treatment failure (HR 0.81; P = 0.025). In the subgroup analysis, REG showed favorable survival compared with TAS-102 in the age of < 65 years patients and unfavorable survival in ≥65 years patients (P for interaction = 0.012). In the PS matched sample (174 patients in each group), the clinical outcomes were similar to the results of the PS adjusted analysis. **Conclusions:** Although REG and TAS-102 showed a similar efficacy in mCRC patients with refractory to standard chemotherapies, the choice of the drug by age might affect the survival. Supported by JSCCR. Clinical trial information: UMIN000020416

3541 Poster Session (Board #164), Sat, 8:00 AM-11:30 AM

A phase II study of pembrolizumab in combination with mFOLFOX6 for patients with advanced colorectal cancer. *First Author: Safi Shahda, Indiana University, Indianapolis, IN*

Background: Pembrolizumab (PEM) has activity in patients with deficient mismatch repair (dMMR) colorectal cancer (CRC). Oxaliplatin (OX) and 5FU lead to immunogenic cell death and increased antigen presentation. We hypothesized that combining mFOLFOX6 and PEM may enhance immunogenic cell death and improve outcome in patients with CRC irrespective of MMR status. **Methods:** Subjects ≥18 years old with untreated, unresectable CRC were assigned to a single arm study. The study had a safety run in cohort of six patients (OX 85 mg/m^2, leucovorin 400 mg/m^2, 5FU 400 mg/m^2, 5FU infusion 2400 mg/m^{2}over 46 hours) and PEM 200 mg Q 3 weeks, followed by a phase II cohort. The primary objective was median progression free survival (mPFS), with secondary objectives: safety and toxicity per CTCAE V4.03, median overall survival, response rate, immune related response, disease control rate, and molecular correlates. **Results:** Between 4/2015 and 9/2016, 30 subjects were enrolled with following characteristics: 11 female, 26 Caucasian, median age: 45 years (25-75), 3 with dMMR, 22 MMR-proficient, and 5 with no available data. During the safety run in, 2 patients had G3 febrile neutropenia (FN) and 1 G4 neutropenia. The data safety monitoring committee recommended dose reduction of mFOLFOX6 to OX 68 mg/m^2, leucovorin 400 mg/m^2, 5FU of 320 mg/m^2, 5FU infusion of 1920 mg/m^{2}over 46 hours and PEM 200 mg Q 3 weeks. At the data cut off (12/29/16), median follow up was 24 weeks (10-66) and 27 patients remained on study. Rate of G3/4 toxicity associated with FOLFOX/PEM and PEM alone was 36.7% and 13.2%, respectively. No further FN was observed. No grade 5 toxicity was seen on study. Best response was recorded as: 1 complete response, 15 partial response (CR +PR = 53%), and 14 stable disease, with 100% DCR at 8 weeks. One patient with dMMR had resection after 2 months of therapy with complete pathologic response. MPFS has not been reached (95% CI: 5.5 months, NR). **Conclusions:** Based on these preliminary results, PEM/mFOLFOX6 has acceptable toxicity though demonstrated a suggestion of increased neutropenia in the initial cohort. Clinical activity was seen in patients with untreated advanced CRC including those with proficient MMR. Clinical trial information: NCT02375672.

3542 Poster Session (Board #165), Sat, 8:00 AM-11:30 AM

Treatments (tx) after progression to first-line FOLFOXIRI plus bevacizumab (bev) in metastatic colorectal cancer (mCRC) patients (pts): A pooled analysis of TRIBE and MOMA studies by GONO group. *First Author: Daniele Rossini, Unit of Medical Oncology 2, Azienda Ospedaliera-Universitaria Pisana, the Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy*

Background: FOLFOXIRI plus bev is regarded by international guidelines as a valuable option in the first-line tx of mCRC pts. One of the major concerns for the adoption of this regimen is the potential limitation of subsequent therapeutic options. The aim of the present analysis was to focus on treatments received after progression in TRIBE (NCT00719797) and MOMA (NCTNCT02271464) studies. **Methods:** We collected data of tx received after progression and their outcome in terms of 2ndPFS (time from 2nd line tx start to disease progression or death) and OS II (time from 2nd line tx start to death). For pts in which the same drugs used in first-line were totally or partially reintroduced, the chemotherapy-free interval (CFI, time from the last administration of irinotecan or oxaliplatin during first-line to disease progression) was calculated. **Results:** Out of 482 pts treated with upfront FOLFOXIRI plus bev, 429 progressed. 303 (70.6%) pts received a 2nd line tx: 93 FOLFOXIRI +/- bev (Group A), 119 FOLFOX/XELOX or FOLFIRI +/- bev (Group B) and 91 other tx (Group C), including an anti-EGFR moAb in 60 cases. No difference was observed among the three groups in terms of 2ndPFS (median 2nd PFS Group A: 5.6 vs Group B: 4.4 vs Group C: 3.9 mos; p = 0.60) or OS II (median OS II Group A: 14.9 vs Group B: 13.8 vs Group C: 11.7 mos; p = 0.49). In the subgroup of pts with a CFI < 6 mos, Group A (n = 52) reported longer 2ndPFS compared to both Group B (n = 58) (median 2ndPFS 5.3 vs 3.0 mos; HR: 0.61,95%CI 0.41-0.89; p = 0.009) and Group C (n = 58) (5.3 vs 3.2 mos; HR: 0.71, 95%CI 0.48-1.05; p = 0.07). Consistent results were achieved in OS II (Group A vs Group B; median OS 13.6 vs 10.8 mos; HR: 0.65, 95%CI 0.42-1.00; p = 0.053; Group A vs Group C 13.6 vs 8.9 mos; HR: 0.60, 95%CI 0.39-0.93; p = 0.002). In the subgroup of pts with a CFI ≥ 6 mos, no significant difference was shown between Group A (n = 41) and Group B (n = 61) or C (n = 33). **Conclusions:** Tx after progression to first-line FOLFOXIRI plus bev are feasible and show expected efficacy results. The reintroduction of the triplet plus bev seems more effective than doublets plus bev or other tx when a more aggressive disease biology is suggested (CFI < 6 mos).

3543 Poster Session (Board #166), Sat, 8:00 AM-11:30 AM

Localization of the primary tumor (LPT) and maintenance strategies after first line oxaliplatin (Ox), fluoropyrimidine (FP), and bevacizumab (Bev) in metastatic colorectal cancer (mCRC): Results from the AIO 0207 trial. *First Author: Anke C. Reinacher-Schick, Ruhr-University Bochum, St. Josef Hospital, Bochum, Germany*

Background: Numerous trials have examined the prognostic and predictive value of the LPT in mCRC, but little is known about the predictive value of LPT on different maintenance strategies. We analyzed progression-free survival (PFS) and overall survival (OS) from start of maintenance according to LPT in patients (pts) from the AIO KRK 0207 trial. **Methods:** Following a 24-week standard induction 471 pts were randomized to FP/Bev, Bev mono or no treatment with 454 pts being evaluable for PFS. Right sided primary tumors were defined as located in the caecum, ascending colon, transverse colon up to the splenic flexure; left colon was defined as splenic flexure, descending and sigmoid colon and rectum. **Results:** Data on LPT was available in 414 pts. for PFS (91%). LPT was left sided (LPTl) in 291 (70%) and right-sided (LPTr) in 123 (30%) of pts, respectively (remaining pts: status was either unknown, n = 37 or LPT was located in both regions, n = 3). Median PFS1 was 3.9 months (mos.) for LPTr and 5.3 mos. for LPTl (p = 0.11; HR 1.19, 95%CI 0.96 - 1.48). Analyses on PFS did not demonstrate a major predictive impact of LPT on the efficacy of the three maintenance strategies. The pairwise comparison of treatment arms showed a better PFS for FP/Bev vs no treatment independent from LPT (left: p < 0.0001; HR = 2.39, 95%CI 1.73-3.31; right: p = 0.011; HR 1.78, 95%CI 1.14-2.80). In addition, Bev mono vs no treatment was superior in LPTl (p = 0.0032; HR 1.54, 95%CI 1.15-2.06) with less difference in LPTr (p = 0.17; HR 1.36, 95%CI 0.87-2.14). Analysis for OS (429 evaluable pts) confirmed the strong prognostic impact of LPT (left vs right: 24.0 vs 16.7 months; p < 0.0001; HR = 1.65, 95%CI 1.32 - 2.06), but without major interaction between LPT and maintenance arms. The impact related to RAS mutational status will be reported. **Conclusions:** The strong prognostic factor of the LPT is confirmed in pts with mCRC undergoing Ox/FP/Bev induction therapy while there seems to be no major predictive impact of LPT on different maintenance strategies. Clinical trial information: EudraCT-Nr: 2008-007974-39.

3544 Poster Session (Board #167), Sat, 8:00 AM-11:30 AM

Impact of FOLFOXIRI and bevacizumab (bev) compared to FOLFOX and bev on health related quality of life (HRQOL) in patients with metastatic colorectal cancer (MCRC): Analysis of the CHARTA-AIO 0209 trial. *First Author: Julia Quidde, Department of Oncology, Hematology and Bone Marrow Transplantation with Section Pneumology, Hubertus Wald-Tumor Zentrum (UCCH), University Hospital Hamburg-Eppendorf (UKE), Hamburg, Germany*

Background: FOLFOXIRI/bev is a highly efficacious first line regimen in MCRC. Despite higher rates of neutropenia, diarrhea and stomatitis, FOLFOXIRI/bev is tolerable and feasible in MCRC patients. To date nothing is known about the impact of this regimen on HRQOL. **Methods:** 250 patients were randomized to FOLFOX/bev (arm A) or FOLFOXIRI/bev (arm B). HRQOL were assessed at baseline, every 8 weeks during induction treatment (6 months) and every 12 weeks during maintenance treatment, using the EORTC QLQ-C30, QLQ-CR29 and QLQ-CIPN20. The mean values of every score were calculated as the average of week 8, 16 and 24 assessment. Test concerning mean values were performed as t-test, with global type I error set at 0.05. HRQOL deterioration and improvement rates were analyzed and compared between treatment groups using chi^2 tests. **Results:** For HRQOL analysis, 237 patients were eligible (arm A: 118; arm B: 119). Compliance rate with the HRQOL questionnaires was 95.4% at baseline, 72.6% at week 8, 59.5 % at week 16 and 43.5% at week 24. Whereas mean global quality of life score (GHS/QOL) was similar between arm A and B (59.8 vs. 58.8; p = 0.726), mean scores for nausea/vomiting (9.4 vs. 16.0; p = 0.015) and diarrhea (23.7 vs. 32.1; p = 0.051) significantly or borderline significantly favored arm A during induction period. Furthermore, at week 8 scores of nausea/vomiting (9.2 versus 17.3, p = 0.006) appetite loss (19.5 vs. 29.4; p = 0.035) and financial problems (18.3 vs. 29.5; p = 0.021) and at the end of treatment physical functioning (75.0 vs. 65.8; p = 0.048) were significantly better for arm A compared to arm B. No significant differences were observed in the remaining EORTC scores. The rates of deterioration and improvement between baseline and week 8 of at least 10 points in the EORTC scores were similar (e.g. deterioration-rate GHS/QOL score 21.5% vs. 26.5% for arm A vs. B; p = 0.461). **Conclusions:** Although no remarkable detriment in HRQOL was noted, the better efficacy of FOLFOXIRI/bev compared to FOLFOX/bev is associated with a decrease in mainly gastrointestinal QOL scores. Further subgroup-analyses will be presented at the meeting. Clinical trial information: NCT01321957.

3545 Poster Session (Board #168), Sat, 8:00 AM-11:30 AM

Phase II trial of the autophagy inhibitor hydroxychloroquine with FOLFOX and bevacizumab in front line treatment of metastatic colorectal cancer. *First Author: Mark H. O'Hara, Abramson Cancer Center, Philadelphia, PA*

Background: Colorectal cancer (CRC) cells can become resistant to chemotherapy and anti-angiogenic therapy through autophagy. The antimalarial agent hydroxychloroquine (HCQ) is a potent inhibitor of autophagy, and *in vivo* studies in CRC cell models show significant decrease tumor volume when these autophagy inhibitors were combined with oxaliplatin and bevacizumab. We previously reported safety with HCQ 600mg BID in combination with standard front-line FOLFOX and bevacizumab in a Phase I study in metastatic CRC patients. We report the results of a single-arm phase II trial of patients with previously untreated stage IV CRC with good performance status and adequate hematologic and biochemical indices. **Methods:** Patients were treated with standard doses of mFOLFOX6 and bevacizumab with HCQ 600mg BID. Imaging was obtained every 2 months. **Results:** 37 patients were enrolled, 62% male, 89% Caucasian, median age 61, 65% ECOG PS 0, and 73% colon primary. Twenty-eight patients were evaluable for response as 2 patients did not start therapy and 7 patients withdrew prior to first response assessment. The ORR was 68% with an 11% CR rate. The median time to response was 3.1 months. Responses were independent of genomic aberrations within tumor tissue, specifically KRAS, TP53, BRAF, and PIK3CA. Median PFS and duration of response were not interpretable given that only 25% of patients came off trial for progression; all other patients withdrew to pursue surgery or liver embolization therapy, to receive therapy elsewhere, or due to toxicity associated with chemotherapy. The 1 year OS rate was 74%, and median OS has not been reached. The most common G3 or higher adverse events included neutropenia (31%), fatigue (11%), thromboembolism (9%), and cardiac events (9%). HCQ-attributable side effects included G1-3 insomnia (26%), G1-3 anxiety (20%), G1 visual disturbances (11%) and G3 allergy (3%). The majority of patients had increase in both LC3 and p62 in peripheral blood mononuclear cells and exhibited an increase in autophagosomes within the cytosol by electron microscopy. **Conclusions:** These data are promising and further evaluation in a randomized controlled trial is planned. Clinical trial information: NCT01206530.

3546 Poster Session (Board #169), Sat, 8:00 AM-11:30 AM

Efficacy of bevacizumab in second-line versus first-line treatment of metastatic colorectal cancer: Results from a new methodological approach based on the ITACa strategy trial. *First Author: Elisabetta Petracci, Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*

Background: Cancer trials collecting information on subsequent treatment lines offer an invaluable opportunity to gain a deeper understanding of therapeutic strategies. Still in the oncological literature, evidence comes from studies ignoring whole patient history. The few studies that consider more than one line of treatment often analyze data for each line separately. **Methods:** Data from the ITACa strategy trial investigating the role of bevacizumab (B) in first- and second-line of treatment in metastatic colorectal cancer patients (mCRC) were analyzed. The trial consisted of two arms with treatment crossover: chemotherapy (CT) plus B followed by CT alone *vs* CT alone followed by CT+B. The primary end-point was Progression-Free Survival (PFS). Our aim was to evaluate if the efficacy of B was greater or smaller in first- or second-line treatment. Survival analysis for repeated events taking into account of potential selection bias was performed. Indeed, patients starting a second-line treatment are a selected subgroup of patients initially enrolled. **Results:** Of the 370 patients in the intention-to-treat population, 175 (47.3%) received second-line treatment. Considering all available information from randomization to first and eventual second progression and accounting for the potential selection bias, the average effect of B in terms of PFS resulted in an HR = 0.80 [95% CI 0.68-0.95]. When evaluating the differential effect of B in first- and second-line, we found that the addiction of B to CT in first-line provided 10% (95% CI -28%; +12%) risk reduction (HR = 0.90, 95% CI 0.72–1.12) respect to CT alone and the addiction of B to CT in second-line provided 36% (95% CI -51%; -16%) risk reduction (HR = 0.64, 95% CI 0.49-0.84) respect to chemotherapy alone. **Conclusions:** The ITACa trial enabled us to analyze data in a unified framework considering first- and second-line treatment together. Results highlight an advantage of B when administered in combination with second-line chemotherapy, suggesting the best strategy for its administration. Clinical trial information: NCT01878422.

3547 Poster Session (Board #170), Sat, 8:00 AM-11:30 AM

Bevacizumab combined with first-line chemotherapy in elderly patients (≥75 years old) with metastatic colorectal cancer: Final results of the noninterventional CASSIOPEE study. *First Author: Eric Francois, Department of Medical Oncology, Centre Antoine-Lacassagne, Nice, France*

Background: Approximately half of the patients (pts) with metastatic colorectal cancer (mCRC) are elderly (≥65 years). Although few elderly pts are included in clinical studies, results in mCRC have shown similar treatment benefits in terms of progression-free survival and overall survival in young and elderly pts. This study was conducted in pts ≥75 years-old with mCRC treated in real life 1st line bevacizumab + chemotherapy in order to improve the knowledge on this population and to contribute in optimizing treatment strategy. **Methods:** CASSIOPEE is a prospective, multicenter, non-interventional study evaluating 1st line combination of bev + chemotherapy over 24 months in pts aged ≥75 years with mCRC. The primary endpoint was to describe progression-free survival (PFS). Secondary endpoints included the description of pts characteristics, overall survival, bev and chemotherapy regimen, safety and autonomy criteria (Lawton Instrumental Activities of Daily Living Scale; Balducci score). **Results:** A total of 402 pts were included between March 2012 and July 2016. In the efficacy population (n = 358), 52% were men, mean age 81 (±4); 54% were≥ 80 years old and 19% were ECOG ≥2; 80% had primary tumor located in the colon; main metastatic sites: liver (66%) and lung (30%). Bev was mainly combined with Folfox (36%) and Folfiri (29%). Median PFS was 9.1 months [8.3;10.2] in the efficacy population and 9.3 months for pts aged < 80, 9.5 months for pts aged ≥ 80 or ≤ 85 and 8.3 months for pts aged > 85. The PFS rate at 24 months was 11.8%. Median OS was 19.0 months [16.5;21.5] in the efficacy population and 20.6 months for pts aged < 80, 17.8 months for pts aged ≥ 80 or ≤ 85 and 13.0 months for pts aged > 85. The OS rate at 24 months was 42.0%. Autonomy and ECOG status remained stable from baseline to 24 months. In the safety population (n = 383), grade ≥ 3 adverse events occurred in 40% pts including 10% pts with bev related AEs. Overall, 4% pts died of an AE and 0.5% were bev related. **Conclusions:** These results suggest that mCRC patients aged ≥75 years-old, can benefit from 1st line bev plus chemotherapy in daily practice in this population. The safety profile is acceptable. Clinical trial information: NCT01555762.

3548 Poster Session (Board #171), Sat, 8:00 AM-11:30 AM

Concordance of DNA mismatch repair deficient (dMMR)/microsatellite instability (MSI) assessment by local and central testing in patients with metastatic CRC (mCRC) receiving nivolumab (nivo) in CheckMate 142 study. *First Author: Scott Kopetz, MD Anderson Cancer Center, Houston, TX*

Background: MMR or MSI testing is recommended for mCRC pts and is often done locally by IHC or PCR testing, respectively (NCCN V1.2017) Nivo, a fully human anti-PD-1 mAb, demonstrated durable responses and a 12-mo OS rate of 73.8% in pts with mCRC locally assessed for dMMR/MSI-H status in the CheckMate 142 study (NCT02060188; Overman M, et al. 2017). Here we describe the results of local and central testing with respect to MMR/MSI status and clinical outcomes in the CheckMate 142 study. **Methods:** MMR/MSI status was assessed locally on archival tumor using IHC/PCR at screening and confirmed centrally by PCR (modified Bethesda panel) testing of tumor biopsy at enrollment. dMMR was defined by IHC as a loss of expression in ≥1 mismatch repair proteins. Stable microsatellite (MSS), low MSI (MSI-L), and high MSI (MSI-H), were defined as instability in 0, 1, or ≥2 markers, respectively. Pts with dMMR/MSI-H mCRC who progressed on or were intolerant of ≥1 prior line of therapy received nivo 3 mg/kg Q2W. **Results:** 74 pts were dMMR/MSI-H by local testing. Of these pts, 53 (72%) were centrally confirmed as MSI-H, 7 pts had insufficient tissue sample for PCR testing, and 14 pts had a central test that did not match local test results. Of the 14 pts, 3 pts with a clinical history of LS were identified locally as dMMR but centrally as MSS (Table). INV-reported ORR was 31.1% in 74 pts locally determined as dMMR/MSI-H, 35.8% in 53 pts locally and centrally confirmed as MSI-H, and 21.4% in 14 pts not centrally confirmed as MSI-H. **Conclusions:** The similar clinical activity between pts locally confirmed as MSI-H and pts who were centrally confirmed as MSI-H suggest local testing is appropriate for identifying the dMMR/MSI-H pts who may benefit from nivo monotherapy. Clinical trial information: NCT02060188.

	Local Testing			
Pt	Method	Result	Central Testing	Clinical History of LS
1	IHC	dMMR	MSS	NA
2	IHC	dMMR	MSS	No
3	IHC	dMMR	MSS	Yes
4	IHC	dMMR	MSS	Yes
5	IHC/PCR	dMMR (IHC)/MSI-H (PCR)	MSS	NA
6	IHC	dMMR	MSS	Yes
7	IHC	dMMR	MSS	No
8	PCR	MSI-H	MSS	NA
9	IHC/PCR	dMMR (IHC)/MSI-H (PCR)	MSS	NA
10	IHC	dMMR	MSS	No
11	IHC	dMMR	MSS	NA
12	PCR	MSI-H	MSS	NA
13	IHC	dMMR	MSI-L	NA
14	IHC	dMMR	MSS	NA

NA = not available.

3549 Poster Session (Board #172), Sat, 8:00 AM-11:30 AM

A randomized phase II study evaluating efficacy and safety of SOX versus mFOLFOX6 as neoadjuvant chemotherapy for patients with resectable rectal cancer (KSCC1301). *First Author: Kenji Katsumata, Department of Gastrointestinal and Pediatric Surgery, Tokyo Medical University, Tokyo, Japan*

Background: Neoadjuvant radiotherapy is the current standard of care for rectal cancer. However, radiation therapy is sometimes associated with short-term severe toxicity and long-term morbidity. Perioperative introduction of new chemotherapy agents without radiotherapy for locally advanced rectal cancer (LARC) may be a promising option. Several studies of combination chemotherapy with oxaliplatin plus S-1 (SOX) have reported promising efficacy and safety in patients with metastatic colorectal cancer, suggesting a potential replacement for mFOLFOX6. **Methods:** A randomized phase II trial was undertaken to compare the efficacy and safety of SOX and mFOLFOX6 as neoadjuvant chemotherapy for patients with LARC. Patients were randomly assigned to receive mFOLFOX6 (every 2 weeks; day 1: 400 mg/m^2 bolus 5-fluorouracil [5-FU]; days 1 and 2: 2,400 mg/m^2 continuous 5-FU; day1: 200mg/m^2 *l*-LV; and day 1: 85 mg/m^2 oxaliplatin) or SOX (every 3 weeks; days 1–14: 80 mg/m^2 oral S-1; and day 1: 130 mg/m^{2}oxaliplatin). The protocol period for neoadjuvant chemotherapy was 3 months. The primary endpoint was the 3-year disease-free survival rate (3y DFS), and the secondary endpoints included pathological effect, R0 resection rate, survival and safety. **Results:** Between September 2013 and October 2015, 110 patients were enrolled and randomized (56 received SOX and 54 received mFOLFOX6). Baseline characteristics were balanced between the two arms. The major adverse events were neutropenia, peripheral neuropathy, loss of appetite, and fatigue. The incidence of grade 3 or higher neutropenia based on the *CTCAE Vers.4.0*was 13.2% in the SOX group and 32.0% in the mFOLFOX6 group. The surgical completion rate was 100% for the SOX group and 96% for the mFOLFOX6 group. The incidence of grade II or more surgical site infection based on Clavien-Dindo classification (CD) was 11.3% and 4.2% for the SOX and mFOLFOX6 groups, respectively. The CD grade III anastomosis-related complications developed in 7 cases in total. **Conclusions:** The KSCC1301 study suggests that neoadjuvant chemotherapy without radiation is active and safe. The results of pathological response will be provided. Clinical trial information: UMIN000011486.

3550 Poster Session (Board #173), Sat, 8:00 AM-11:30 AM

Classic or simplified LV5FU2 regimen: Multivariate analysis from a phase III study in metastatic colorectal cancer in elderly patients. *First Author: Jean-Louis Legoux, Centre Hospitalier Régional Universitaire, Orléans, France*

Background: In the early 2000s, classic LV5FU2 (C) (folinic acid, 5FU bolus, then 5FU infusion on D1 and D2) was replaced with simplified LV5FU2 (S) (folinic acid and 5FU bolus on D1 only), considered as effective and less toxic. No trial proved this assertion. The LV5FU2 companion in the FOLFIRI or FOLFOX regimen was C or S. The FFCD 2001-02 study compared in a 2 x 2 factorial design, in not-pretreated elderly patients (75+) with metastatic colorectal cancer, C or S, with or without irinotecan. No significant differences in PFS and OS were observed in the comparison with or without irinotecan. The median OS was 15.2 months in C versus 11.4 months in S, HR = 0.71 (0.55–0.92) and objective response rate was 37.1% in C vs S 25.6% in S, p = 0.004. The aim of this study was to present the factors associated with these differences. **Methods:** Prognostic factors associated with OS were studied using a Cox model. The multivariate analysis used the significantly different items from the univariate analysis and the differences observed at the inclusion. For each of these items, a subgroup analysis was performed. The second- and third-line treatments were analysed. **Results:** The 282 patients from the intent-to-treat study were included in the model. In OS, the prognostic factors were C versus S, number of metastatic sites, alkaline phosphatases (AP) and CEA. The interaction test in each subgroup for OS was not significant but C was significantly better in the following subgroup: age > 80 years, male, Karnofsky 100%, 1-2 Charlson index, AP ≤ 2N, leucocyte count > 11,000, CEA > 2N, CA 19-9 ≤2N. No differences were observed in the NCI toxicities but 130 serious adverse events in S versus 102 in C. A second-line was used for 55% patients in C, 46% in S, 81% of them with oxaliplatin or irinotecan in C, 76% after S. The third-line administration (20%) and targeted therapy (15%) were similar in C and S. **Conclusions:** C-LV5FU2 was superior both in subgroups with better and lower prognostics and this difference cannot be explained by an imbalance between the populations. The toxicity was not higher and a second-line was more often possible after C. The switch from C to S without scientific proof was perhaps a mistake in our practices. Clinical trial information: NCT00303771.

3551 Poster Session (Board #174), Sat, 8:00 AM-11:30 AM

Hand-foot skin reaction (HFSR) and outcomes in the phase 3 CORRECT trial of regorafenib for metastatic colorectal cancer (mCRC). *First Author: Axel Grothey, Mayo Clinic, Rochester, MN*

Background: Cutaneous toxicity is a known adverse effect of multikinase inhibitors and has been associated with clinical outcomes (Granito 2016). In the phase 3 CORRECT trial (NCT01103323), the multikinase inhibitor regorafenib significantly improved overall survival (OS) vs placebo in patients with mCRC (hazard ratio [HR] 0.77, 95% CI 0.64, 0.94; 1-sided P = 0.0052). This retrospective analysis explored whether HFSR was associated with outcomes in CORRECT. **Methods:** Patients randomized to receive regorafenib 160 mg/day during the first 3 weeks of each 4-week cycle were divided into subgroups based on whether or not they had HFSR. Estimates of OS and progression-free survival (PFS) (95% CI) were calculated using the Kaplan–Meier method. Patients who were randomized, but not treated, were included in the no HFSR group for the analysis of survival. **Results:** Of the 505 randomized patients, 500 received at least one dose of regorafenib. Among the treated patients, 47% (n = 235) had HFSR of any grade and 17% (n = 83) had HFSR grade 3. Of the patients who had HFSR, 69% (n = 162) had their first HFSR event (any grade) during the first treatment cycle. There was some imbalance in baseline characteristics between groups (Table). Survival was improved in patients who had HFSR at any time vs those who did not (Table). The OS benefit was also observed in patients who had the first HFSR event during Cycle 1 vs those who did not (median OS 7.2 vs 5.7 months; HR 0.66, 95% CI 0.51, 0.87). **Conclusions:** This post-hoc exploratory analysis suggests that patients who had HFSR had a greater treatment benefit from regorafenib. Since HFSR and survival are post-baseline assessments, results may be confounded by baseline factors or other unknown factors. Clinical trial information: NCT01103323.

	Yes HFSR (all grades) (n = 235)	No HFSR (all grades) (n = 270)
Age in years, median (range)	60 (22–80)	63 (36–82)
ECOG performance status 0/1, %	60/40	46/54
KRAS mutation, %	51	57
Primary site of disease – colon/rectum/both, %	60/35/5	67/26/7
Months since diagnosis of metastatic disease, median (IQR)	32 (22–46)	27 (19–41)
Median OS (95% CI), months	9.5 (7.8, 11.8)	4.7 (4.2, 5.2)
HR (95% CI)	0.41 (0.32, 0.53)	
Median PFS (95% CI), months	3.4 (2.4, 3.6)	1.8 (1.8, 1.9)
HR (95% CI)	0.54 (0.45, 0.66)	

3552 Poster Session (Board #175), Sat, 8:00 AM-11:30 AM

Prolonged (PI) vs short-term irinotecan (STI) administration: The Martha trial—A SICOG (Southern Italy Cooperative Oncology Group) randomized phase III study in the first-line setting of metastatic colorectal cancer (mCRC) patients (pts). *First Author: Vincenzo Formica, Tor Vergata University, Roma, RM, Italy*

Background: FOLFIRI+bevacizuamab(B) is a standard first-line regimen for mCRC pts. It should be delivered until progression, though an early switch to a de-intensified maintenance regimen is often adopted because of toxicity. The MARTHA trial compared FOLOFIRI+B for 6 months(mo) followed by maintenance B monotherapy up to 12mo (PI arm) vs FOLOFIRI+B for 3mo followed by capecitabine+B for further 3mo followed by B monotherapy up to 12mo (STI arm). **Methods:** Chemotherapy-naïve pts with histologically confirmed mCRC and measurable disease were deemed eligible and randomized to PI or STI arm in a 1:1 ratio. Co-primary endopoints were progression free (PFS) and overall survival (OS). The Kaplan-Meier method was used for survival analysis. A novel analysis (the Death Pace Analysis, DPA) was performed to identify pts benefiting more from a specific treatment. A multivariable logistic regression analysis (MLRA) was used to identify clinicopathological predictors of DPA-defined patient subsets. **Results:** 199 pts (100 in PI arm, 99 in STI arm) were enrolled. A non-significant superior OS was observed for STI (HR 0.81, p 0.26), no PFS differences were seen. The DPA demonstrated a 6% of pts identifiable as STI-benefiting pts. According to MLRA including 15 common clinicopathological variables, baseline Hemoglobin (Hb) level was the only independent predictor of the DPA-defined STI-benefit status (OR 2.3, p 0.009, i.e. 2.3-fold increased risk of not being a STI-benefiting patient for 1-point increase in Hb). Indeed, among pts with low baseline Hb ($<$ 13 gr/dL, cutoff determined upon ROC analysis), n = 128, a statistically significant prolonged OS was observed for STI over PI arm (median OS: 21.8 vs 14.4 mo, respectively, HR 0.64, p 0.04).No survival difference was seen between arms in pts with high Hb. **Conclusions:** mCRC pts with low baseline Hb levels are better treated with a STI first-line strategy. Published preclinical data suggest that low Hb may increase the risk of developing early chemo-resistant and aggressive disease with the prolonged use of irinotecan. Clinical trial information: EudraCT 2008-004890-17.

3553 Poster Session (Board #176), Sat, 8:00 AM-11:30 AM

Safety and feasibility of adding tumor debulking to palliative chemotherapy in multi-organ metastatic colorectal cancer: The ORCHESTRA trial. *First Author: Elske C. Gootjes, Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: For selected patients with oligometastatic colorectal cancer (mCRC), local treatment of metastases is standard of care based on retrospective reports showing long term survival rates. Local treatment of metastases is technically feasible in an increasing number of patients with multi-organ mCRC. It is unknown if patients with extensive disease will benefit from tumor debulking when added to first line palliative chemotherapy. The ORCHESTRA trial (NCT01792934) was designed to prospectively evaluate overall survival (OS) benefit from tumor debulking in patients with multi-organ mCRC. **Methods:** Patients with multi-organ mCRC were eligible if $>$ 80% tumor debulking was deemed feasible by resection, radiotherapy and/or thermal ablative therapy. All patients received oxaliplatin based chemotherapy $\pm$ bevacizumab. In case of stable disease or response at first evaluation (9 weeks), patients were randomized to continuation of chemotherapy or tumor debulking followed by chemotherapy. Adverse events were reported. If patient withdrawal after randomization was $<$ 10%, the study was deemed feasible. Study continuation was based on the interim report on safety and feasibility after inclusion of 100 (of 478) patients. **Results:** Patients were randomized to the standard (N = 43) or intervention arm (N = 45). No patients withdrew after randomization. In 6.8% of patients debulking was not performed due to progressive disease (N = 5) or death (N = 1) prior to local treatment. Two patients had no lesions left to treat, 37 patients underwent tumor debulking. In 15 patients (40%) 21 serious adverse events related to debulking were reported, 83.7% of patients had no SAEs or recovered within 30 days. Postoperative 90-day mortality was 2.7% (N = 1). Chemotherapy was resumed in 86.5% of patients, median time to restart was 12.7 weeks (SD 5.6) and 78.4% completed $\geq$24 weeks of chemotherapy. **Conclusions:** Tumor debulking is feasible and safe and does not prohibit administration of palliative chemotherapy in the majority of patients with multi-organ mCRC. The ORCHESTRA trial will continue accrual to determine whether the aim of $>$ 6 months OS benefit from tumor debulking will be achieved. Clinical trial information: NCT01792934.

3554 Poster Session (Board #177), Sat, 8:00 AM-11:30 AM

Assessing outcome differences in the second line treatment of metastatic colorectal cancer (mCRC): An ARCAD analysis comparing sequence after first line trials (SAFL) and dedicated second line trials (DSLT). *First Author: Alexis Diane Leal, Mayo Clinic, Rochester, MN*

Background: There is considerable variability in the outcomes between second line (SL) trials in mCRC. The aim of this analysis is to compare the outcomes of patients (pts) with mCRC treated either on SAFL, with protocol defined SL treatment, or DSLT. **Methods:** Individual pt data was available on pts with mCRC enrolled in 1 of 10 trials (7 DSLT, 3 SAFL) in the ARCAD database. Regimens included FOLFIRI, FOLFOX, and irinotecan (IRI), since pts did not receive biologic agents in SL on SAFL. For pts on a SAFL, PFS and OS were defined as time from initiation of SL treatment to second progression (SP)/death and death, respectively. Descriptive statistics and multivariable Cox models were used to assess differences in PFS and OS. **Results:** 5,076 pts were included; 63% were male; median age was 62. See Table for treatment details. Pts treated on SAFL had shorter OS (0.7-1.5 months (mos$>$) shorter) and PFS (0.6-2.6 mos shorter), compared to those treated on DSLT. These findings were statistically significant and differences in OS did not attenuate after adjustment for age, gender, and prior treatment. PFS differences in FOLFOX became insignificant after multivariable adjustment. **Conclusions:** There are modest differences in both PFS and OS between pts with mCRC treated on SAFL and those on DSLT, suggesting differences in these pt populations. Caution is needed when applying these data to pts, as we were unable to control for potential confounders (ECOG PS, number and sites of metastases) at initiation of SL in SAFL, which may impact outcomes.

Second line outcome comparison.

			OS				PFS			
Regimen	# Studies	# Patients	DSLT[$]	SAFL[$]	LR p-value[@]	Adj p-value[@,*]	DSLT[$]	SAFL[$]	LR p-value[@]	Adj p-value[@,*]
FOLFIRI	5	1648	11.7 (11.1-12.4)	11.0 (9.8-12.2)	0.014	0.001	5.1 (4.4-5.4)	2.5 (2.1-3.9)	<.001	<.001
FOLFOX	7	1906	11.7 (11.0-12.2)	10.2 (9.6-10.9)	0.048	0.028	4.8 (4.6-5.2)	4.2 (3.7-5.3)	0.064	0.315
IRI	4	1522	11.1 (10.1-11.9)	10.1 (9.4-11.1)	0.030	<0.001	2.7 (2.6-2.8)	&	&	&

LR: Log-Rank; Adj: Adjusted; [$]Median (CI) time to event in months; [@]p-value for comparison between DSLT and SAFL; *Adjusted for age, gender, and prior treatment; [&]SP date not available.

3555 Poster Session (Board #178), Sat, 8:00 AM-11:30 AM

Age as a predictive and prognostic factor for targeted therapy treatment in metastatic chemorefractory colorectal cancer (CRC): An analysis of NCIC CTG CO.17 and CO.20. *First Author: Connor Wells, Tom Baker Cancer Centre, Calgary, AB, Canada*

Background: There is minimal data on the efficacy and improvement of quality of life (QoL) of these targeted therapies, like cetuximab, in elderly CRC patients ($\geq$70yo). We analyzed outcomes from two randomized phase III clinical trials from the Canadian Clinical Trials Group, CO.17 and CO.20. **Methods:** CO.17 and CO.20 were retrospectively analyzed. CO.17 compared cetuximab (CETUX) with best supportive care (BSC), CO.20 compared CETUX + brivanib (BRIV) with CETUX + placebo. Key eligibility criteria were similar between each trial. Patients were dichotomized by age ($\geq$70yo/ $<$ 70yo) for comparisons. Outcomes included overall survival (OS), progression free survival (PFS), adverse events (AEs), and QoL deterioration. In CO.17, only patients with wild type *K-RAS* were included in analysis. Multivariate analysis with Cox regression controlled for additional variables. **Results:** 980 patients were included in this analysis. 257 (26.2%) were $\geq$70yo at the time of enrollment. In CO.17, OS and PFS were similar between young and elderly patients treated with CETUX (OS 9.7m vs 8.0m, p = 0.45; HR 0.73 95%CI 0.39-1.37). Compared to the BSC arm, elderly patients treated with CETUX had a non-significant increase in OS (8.0m vs 5.1m, p = 0.11). In patients treated with CETUX, grade 3/4 AEs were similar between age groups, however elderly patients had a faster deterioration in global QoL than younger patients (3.6m vs 5.7m p = 0.046). In CO.20, younger patients had longer OS than elderly (9.2m vs 7.6m, p = 0.02; HR 0.81 95% 0.68-0.97, p = 0.02). AEs in the BRIV+CETUX arm were higher in the elderly than young (88% vs 77%, p = 0.03). Both young and elderly treated with BRIV+CETUX had more rapid decreases in global QoL than the CETUX arm. **Conclusions:** Age was neither prognostic nor predictive of response to targeted therapy in the single agent CO.17 trial. In CO.20, age conferred a worse prognosis. Elderly patients who are eligible for clinical trials may garner similar survival benefits as younger patients with single agent therapy, but may not derive the same improvement in QoL.

3556 Poster Session (Board #179), Sat, 8:00 AM-11:30 AM

A curative intent trimodality approach for advanced isolated abdominal nodal metastasis in metastatic colorectal cancer: Update of a single-institutional experience. *First Author: Benny Johnson, Mayo Clinic Cancer Center, Rochester, MN*

Background: To define and update survival rates and relapse patterns in patients (pts) with isolated advanced abdominal nodal metastasis secondary to colorectal cancer (CRC), treated with curative intent using aggressive trimodality therapy. **Methods:** Fifty-seven pts with isolated advanced abdominal lymph node metastasis (retroperitoneal and mesenteric) secondary to colorectal cancer received trimodality therapy defined as chemotherapy delivered in conjunction with external beam radiotherapy (EBRT) followed by lymphadenectomy and intraoperative radiotherapy (IORT). Infusional 5-FU was the most common radiosensitizer used (66%, 38 pts). The median dose of EBRT was 50 Gy & the median dose of intraoperative radiotherapy was 12.5 Gy. End points included distant metastasis, toxicities, local failure within EBRT field, recurrence within the intraoperative radiotherapy field, and survival. **Results:** 49% of pts were male, median age 50.5 yrs. All patients had ECOG $\leq$ 1. 27 pts had primary right sided colon cancer, 16 left sided colon cancer and 14 rectal primaries. Median time from initial CRC diagnosis to development of abdominal lymph node metastatic disease was 24 months (95% CI, 23.5-45.1 months). 84% (48 pts) had paraaortic nodal metastases, 12% (7 pts) had mesenteric nodal metastases, and 3% (2 pts) had both. With a median follow up of 89.4 months, the median overall survival and 5-year estimated survival rate were 53.2 months (95% CI, 46.4-78.8 months) and 42%, respectively. Median progression free survival was 19.3 months (95% CI, 15.6-32.8 months). 21 (37%) pts never developed distant disease. Outcome was not affected by disease sidedness, rectal primary, or mutational profile. Treatment was well tolerated without any grade 3/4 toxicities. **Conclusions:** The use of trimodality therapy including EBRT with radiosensitizing chemotherapy, lymphadenectomy and IORT produces sustainable long-term survival in selected metastatic CRC pts presenting with isolated retroperitoneal/mesenteric nodal relapse.

3557 Poster Session (Board #180), Sat, 8:00 AM-11:30 AM

A phase I/II trial of combined BRAF and EGFR inhibition in patients (pts) with BRAF V600E mutated (BRAFm) metastatic colorectal (mCRC): The EViCT (Erlotinib and Vemurafenib in Combination Trial) study. *First Author: Jayesh Desai, Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Pts with BRAFm mCRC have an exceedingly poor prognosis. Unlike melanoma, BRAF inhibitor monotherapy has limited activity in BRAFm mCRC. Preclinically, BRAF inhibition results in rapid feedback activation of EGFR and ongoing tumor proliferation, which can be readily overcome by combining BRAF and EGFR inhibition. EViCT examined the safety and efficacy of combining two oral agents targeting BRAF with Vemurafenib (Vem) and EGFR with Erlotinib (Erl), in BRAFm mCRC pts. Herein, we report safety and preliminary efficacy data. **Methods:** EViCT had 2 parts: a Phase I dose escalation of Erl (cohort 1: 100mg qd; cohort 2: 150mg qd) together with Vem 960mg bd, to determine the maximum tolerated dose (MTD). The Phase II component involved dose expansion at MTD using a Simon 2-stage design to treat 9 pts in stage 1 and 15 pts in stage 2. Cycles were 28 days. Eligible pts had ECOG $<$ 1, $<$ 2 lines of systemic therapy for metastatic disease, and acceptable organ function. Staging CT scans were performed every 2 cycles, response assessed using RECIST 1.1. Primary endoint was clinical benefit rate (CR, PR and SD). A number of pharmacodynamics correlates were assessed including serial ctDNA, FDG-PET and optional tumour biopsies. Pts were treated until disease progression or toxicity requiring discontinuation. **Results:** Between Jul-2014 and Oct-2016, 30 BRAFm mCRC pts were enrolled. The Phase I Lead-in enrolled 4 pts in cohort 1 and 7 pts in cohort 2. There was 1 DLT (grade 3 hand-foot syndrome) in cohort 2. MTD/Recommended Phase 2 Dose was Erl 150mg qd and Vem 960mg bd, the full dose for each agent. The Phase II expansion enrolled 19 pts. Overall, 23 pts are evaluable for this interim analysis. Median age was 61 years, 11 (48%) pts were male. Most pts had 1(50%) or 2 (41%) lines of prior treatment. Overall response rate was 39% (95%CI = [20%, 61%]), including 5 (22%) confirmed PR, 4 (17%) unconfirmed PR, 3 (13%) stable disease and 11 (48%) progressive disease. **Conclusions:** Vem and Erl can both be given safely at their individual full doses when used in combination. In BRAFm mCRC, this combination resulted in clear clinical activity. Clinical trial information: ACTRN12614000486628.

3558 Poster Session (Board #181), Sat, 8:00 AM-11:30 AM

Response to pembrolizumab in patients with mismatch repair deficient (dMMR) colorectal cancer (CRC). *First Author: Alexis Diane Leal, Mayo Clinic, Rochester, MN*

Background: Anti-programmed death-1 (PD-1) antibodies have been shown to be effective in the treatment of dMMR CRC. We describe an updated analysis from a cohort of 19 patients (pts) with dMMR CRC treated with pembrolizumab. **Methods:** Pts were identified through review of the Mayo Clinic electronic medical record (EMR) and chemotherapy administration records from May 2015 through January 2017. All pts with dMMR CRC who received treatment with pembrolizumab were included. The EMR was reviewed to identify demographic, clinical, pathologic and treatment details. Overall survival (OS), progression free survival (PFS) and disease control rate (DCR = CR+PR+SD) are reported. Time to event analysis was calculated using the Kaplan-Meier method. **Results:** Nineteen pts were included in this analysis; median age at diagnosis was 48.6 years (range 25-93); 53% were female. Most primary tumors were right sided (n = 12; 63%), 6 (32%) were left sided and 1 (5%) was a tumor of unknown primary within the bowel. Twelve (63%) pts received $\geq$2 lines of therapy prior to pembrolizumab (range 1-4). Five pts received 2 mg/kg every 3 weeks, 11 received 200 mg/day every 3 weeks and 2 pts received 10 mg/kg (1 every 2 weeks, the other every 3 weeks). The most common alterations identified were loss of MLH1 (11/15) and PMS2 (12/15); 4 pts had germline mutations (mut) identified. KRAS mut was identified in 6/16 pts and 2 pts had BRAF mut. Three pts had MLH1 hypermethylation. Median number of cycles of pembrolizumab was 8 (range 1-35+), with 13 (68%) pts receiving $\geq$6 cycles. DCR at first assessment was 68%, with 5% CR, 47% PR and 16% SD. Median follow-up from diagnosis was 29 months (95% CI 18-42). Median OS was 103 months (95% CI 85-103); 12-month OS was 89%. Median OS from PD-1 therapy was 16.1 months (95% CI 16-NR); 12-month OS from PD-1 therapy was 79%. Median PFS was NR (95% CI 5-NR); 12-month PFS was 54%. At time of analysis, 9 pts remain on PD-1 therapy; 5 pts have died; 3 have received subsequent therapy. **Conclusions:** Anti-PD1 blockade with pembrolizumab can provide long lasting benefit in dMMR mCRC, even in heavily pretreated pts.

3559 Poster Session (Board #182), Sat, 8:00 AM-11:30 AM

An open-label expanded-access study of trifluridine/tipiracil for metastatic colorectal cancer. *First Author: Robert J. Mayer, Dana-Farber Cancer Institute/Partners CancerCare, Boston, MA*

Background: A Phase 3 clinical trial (RECOURSE) showed that trifluridine/tipiracil (FTD/TPI) was effective in the treatment of refractory metastatic colorectal cancer (mCRC) treated with standard chemotherapy and targeted-therapy drugs (Mayer et al. N Engl J Med 2015;372:1909-19). An expanded-access program (EAP) was started to provide access to FTD/TPI for patients with mCRC with similar eligibility and to further assess the safety of FTD/TPI in a "real-world" setting in US patients. **Methods:** Patients aged $\geq$18 years with refractory mCRC resistant to $\geq$2 regimens of standard chemotherapy with appropriate biologics and an Eastern Cooperative Oncology Group performance status of 0 or 1 were enrolled to this open-label EAP. Patients received FTD/TPI 35 mg/m^{2}twice daily for 5 days followed by 2 days' rest repeated twice followed by 14 days' rest over a 28-day treatment cycle until drug discontinuation. Sites reported duration of therapy, discontinuation due to disease progression, and adverse events (AEs) for each patient. **Results:** 549 patients were enrolled; 53.2% were male. Median duration of FTD/TPI therapy was 9.7 weeks, which was similar to US patients from RECOURSE (8.9). 10.2% of patients died during the study period, 9.7% due to disease progression. 76.1% of patients discontinued treatment due to disease progression and 4% discontinued due to AEs. Drug-related clinically significant AEs (all grades) are summarized in the table. **Conclusions:** Patients with refractory mCRC in this EAP had a similar exposure duration to that reported in US patients from RECOURSE, with no unexpected safety concerns. While gastrointestinal toxicity was lower in this population, this may be due to reporting of "significant" events. The clinical profile of FTD/TPI is confirmed in this larger, non-randomized "real-world" experience. *Sponsorship:* Taiho Oncology, Inc. *Editorial Assistance:* Complete HealthVizion. Clinical trial information: NCT02286492.

	Patients (%)	
Related AEs	EAP (N=549)	US RECOURSE (N=64)
Anemia	25.3	39.1
Decreased hemoglobin	2.2	1.6
Neutropenia	25.1	45.3
Decreased neutrophil count	24.4	17.2
Gastrointestinal toxicities	40.8	60.9
Nausea	29.3	43.8
Diarrhea	16.4	14.1
Vomiting	13.1	25.0

3560 Poster Session (Board #183), Sat, 8:00 AM-11:30 AM

The outcome of patients (pts) with metastatic colorectal cancer (mCRC) based on site of metastases (mets) and the impact of molecular markers and site of primary cancer on metastatic pattern. *First Author: Thiruvarudsothy Prasanna, The Canberra Hospital, Woden, Australia*

Background: Although liver is the commonest site of mets in pts with CRC, pattern of spread is variable and may reflect different biology in different subsets of pts. **Methods:** This is a retrospective analysis to explore the outcome of pts with mCRC based on their site of mets at diagnosis and to identify tumor characteristics which could predict the site of mets. Pts from 2 Australian databases, BioGrid (BG) and South Australian Cancer Registry (SA), from 01/2006 to 12/2015 were grouped into 5 cohorts; lung only, liver only or any pts with brain, bone or peritoneal mets. Overall survival (OS) for each group was compared with the rest of the sample using Kaplan Meier analysis and the log rank test separately in each dataset. Mantel-Haenszel Chi-squared test was performed in pooled data to assess the association between KRAS, BRAF, Micro satellite instability (MSI), site of primary and site of mets. **Results:** 5967 pts were included. In both datasets median OS was significantly higher when mets were limited to lung or liver and shorter for those with brain, bone or peritoneal mets. BRAF, KRAS and MSI data were available for 20%, 37% and 21% of the sample. In the pooled analysis BRAF mutation was associated with brain (Relative Risk=5.2) and peritoneal mets (RR=1.8) with lower incidence of lung (RR=0.3) and liver (RR=0.7) limited mets. KRAS mutation was associated with lung only mets(RR=1.4). Left colon tumors were associated with bone (RR=1.6) and lung only mets (RR=2.3) while peritoneal spread was less frequent compared with right colon tumors(RR=0.6). Rectal cancer was strongly associated with brain, bone and lung mets (RR=1.7, 1.7, 2.0). MSI status was not associated with site of mets though liver only mets was less frequent in MSI high tumors. **Conclusions:** Survival duration with mCRC is related to the site of mets. OS was significantly better when mets were confined to either lung or liver. BRAF mutation and primary rectal cancer were associated with poor prognostic metastatic sites like brain and bone.

Site of mets	SA	BG
	OS months (each group vs overall were significant p≤0.0001)	
Overall	15	25
Liver only	20	30
Lung only	29	39
Brain	6	6
Bone	7	12
Peritoneum	12	17

3561 Poster Session (Board #184), Sat, 8:00 AM-11:30 AM

Early tumor shrinkage (ETS) and depth of response (DpR) in wild-type (WT) RAS tumors from the phase III trial of panitumumab (pmab) plus best supportive care (BSC) versus BSC in chemorefractory metastatic colorectal cancer (mCRC). *First Author: Tae Won Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Activating *RAS* mutation is a negative predictor of anti-EGFR therapy. In the final analysis of 20100007, the first phase 3 study to prospectively evaluate efficacy and safety of WT *RAS* (*KRAS* and *NRAS* exons 2, 3, 4) mCRC, pmab + BSC continued to show improved survival (OS and PFS) and ORR. Recent data suggest that tumor burden reduction and ETS may contribute to improved OS. Previous studies have shown that pmab plus chemotherapy results in ETS, which correlates with OS benefit (Douillard et al, EJC, 2015; Rivera et al, JCO, 2015; Mansmann et al, JCO 2013). Here we report analyses of ETS and DpR and the effect on OS in patients (pts) with WT *RAS* mCRC treated with pmab monotherapy in the '0007 trial. **Methods:** Anti-EGFR naïve pts with WT *KRAS* exon 2 mCRC were randomized 1:1 to pmab + BSC or BSC. Pt tumors were further evaluated for *RAS* status, and DpR (percent tumor shrinkage at nadir or progression) and ETS (≥/< 0% or ≥/< 20% by week 8) were analyzed in WT *RAS* pts. OS and PFS were compared for each ETS group. **Results:** Of 377 pts with WT *KRAS* exon 2 mCRC, 270 were WT *RAS* (142 pmab + BSC, 128 BSC alone). In the pmab + BSC arm, 69.5% and 38.2% of pts had ≥0% and ≥20% ETS, respectively, and median (Q1, Q3) DpR was 16.9% (0%, 37.5%). OS was improved in pts with higher ETS (≥0% or ≥20%) compared with lower ETS (<0% or <20%; Table). **Conclusions:** In this post-hoc analysis, pmab monotherapy provided any ETS benefit (≥0%) in 69.5% of WT *RAS* mCRC pts, and ETS was associated with improved PFS and OS. Pmab should be considered both in combination and as monotherapy for its significant impact on OS and also for its ability for substantial ETS in pts with WT *RAS* mCRC. Validation is necessary to investigate the value and cutoff of ETS in a prospective study. Clinical trial information: NCT01412957.

	Pmab + BSC			
	ETS cutoff = 20%		ETS cutoff = 0%	
	≥ 20% (n=50)	< 20% (n=81)	≥ 0% (n=91)	< 0% (n=40)
OS				
Median, m	13.6	8.5	11.5	6.1
95% CI	10.5, 16.9	7.1, 10.6	10.0, 13.7	4.0, 10.6
HR	0.582		0.624	
95% CI	0.398, 0.852		0.420, 0.926	
P-value	0.0054		0.0192	
PFS				
Median, m	5.4	3.5	5.4	1.7
95% CI	5.3, 7.1	2.7, 5.3	5.3, 5.7	0.9, 2.8
HR	0.568		0.389	
95% CI	0.395, 0.817		0.265, 0.571	
P-value	0.0023		<0.0001	

CI = confidence interval; HR = hazard ratio

3562 Poster Session (Board #185), Sat, 8:00 AM-11:30 AM

Primary tumor sidedness associates with prognosis of patients with brain metastases of colorectal cancer. *First Author: Anna Sophie Berghoff, University of Vienna, Vienna, Austria*

Background: Brian metastases (BM) are a rare but devastating complication of colorectal cancer. We aimed to analyse prognostic factors in patients suffering from colorectal cancer (CRC) BM. **Methods:** Patients with histological proven CRC and BM were identified from the brain metastasis database of the Comprehensive Cancer Center Vienna. Clinical characteristics including established prognostic factors were retrieved by chart review. Established clinical prognostic scores for BM patients including the graded prognostic assessment (GPA) and the GPA for gastrointestinal tumours (GI-GPA) were calculated based on clinical characteristics as previously published. **Results:** 215 (male: 125/215 (58.1%); female 90/215 (41.9%)) patients with CRC BM were available for this study. The following established clinical prognostic factors showed a significant association with median overall survival (OS) times from BM diagnosis: number of brain metastases (n = 1: 6 months; n = 2-3: 4 months; n > 3: 3 months; p = 0.001), age at BM diagnosis (< 65 years: 6 months; > 65 years: 4 months; p = 0.047), extracranial disease (present: 4 months; absent: 8 months; p = 0.002) and Karfnofsky performance score (KPS < 70%: 3 months; KPS > 70%: 5 months; p = 0.002), graded prognostic assessment (GPA) class (class I: 15 months; class II: 13 months; class III: 4 months; class IV: 4 months) and the gastro-intestinal disease-specific GI-GPA (class I: 11 months; class II: 6 months; class III: 6 months; class IV: 3 months; p < 0.001). In addition, the location of the primary tumour in the left colon (n = 176 (81.9%); 5 months) was associated with significantly longer median overall survival times from diagnosis of BM than primary tumour location in the right colon (n = 39 (18.1%); 3 months; p = 0.010). Primary tumor sidedness (HR 0.577; 95% CI 0.397-0.841; p = 0.004) remained a strong prognostic factor at multivariate analysis independently of GI-GPA (HR 0.718; 95% CI 0.612-0.842). **Conclusions:** Primary tumor sidedness is an independent prognostic factor in patients with CRC BM and should be included in disease-specific prognostic scores.

3563 Poster Session (Board #186), Sat, 8:00 AM-11:30 AM

Clinical and molecular characterization of patients with metastatic colorectal cancer harbouring DNA mismatch repair deficiency. *First Author: Romain Cohen, Medical Oncology Department, Saint-Antoine Hospital, Paris, France*

Background: Prognosis of patients (pts) with metastatic colorectal cancer (mCRC) harboring microsatellite instability (MSI) is poorly characterized. We aimed to assess the clinical relevance of distinguishing sporadic (SP) from Lynch syndrome (LS)-related mismatch repair deficiency (dMMR). **Methods:** Pts with diagnostic of dMMR and/or MSI mCRC between 1998 and 2016 were retrospectively identified in 6 French hospitals. Tumor samples were systematically collected and screened for *RAS/RAF* mutations and *MLH1* promotor methylation. dMMR and MSI statuses were confirmed using immunohistochemistry and Pentaplex© PCR assay. Sporadic cases were molecularly defined as those displaying MLH1 loss of expression with *BRAF*V600E mutation and/or MLH1 hypermethylation. Clinical data (demographic data, metastatic sites, therapeutic strategies) were recorded. **Results:** 129 pts, of which 48 SP and 81 LS, were included. Compared with LS, SP were associated with female (P < .001), older age at diagnostic (P < .001), proximal colon (P = 0.002), and less liver metastasis (25% vs 47%, P = .02). For initially localized CRC, median disease free survivals (DFS) were 9.1 months (m) for SP (n = 22) and 12.3 m for LS (n = 47) (hazard ratio (HR) = 0.5, 95%CI 0.28-0.90, P = .02). Median overall survivals (OS) from stage IV diagnosis were 43.9 m in the overall population, 23 m for SP and not reached for LS (HR = 0.23, 95%CI 0.10-0.52, P < .001). *BRAF* mutation was harbored by 29 SP tumors (60%) and did not impact OS among SP pts (P = .52). Metastatic disease was less frequently resectable for SP than LS (21% vs 56%, P < .001). Median DFS for pts with resected metastatic disease (n = 55) were respectively 6.7 and 10.5 m (HR = 0.28, 95%CI 0.10-0.73, P = .01). At the data cut-off date, 16 pts (15 LS and 1 SP) were still in complete remission. Median progression free survivals with first-line chemotherapy for pts with unresectable metastasis (n = 61) were 3.9 m for SP and 5.0 m for LS (P = .71). **Conclusions:** This retrospective study suggests a worse prognosis of pts with SP MSI mCRC compared to these with LS-related mCRC.

3564 Poster Session (Board #187), Sat, 8:00 AM-11:30 AM

The impact of cumulative toxicity on physical quality of life in patients with metastatic colorectal cancer receiving first line chemotherapy. *First Author: Claudia Schuurhuizen, Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: We have previously suggested that treatment related toxicity has impact on physical quality of life (QOL) scores, as opposed to global QOL. Moreover, the cumulative effect of experienced toxicities, including low-grades AEs, may be of more importance. The purpose of this observational cohort study was to evaluate the association between cumulative toxicity and physical and global QOL in patients with metastatic colorectal cancer (mCRC) receiving chemotherapy. **Methods:** 105 patients with mCRC starting first line chemotherapy were evaluated. All patients completed the EORTC-QLQ-C30 questionnaire at baseline and after 10 weeks. Toxicity, clinical outcomes and demographics were retrieved from patient records. For each patient, we calculated cumulative toxicity in three different ways: i) total number of adverse events (AEs) (all grades), ii) total number of grade 3-4 AEs, and iii) total number of AEs multiplied by their grade. The relation between each cumulative toxicity score and QOL assessed at 10 weeks, was studied. **Results:** The mean age of patients was 64.8 $\pm$ 9.7 years, 70.5% were male, and 83.8% received first line oxaliplatin based combination chemotherapy. AEs occurred in 98.1% of patients, grade 3-4 AEs in 37.1%, and grade 1-2 AEs in 61.0%. The mean number of experienced AEs (all grades) was 5.3 $\pm$ 2.7. The most common toxicities included diarrhea, neuropathy and fatigue. None of the toxicity scores was related to global QOL outcome. A higher total number of all grades AEs (β = - 2.2, 95%CI = -3.7; -6.6) and total number of AEs multiplied by grade (β = -1.3, 95%CI = -2.2; -3.5) were significantly associated with worse physical QOL. **Conclusions:** Cumulative toxicity, defined as the total of all grades AEs, significantly affects physical QOL in patients with mCRC receiving first line chemotherapy. Improvement of treatment related toxicity management by reducing the total number of AEs, may result in relevant improvements in patients' QOL. Our results emphasize that future RCTs should present physical QOL outcomes instead of global QOL, as well as all grades and total number of toxicities for individual patients.

3565 Poster Session (Board #188), Sat, 8:00 AM-11:30 AM

Effect of postoperative morbidity on survival after cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC) for peritoneal metastasis in a series of 700 cases. *First Author: Clarisse Eveno, Hopital Lariboisiere AP-HP, Service de Chirurgie Digestie et Cancérologie, Paris, France*

Background: Major morbidity (MM) after cytoreductive surgery with heated intraperitoneal chemotherapy (CRS/HIPEC) is associated with worsening of disabilities and length of the hospital stay. This study aimed to identify MM prognostic factors and to measure its impact on oncological outcomes. **Methods:** A post-hoc analysis of a prospective cohort of 734 patients with peritoneal metastasis (PM) from 2006 to 2015 was undertaken. Five hundred and two patients who had complete CRS and HIPEC for PM were included. **Results:** Major morbidity was identified in 31% (156/502) of CRS/HIPEC procedures, including 67 hemorrhagic complication (13.3%), 87 anastomotic leaks (17.4%), 121 reoperation (24.1%), and 65 pulmonary complication (12.9%). The multivariate predictors of MM were American Society of Anesthesiologists (ASA) score (ASA 3 vs. 1-2, OR 95%CI: 3.58 [1.54 – 8.34]), origin of PM colorectal adenocarcinoma vs. other, OR 95% CI: 1.62 [1.06 – 2.48]), type of HIPEC drug (oxaliplatin vs. other, OR 95% CI: 2.85 [1.28 – 6.32]), number of anastomosis (no vs. at least 1, HR 95% CI: 1.85 [1.19 – 2.88]), blood transfusion (OR 95%CI: 1.84 [1.05 – 3.23]) and length of surgery longer than the median value (OR 95%CI: 1.88 [1.22 – 2.91]). The in-hospital mortality rate for the entire cohort was 1.7% (9/502). Rate of adjuvant chemotherapy after CRS/HIPEC was comparable between the two groups (70.3% vs. 72.4%, p = 0.64). The median duration of follow-up was 18 months. The MM group had worst OS and DFS comparing non-MM (Hazard ratio and 95% confidence interval at 3.48 [1.90 ; 6.35] and 1.91 [1.43 ; 2.57], respectively). **Conclusions:** Major morbidity after CRS/HIPEC for peritoneal metastasis is a source of significant reoperation and longer hospital and intensive care unit stay; with a decrease in overall survival and disease free survival even after complete CRS. Preoperative ASA score, number of anastomoses, colorectal origin of PM, HIPEC with oxaliplatin, blood transfusion and length of surgery are independent predictors of MM for CRS/HIPEC patients.

3566 Poster Session (Board #189), Sat, 8:00 AM-11:30 AM

Conditional survival analysis of stage IV colorectal cancer patients living >24 months. *First Author: Nadia Dawn Ali, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ*

Background: The overall survival of patients with stage IV colorectal cancer (both in unresectable and resectable settings) has been increasing over recent decades due to improvements in chemotherapy, liver surgery and other liver-directed therapies. As a result of more patients living longer, there is a need to refine prognostic information to more accurately predict survival to assist multi-disciplinary cancer management teams in treatment decisions but also for patient quality of life. **Methods:** We performed a retrospective analysis of all patients with stage IV colorectal cancer seen at Rutgers Cancer Institute of New Jersey between Jan 1, 2005 to March 10, 2015 by ICD-9 code (N = 318 patients). This included patients who were deemed unresectable and patients who were resected with curative intent. Our study population was patients with documented survival for > 24 months (N = 158). Variables gathered included patient demographics, disease related (primary location, KRAS status, metastasis location, interval to metastases) and treatment related (chemotherapy regimens, radiation and surgery) data. Survival curve estimates are conditional on having survived 24 months. **Results:** Complete data was available for 125 patients (75 were resected for cure and 50 were not). Median overall survival of resected patients was not reached. The median overall survival of non-resected patients was 75.9 months. Univariate and multivariate analysis for surgery and non-surgery groups was performed. No statistically significant covariates were found beyond surgical resectability. The conditional survival probabilities of living 1, 2 or 3 years longer after 24 months of survival are 91.7%, 71.6% and 51.6% respectively in the patients with unresectable disease, and 98.1%, 92.2% and 88.8% in patients who were able to be resected with curative intent. **Conclusions:** These results indicate that patients who survive 24 months with stage IV colorectal cancer have an excellent prognosis. For patients who are unresectable and survive 24 months, this study suggests that they may benefit from resection of remaining metastatic sites if feasible. For resected patients this information may propose a possible benefit from repeat metastasectomy.

3567 Poster Session (Board #190), Sat, 8:00 AM-11:30 AM

Impact of tumor location on outcomes in patients with metastatic colorectal cancer (mCRC) treated with regorafenib (REG): An interim analysis from the prospective, observational CORRELATE study. *First Author: Michel Ducreux, Gustave Roussy Cancer Campus, Villejuif, France*

Background: The anatomical location of the primary tumor has been associated with outcomes in mCRC, with left-sided (L) tumors having a better prognosis than right-sided (R) tumors and location predicting response to treatment. REG significantly improved overall survival (OS) vs placebo in patients with mCRC who progressed on available treatments in 2 randomized, phase 3 trials (CORRECT, CONCUR). This exploratory analysis evaluated outcomes by primary tumor location in patients with mCRC treated with REG in the CORRELATE study. **Methods:** CORRELATE is an observational study designed to characterize the safety and effectiveness of REG in unselected patients for whom the decision to treat with REG has been made by the treating physician according to the local health authority label. Primary L tumors were located in the rectum, splenic flexure, recto-sigmoid, descending, or sigmoid colon; R tumors were in the appendix, hepatic flexure, cecum, or ascending colon. OS was analyzed by the Kaplan–Meier method and comparisons were by a 2-sided log-rank test. **Results:** Primary tumor location was available for 474 patients (L, n = 375 [79%]; R, n = 99 [21%]). Median time from initial diagnosis and from diagnosis of metastatic disease to treatment was slightly longer in L vs R tumors (32 vs 28 months and 25 vs 22 months, respectively). A higher proportion of patients with L vs R tumors, respectively, had prior radiotherapy (34% vs 13%) and a lower proportion had a partial colectomy (40% vs 70%). Best response to prior systemic therapy (partial response + stable disease) was 72% for L tumors and 68% for R tumors with a median duration of treatment of 26 and 22 months, respectively. REG treatment duration was similar in the 2 groups. Median OS (95% CI) was 6.7 months (6.1, 7.7) for L tumors vs 6.3 months (4.9, 8.1) for R tumors (P = 0.3); median progression-free survival (95% CI) was 2.8 months (2.6, 3.0) vs 2.6 months (2.4, 3.0) (P = 0.5), respectively. **Conclusions:** Interim results from this observational study suggest that OS is similar in patients with R and L tumors treated with REG. Clinical trial information: NCT02042144.

3569 Poster Session (Board #192), Sat, 8:00 AM-11:30 AM

Bevacizumab and its impact on survival for patients receiving subsequent anti-EGFR therapy: Updated results from the SA metastatic CRC registry. *First Author: Timothy Jay Price, Queen Elizabeth Hospital and Lyell McEwin Hospital, Adelaide, Australia*

Background: Debate exists as to whether first line bevacizumab effects subsequent sensitivity to anti-EGFR therapy. Authors hypothesize that initial anti-VEGF therapy may induce biological changes that then increase the risk of acquired resistance to subsequent EGFR inhibitors. **Methods:** A retrospective cohort study was performed to compare the characteristics and survival of patients who were treated with an anti-EGFR therapy 2nd line and beyond by two groups defined by the first line therapy; 1. chemotherapy (chemo) plus bevacizumab (bev) and 2. chemo alone. Survival for this analysis is from the time of commencing first line chemotherapy and secondly from anti-EGFR therapy. Pearson chi test analysis was performed to determine whether receiving first line bev was associated with worse overall survival (OS). **Results:** 348 mCRC patients who received chemo with or without bev and then an anti-EGFR therapy were studied. Patient characteristics are summarised in the table below. The significant differences between group 1. Vs. 2. were as follows; median age 63.8 years v 67.9 years ($p = 0.005$), lower use of single agent FU 6.4% v 19.2%, KRAS status not tested (reflecting the practice changes over time) 19.3% v 39.2%, KRAS MT 2% v 4%, and where BRAF MT status was known (11%); BRAF MT rate 23% v 0. Median OS for the 2 groups was 34.2 months, and 28.2 months respectively ($p = 0.12$) from first line therapy. Median OS for patients who underwent single agent anti-EGFR as subsequent therapy was also not significantly different, 31.1 months group 1 ($n = 60$) versus 27.7 months group 2 ($n = 85$), $p = 0.52$. Results based on commencement of anti-EGFR therapy are under way. **Conclusions:** Survival was not significantly different between the two groups, and the trend was towards higher OS with chemo plus bev suggesting that in our registry population, bev administration in first line therapy with chemo did not lead to a worse outcome overall for those patients subsequently receiving anti-EGFR therapy, either with chemotherapy or as a single agent. Updated results from commencement of anti-EGFR therapy will give further insights and will be presented at the meeting.

3570 Poster Session (Board #193), Sat, 8:00 AM-11:30 AM

Upfront short course radiotherapy (SCRT) in metastatic rectal cancer (mRC): A way forward. *First Author: Shanu Jain, Tata Memorial Hospital, Mumbai, India*

Background: To evaluate the feasibility and efficacy of SCRT followed by chemotherapy (CT) in locally advanced metastatic rectal cancer (LAmRC). **Methods:** Between May 2012 and August 2015, 70 patients having LAmRC with or without circumferential resection margin (CRM) positive disease treated with SCRT (25Gy/5#) followed by 3-6 cycles of capecitabine/5-FU, oxaliplatin or irinotecan based CT were assessed. **Results:** Fifty one had single site metastases (23 liver, 16 lung, 10 retroperitoneal lymph nodes and 2 peritoneum), 9 had combined lung and liver metastases and 10 had combined nodal and organ metastases. Sixty five (93%) patients could complete planned SCRT and 3-6 cycles of chemotherapy (starting 7-10 days after RT completion) with dose reduction in 21 (32%) patients owing to CT induced toxicities. Local tumor down-staging was achieved in 43 (61.4%) patients and the rest had a stable primary disease. Radiologically, CRM was free in 25 (46.3%) patients out of 54 initially involved. Surgery of the primary was planned in 38 (58%). R0 resection in 26 (40%), R1 in 7 (pCRM positive). Five refused surgery in spite of being resectable. Rest of the 27 (41%) received palliative CT due to progression of distant disease. Metastatectomy along with primary surgery was done in 16 (25%) patients. Median follow up was 29 months. Overall survival (OS) of entire cohort at 2 years was 40%. Median progression free survival (PFS) and OS of patients with resected primary was 17 (10-24) and 37 (28-45) months, respectively, which is significantly better than those who were not resected ($p = < 0.001$). Of these 33 resected patients, 13 (39.4%) are disease free and 20 have progressed (16 distant, 2 loco-regional and 2 local and systemic). **Conclusions:** Upfront SCRT followed by systemic CT in an unresectable group of metastatic rectal cancer patients is safe and feasible and is having encouraging results in terms of downstaging and resectability of the primary.

Patient group	PFS in months	OS in months
Whole cohort (n = 70)	10 (7-13)	16 (8-24)
Operated for Primary (n = 33: 47%)	17 (10-23.6)	37 (28-46)

3571 Poster Session (Board #194), Sat, 8:00 AM-11:30 AM

PEGylated human IL-10 (AM0010) monotherapy in refractory metastatic colorectal cancer. *First Author: Jeffrey R. Infante, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: Colorectal Cancer (CRC) has been refractory to immune therapies. The clinical benefit of immunotherapy is thought to depend on the expansion of activated, intratumoral, tumor specific cytotoxic CD8+ T cells which are low in most CRCs. AM0010 stimulates the survival, expansion and cytotoxicity of intratumoral CD8+ T cells. Patients with CRC who have progressed on SOC first and second line of therapy have a reported 7.1 months OS with TAS-102 (Meyer et al. NEJM372;20, 2015). In this Phase 1 study the efficacy of AM0010 was studied in refractory metastatic CRC patients. **Methods:** CRC pts progressing on a median of 4 prior therapies (range 2-7) were treated daily with AM0010 in doses of 1 ug/kg SQ daily to 40 ug/kg in a dose escalation design. Tumor responses were assessed using irRC. Serum cytokines, activation of blood derived T cells and peripheral T cell clonality were analyzed. Pretreatment archival tissue samples were evaluated by IHC for tumor infiltration by CD8+T cells. **Results:** AM0010 was tolerated with reversible TrAEs. 10 pts (of 27) had a G3/4 TrAE. There were no objective responses. 11 patients were treated in dose escalation cohorts (1-10 ug/kg) and 16 pts were treated at or above RP2D (20 ug/kg or 40 ug/kg). Seven of 25 pts with at least one radiographic response evaluation had stable disease at 8 weeks. One patient had SD for 19.4 months. The mPFS (ITT n = 27 pts) was 1.6 months, mOS was 11.7 (range 2.4 – 32+) months. The median follow-up is 25.2 months (range 13-35). AM0010 increased Th1 cytokines IL-18 and IFNg in the serum of patients, while decreasing mediators of chronic, tumor promoting inflammation (Th17 cytokines) and TGFb. Tumor infiltrating granzyme B+ CD8+ T cells increased during the treatment. AM0010 induced de-novo oligoclonal expansion of T cell clones in patients. **Conclusions:** AM0010 is well tolerated in patients with refractory CRC. Although objective tumor responses were not seen in this very advanced CRC population, the observed immune activation including clonal T cell expansion, prolonged stable disease, and the mOS of 11.7 months is encouraging in this advanced CRC population. Future study of AM0010 in combination with FOLFOX in a second – line of therapy colorectal cancer patients is being planned. Clinical trial information: NCT02009449.

3572 Poster Session (Board #195), Sat, 8:00 AM-11:30 AM

Results of the Quad wild type arm of the AGITG ICECREAM study: A randomised phase II study of cetuximab alone or in combination with irinotecan in patients with refractory metastatic colorectal cancer with no mutations in *KRAS, NRAS, BRAF* or *PIK3CA*. *First Author: Jeremy David Shapiro, Department of Medical Oncology, Cabrini Hospital, Melbourne, Australia*

Background: Cetuximab (cet) increases survival in *RAS* wild-type (WT) metastatic colorectal cancer (mCRC) in first-line and chemorefractory patients (pts). Adding irinotecan (iri) to cet in refractory pts who had progressed on iri increased response and delayed progression in the BOND trial, which was conducted prior to recognition that *RAS* mutations are predictive of EGFR-inhibitor (EGFR-I) resistance. Subsequent trials in chemorefractory pts used single agent EGFR-I as standard. In the era of biomarker selection, the benefit of continuing iri versus single agent EGFR-I had not been resolved. **Methods:** ICECREAM is a randomised phase II trial evaluating cet v cet + iri in chemotherapy-refractory mCRC, stratified for *KRAS* G13D mutation (previously reported) or no mutations in *KRAS*, *NRAS*, *BRAF* and *PI3KCA (*Quad WT*)*. EGFR-I naïve, ECOG PS 0-1 pts, progressing within 6 months of iri and refractory (or intolerant) to fluoropyrimidine and oxaliplatin were randomised to cet 400mg/m^2 IV loading then 250mg/m^2 weekly +/- iri 180mg/m^{2}q2 wks. The primary endpoint was progression-free survival at 6 months (6m PFS); secondary endpoints were response rate (RR), overall survival (OS), toxicity and quality of life (QOL). **Results:** From Nov 2012 to June 2016, 48 Quad WT pts were recruited: 2 ineligible (not iri-refractory, *BRAF* mutation) wre not included for analyses and a further 2 not evaluable for response. Characteristics were balanced between cet ($n = 21$) v cet-iri ($n = 25$), except for sex (male 62 v 72%) and primary site (left 95 v 68%). 6m PFS rate was 14% v 41%; HR 0.39 (95% CI: 0.20–0.78, $p = 0.008$). RR was 10% (2 PR) v 36% (1 CR, 8 PR); $p = 0.04$. Toxicities were higher with cet-iri; at least one grade 3/4 adverse event in 50 v 23%. No differences in global or specific QOL were seen. **Conclusions:** The AGITG ICECREAM trial confirms a significant synergy for the addition of iri to cet and improved PFS in Quad WT chemorefractory mCRC, echoing data in molecularly unselected pts. Clinical trial information: ACTRN12612000901808.

3573 Poster Session (Board #196), Sat, 8:00 AM-11:30 AM

Rapid in vitro evaluation of immune responses to tumor-derived organoids as an adjunct to immunotherapy trials. *First Author: Robert George Ramsay, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Cancer immunotherapy has made rapid advances with the development of agents that subvert the negative arm of the immune system. This has been important because patients can mount anti-tumor immune responses. In the case of colorectal cancer (CRC), the presence of tumour infiltrating lymphocytes (TILs) appears to have predictive power regarding outcome. Nevertheless, assays that directly evaluate the quality, phenotype and anti-tumor activity of TILs are lacking. Here a novel immune assay platform is presented that measures the kinetics of TIL killing which correlates with pathological tumour response after treatment. **Methods:** Treatment naïve fresh cancer biopsies were processed to generate organoids and TILs from patients (n = 12) with pathological complete response (pCR) verses non-responding tumours (NRT). These were co-cultured with TILs to organoid ratios of 1:1, 5:1 and 10:1 for 48 hs and TILs function were measured by cytokine release and mean fluorescence intensity (MFI) based upon activated caspase activity. Additionally, TILs from patients with metastatic CRC (n = 20) have also been evaluated. **Results:** Ten thousand+ organoids are routinely cultured while millions of TILs are retrieved and expanded from biopsies. TIL-mediated killing of patient-matched tumor organoid confirm CD8+ve specific killing. At 24hrs MFI was significantly higher in pCR organoid indicative of immune-mediated cell death compared to NRT organoids at a ratio of 1:1. The efficiency of TIL killing was further enhanced as the ratio increased to 5:1 and 10:1. Gamma interferon production by cytotoxic (CD8+) T-cell is a robust measure of TIL activation state and was also significantly higher by pCR TILs compared to NRT TILs. Substantive differences in TIL subsets were also found in mCRC-derived samples compared to primary CRC. **Conclusions:** This is a novel functional immune assay and the first of its kind that successfully demonstrated the differences in patient-matched TIL killing between non-responding and responding CRC. This assay can be performed within in two weeks and thus it has translational potential that may change clinical management in the future and immunotherapy strategy design.

3574 Poster Session (Board #197), Sat, 8:00 AM-11:30 AM

Prognostic implications of TAMs in colorectal cancer hepatic metastases. *First Author: Matthew Reilley, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: A limited understanding of the immune microenvironment of mismatch repair-proficient metastatic colorectal cancer (mCRC) impedes efforts to develop effective immunotherapy treatments for the majority of CRC patients. Liver metastatic disease is common and associated with poor outcomes. While T-cell infiltration of liver metastases positively correlates with survival, most mCRC patients do not benefit from checkpoint-blockade therapy. Tissue associated macrophages (TAMs) have been associated with an immune suppressive environment, but their prognostic role in mCRC is largely unknown. **Methods:** Comprehensive analysis of gene expression and immunohistochemistry (IHC) in 25 microsatellite stable (MSS) untreated liver metastatectomy (LM) specimens was performed. Clinical outcomes including recurrence, immunologic data, and tumor microsatellite status were evaluated and correlated. **Results:** Principal component analysis of immune and cancer pathway related genes were performed and compared with recurrence status. All samples were confirmed MSS. There were distinct differences in gene expression between patients who remained disease free and those who recurred. Among immune related genes CXCL5, IRF4, IL6R, TNF, CTLA4, ICOS, and ARG1 were relatively over-expressed in non-recurrent tumors, while PPARG, AIRE, and EPCAM were over-expressed in recurrent tumors (FDR 0.2, $p < 0.05$). Cibersort analysis predicts a significantly higher number of M2 versus M1 macrophages regardless of recurrence status ($p < 0.05$), with an approximate M1:M2 ratio of 1:2 and a higher total number of M1/M2 macrophages in tumors that recur. On IHC, an average of 29% of cells per sample expressed macrophage marker CD68. Relatively fewer CD3, CD4, and CD8 T cells were observed with average infiltration rates of 7.4%, 3.6%, and 2.6% respectively. **Conclusions:** CRC liver metastases demonstrate evidence of a large TAM population with significant M2 component and a smaller T cell population. A greater number of TAMs appear to correlate with recurrence, while a more immunogenic phenotype correlates with lower recurrence risk.

3575 Poster Session (Board #198), Sat, 8:00 AM-11:30 AM

Robotic procedure versus open surgery for simultaneous resection of colorectal cancer with liver metastases: Short-term outcomes of a randomized controlled study. *First Author: Jianmin Xu, Institute of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: The simultaneous resecting both colorectal cancer and liver metastases is a safety and efficacy surgical procedure for treating colorectal cancer patients with liver metastases (CRCLM).The safety and efficacy of robot-assisted simultaneous resection of CRCLM is unclear. Furthermore, what kind of selective CRCLM patients would obtain benefits from robotic procedure need identify. The aim of this study was designed to compare robotic procedure with open surgery, and establish robotic surgery indications to identify benefit population of CRCLM. **Methods:** CRCLM patients were evaluated and confirmed with surgical indication by multidisciplinary team (MDT), and randomized to two groups, robotic arm (n = 58) and open arm (n = 57). The primary endpoint is 3-year DFS, the second endpoints include short-term surgical outcomes, complications and safety. **Results:** A total of 115 patients were randomized between September 2013 and September 2016. Despite longer operating time, patients assigned to robot-assisted surgery had less blood loss (100ml vs. 150ml, $P < 0.001$), a shorter time to pass first flatus (3 d vs. 4 d, $P < 0.001$) and return to diet (3 d vs. 5 d, $P = 0.002$), shorter hospital stay with improved sexual function. Furthermore, followed benefits were observed in robotic arm versus open arm: lower serum C reactive protein (CRP) level on postoperative day 1 (POD1) (16 mg/L vs. 37 mg/L,$P < 0.001$), and POD3 (112 mg/L vs. 160 mg/L, $P < 0.001$), lower level of liver transaminase on POD5, and lower liver-related complication morbidity(10.3% vs 28.1%, $p = 0.016$). In addition, we identified and recommended selective CRCLM patients with the number of liver metastases < 3, maximal tumor size < 5cm, tumor not located in segment I to accept robotic procedure. **Conclusions:** We identified and recommended selective CRCLM patients to accept robotic surgery for treating liver metastases. Robotic surgery result in similar safety as open procedure, with shorter recovery time, decreased morbidity, and improved sexual function. Clinical trial information: NCT02642978.

3576 Poster Session (Board #199), Sat, 8:00 AM-11:30 AM

Comparison of 5-FU vs capecitabine in combination with mitomycin or cisplatin in the treatment of anal cancer. *First Author: Irene Yu, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: The patterns of capecitabine use as an alternative form of fluoropyrimidine to infusional 5-FU in the non-operative management of anal cancer in the real world are poorly described. Our objectives were to determine the frequency of capecitabine use, compare the observed outcomes between oral and intravenous fluoropyrimidines, and examine for variations in treatment-related adverse events between the two agents. **Methods:** All anal cancer patients who received either capecitabine or infusional 5-FU as part of their chemoradiation treatment from 2004 to 2013 at any 1 of 6 cancer centers in British Columbia were included. Chi-square and Wilcoxon-Mann tests were used to assess for associations between treatment groups and clinical characteristics and outcomes. **Results:** A total of 486 patients were identified: median age was 59 (IQR 53-67) years, 175 (36%) were men, 418 (86%) had ECOG 0/1, and 30 (6%) were HIV positive. Median total radiation dose was 54 cGy (IQR 50-54) and 47 (10%) underwent a colostomy prior to chemoradiation. Baseline characteristics were balanced between the two groups with respect to age, gender, ECOG, and HIV status (all $p > 0.05$). Prior to 2010, only 5-FU was utilized. From 2010 to 2013, 155 and 82 patients (65% vs 35%) received capecitabine vs 5-FU, respectively. Overall (68% vs 67%, $p = 0.831$) and disease-free survival rates (59% vs 59%, $p = 0.926$) at 3 years were similar in the capecitabine vs 5-FU groups. Rates of subsequent abdomino-perineal resection were also similar (10% vs 14%, $p = 0.164$). Patients who received 5-FU were more likely to report adverse effects (76% vs 57%, $p < 0.01$). The capecitabine group had a lower incidence of stomatitis (7% vs 43%, $p < 0.01$) whereas the 5-FU cohort reported less frequent hand-foot syndrome (1% vs 7%, $p < 0.01$). The rates of myelosuppression, nausea/vomiting, diarrhea, and rash were similar between the two groups (all $p > 0.05$). **Conclusions:** This represents one of the largest population-based studies to demonstrate a preference for capecitabine in place of 5-FU in the management of anal cancer. Survival outcomes were similar between the two treatment groups, but capecitabine may be better tolerated in the real world.

3577 Poster Session (Board #200), Sat, 8:00 AM-11:30 AM

Prospective study of biomarkers in squamous cell carcinoma of the anal canal (SCCAC) and their influence on treatment outcomes: Final results. *First Author: Camila Motta Venchiarutti Moniz, Instituto Do Câncer Do Estado De São Paulo, São Paulo, Brazil*

Background: While chemoradiation (CRT) is a curative treatment for SCCAC, many patients (pts) present primary resistance. As a rare tumor, the predictors of response in this setting remain unknown. **Methods:** Prospective cohort study aimed to evaluate predictive biomarkers (Ki-67, PD-L1, Human papillomavirus (HPV), HIV status and mutations in tumoral DNA) associated with complete response (CR) following standard CRT for localized SCCAC. Eligible pts had T2-4/N0-3/M0 disease and were candidates to standard CRT. CR at 6 months (m) measured by RECIST 1.1 was the primary endpoint. DNA mutations were analyzed by next-generation (NGS) TruSight Tumor26 panel. HPV positivity was tested by PapilloCheck Test. KI-67 and PD-L1 were evaluated by immunohistochemistry. **Results:** 78 pts were recruited from Jan/2011 to Dec/2015. 75 were evaluable for response. Median age 57 years; 49 (65%) were stage III, and 9 (12%) were HIV+. At 6m 47 (62.7%) had CR, 18 (24%) partial response (PR) and 10 (13.3%) disease progression. HPV was evaluated in 67 and found in 47 (70.1%), the majority HPV16. PD-L1 was tested in 61, 10 (16.4%) had $>$ 1% positive expression. Ki-67 was performed in 65, a median was 50% (1-90%) per patient. Clinical stage, HIV status, median KI-67, HPV and PD-L1 positivity, and treatment interruption were tested as predictive factors of CR in 6m by logistic regression. On multivariable analyses, ECII patients were 4.7 more likely to achieve CR than ECIII (OR 4.70 CI95%1.36-16.30; p = 0.015). HIV was borderline significant (OR 2.53 CI95% 0.9-7.1; p = 0.079). Analyzing the patients with PR and CR HIV+ was significantly associated with poor response. Patients HIV- were 5.7 more likely to achieve CR or PR (OR 5.72 CI95%2.5-13.0; p $<$ 0.001). 25 patients had tumor samples proper for NGS, 17 had at least one pathogenic mutation. The most common mutated genes were PIK3CA and MET in 6. There was no differences in CR rates according to MET (50% vs 47.3%, p = 1) or PIK3CA (33.3% vs 47.3%, p = 0.6) mutation status. TP53 codon 72 polymorphism was present in 72% (n = 18) and was not associated with CR (44% VS 57%, p = 0.6). **Conclusions:** Our study suggests that HIV+ pts are less responsive to CRT.

3578 Poster Session (Board #201), Sat, 8:00 AM-11:30 AM

Colorectal cancer: Impact of primary tumor location on genetic alterations. *First Author: Mohamed E. Salem, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Recent data show that patients with left sided colon tumors (LT) have better survival and respond differently to biologics compared to patients with right-sided tumors (RT), likely due to molecular differences. We sought to examine these differences. **Methods:** Primary colorectal tumors (n = 1730) with origins clearly defined as RT (cecum to hepatic flexure; n = 273), LT (splenic flexure to sigmoid colon; n = 585), or rectal (RC; n = 872) were examined by NextGen sequencing, protein expression and gene amplification. Tumor mutational load (TML) was calculated in 1001 of these tumors using only somatic nonsynonymous missense mutations. Chi-square was used for comparison. **Results:** When compared to LT, RT carried a significantly higher rate of BRAF (25% vs 7%; p $<$ 0.0001), PTEN (5.4% vs 1.3%; p = 0.008), and ATM (4% vs 1%; p = 0.04) mutations. RT were likely to have more MSI-high tumors (22% vs 5%; p $<$ 0.0001) and PD-1 overexpression (58% vs 44%; p = 0.01). There were no differences in the rate of KRAS (50% vs 42%; p = 0.07) or NRAS mutations (2.2% vs 3.4%; p = 0.4). When compared to RC, RT had a higher rate of BRAF (25% vs 3%; p = $7E^{-07}$), PIK3CA (22% vs 11%; p = 0.001), CTNNB1 (3% vs 0.3%; p = 0.02); ATM (3% vs 1%; p = 0.04), PTEN (5% vs 1%; p = 0.004), and BRCA1 mutations (4% vs 0%; p = 0.02), and a lower rate of TP53 (56% vs 71%; p = 0.001) and APC (53% vs 66%; p = 0.003) mutations. When compared to RC, LT showed higher rates of BRAF (6.7% vs 3.2%; p = 0.04) and CTNNB1 (2.1% vs 0.3%; p = 0.04) mutations, and a higher rate of MSI-high tumors (4.6% vs 0.7%; p = 0.04), whereas RC had a higher rate of KRAS mutation (50% vs 42%; p = 0.04). There were no differences between RT, LT, and RC for the frequency of PD-L1 (2%, 2%, and 1%) or Her-2 (1%, 2%, and 3%) overexpression, although Her-2 amplification was significantly different (1%, 3%, and 5%, RT vs RC; p = 0.03). Mean TML was 12, 11, and 8 mutations/megabase for RT, LT, and RC, respectively (RT vs RC; p = 0.01). There was a correlation between TML and PD-L1 (p = 0.04) and PD-1 (p = 0.01). **Conclusions:** Tumors arising in the right colon carry genetic alterations that are different from LT as well as RC. However, it appears that CRCs carry a continuum of molecular alterations from the right to the left side, rather than displaying sharp, clear-cut differences.

3579 Poster Session (Board #202), Sat, 8:00 AM-11:30 AM

Association of immune markers and Immunoscore with survival of stage III colon carcinoma (CC) patients (pts) treated with adjuvant FOLFOX: NCCTG N0147 (Alliance). *First Author: Frank A. Sinicrope, Mayo Clinic, Rochester, MN*

Background: Tumor infiltrating lymphocytes (TIL) indicate a host immune response that may influence survival. Immunoscore was developed using $CD3^+$ and $CD8^+$density and location in primary CC pts with pooled stages, varying treatment and follow-up. We determined if individual immune markers and/or Immunoscore are prognostic in resected stage III CC pts (N=600). **Methods:** $CD3^+$ and $CD8^+$ T-cell or $CD20^+$ B lymphocyte density in central tumor (CT) and invasive margin (IM) was evaluated by immunostaining and quantified by image analysis. Immunoscore was calculated on a scale of I0 to I4 with high densities of $CD3^+$ and $CD8^+$in both CT and IM scored as I4; low densities scored as I0. Associations with disease-free survival (DFS) were evaluated by multivariable Cox regression adjusting for covariates. **Results:** Data for $CD3^+$, $CD8^+$ and $CD20^+$ were generated (N=595). Higher density of $CD3^+$ CT, $CD3^+$ IM and $CD8^+$ IM were associated with longer DFS adjusting for covariates (Table). $CD3^+$ IM had the strongest association with DFS, and was stronger in left-sided ($HR_{adj.}$=0.81, 95% CI, 0.70-0.94, $p_{adj.}$= 0.0049) vs right-sided ($HR_{adj.}$=0.93, 95% CI, 0.85-1.0 $p_{adj.}$=0.52) tumors ($p_{interaction}$=0.039). Higher density of $CD3^+$ IM was associated with older age (p=0.034), $T_{1/2}$ (p$<$.0001), N_1 (p=0.017), right-sided (p=0.013), high TILs (p=0.0008), and deficient MMR (p=0.0003). Using a prior Immunoscore risk stratification, higher scores were associated with better DFS ($HR_{.}$=0.62, CI, 0.44-0.87, p=0.006) (Table). **Conclusions:** Densities of $CD3^+$ and $CD8^+$, especially at IM, are individually prognostic in FOLFOX-treated pts. Association of $CD3^+$IM with prognosis differed by primary CC site. Immunoscore was strongly prognostic, and this result provides validation in a clinical trial cohort.

Immune marker	HR_{adj} (95% CI)	P_{adj}
$CD3^+$ CT	.89 (.79, .99)	.033
$CD3^+$ IM	.89 (.83, .96)	.0018
$CD8^+$ IM	.79 (.65, .95)	.013
Immunoscore		
I2-I4 vs I0-I1 (ref)	.64 (.45, .92)	.015
I1-I4 vs I0 (ref)	.62 (.44, .87)	.0063

Support: U10CA180821, U10CA180882, U10CA180820, U10CA180863, U10CA180888, CCSRI 021039, Eli Lilly and Company, Pfizer, Bristol-Myers Squibb. ClinicalTrials.gov Identifier: NCT00079274.

3580 Poster Session (Board #203), Sat, 8:00 AM-11:30 AM

Identification of a novel predictive genomic biomarker for response to combination bevacizumab in metastatic colorectal cancer (mCRC). *First Author: Annette T. Byrne, Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin, Ireland*

Background: Somatic copy number alterations (SCNA) are genomic alterations evident in cancers including mCRC. These alterations support biomarker discovery, allowing identification of variants that can be used to predict response to therapy. Herein, we studied the impact of SCNAs on mCRC patient response to bevacizumab (BVZ). **Methods:** SCNA data was assembled from mCRC tumors in the TCGA cohort (n = 676), from the CAIRO 2 study [n = 143] and from the ANGIOPREDICT cohort (n = 258) [Betge et al. Digestion 2016 94(3):129-137]. GISTIC v2.0 was used to identify the most frequent and overrepresented chromosomal aberrations. A region was considered deleted if the logR value was $<$ 0.1 and amplified when the logR was $>$ 0.1. A cutoff q-value of 0.25 was used to select significantly overrepresented SCNAs. To further explore the impact of new ANGIOPREDICT clusters and consensus molecular subtypes (CMS), [Guinney J et al Nat Med. 2015 21(11):1350-6], a panel of seven xenografts representing each CMS subtype was treated with FOLFOX (40mg/kg 5-FU, 13.4mg/kg folinic acid & 2.4mg/kg oxaliplatin) + B20 antibody (mouse avastin, 10mg/kg) for 4 weeks. **Results:** Unsupervised hierarchical clustering classified all 1077 tumors into 3 consensus SCNA subgroups termed 'ANGIOPREDICT' clusters 1-3. Concordance between CMS and ANGIOPREDICT clusters was evident: CMS1 - Cluster 1 78%, CMS3 - Cluster 1 50%. CMS2 - Cluster 2/3 92% and CMS4 - Cluster 2/3 84%. Tumors with intermediate or high copy number instability (ANGIOPREDICT cluster 2 & 3) showed improved progression free survival (PFS): 369d *vs.* 227d p = $1.36e^{-7}$) whereas tumors with low copy number alterations displayed a poor response to BVZ therapy (PFS: 147d *vs* 152d p = 0.906). Xenografts corresponding to CMS 2&4/ ANGIOPREDICT cluster 2-3 showed improved response to FOLFOX + B20 therapy and increased PFS (p $<$ 0.001) *vs.* CMS1&3/ ANGIOPREDICT cluster 1. **Conclusions:** For the first time, in a large test and validation cohort including retrospectively collected and randomized controlled trial patient samples, we have identified a predictive genomic biomarker for BVZ therapy in mCRC. We have further demonstrated the utility of CMS subtyping to stratify patients to BVZ .

3581 Poster Session (Board #204), Sat, 8:00 AM-11:30 AM

Extraordinary survivorship after colorectal liver metastasis resection to identify a distinct molecular profile associated with survival in an independent cohort of 965 patients. *First Author: Jesse Joshua Smith, Colorectal Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Half of patients diagnosed with colorectal cancer (CRC) develop metastases and most are CRC liver metastasis (CRLM). A mere 20% of these patients undergo complete resection of their liver disease and 5-year overall survival (OS) is only 50%. We hypothesized that we could identify a specific molecular profile associated with extraordinary survivorship in CRLM patients that would more precisely inform underlying tumor biology beyond standard clinical and pathologic features. **Methods:** Tumor samples were identified from patients who underwent curative resection. Patients with disease-specific survival (DSS) ≥10 years following resection were compared to those with ≤2-year survival (10yr vs. 2yr). Evaluable DNA was obtained from 36 cases (2yr, n = 17; 10yr, n = 19) then sequenced and analyzed with MSK-IMPACT (MSK-I), a hybridization capture, next generation sequencing platform. Differentially altered genes in 10yr vs. 2yr cohorts were identified (Fisher's exact). Findings in the extraordinary survivors group were validated using MSK-I in an independent cohort of 965 metastatic CRCs (metCRCs). Kaplan-Meier estimates and log-rank test were used. **Results:** In the 2yr group, we noted higher clinical risk scores and more complex chemotherapy regimens vs. the 10yr group. Molecularly, mutually exclusive KRAS and TP53 mutations were noted in the 10yr group, whereas significant co-occurrence of KRAS and TP53 mutations was seen in the 2yr group. Further, we noted significant enrichment of VEGF copy number gains in the 2yr group vs. the 10yr group. APC mutation was equally common. In the validation cohort, $KRAS^{mut}/TP53^{wt}$ and $TP53^{mut}/KRAS^{wt}$ patients (median OS of 10 and 15 years respectively) had significantly better OS than the co-occurring $KRAS^{mut}$ / $TP53^{mut}$patients (median OS of 4.9 years; (P = 0.0001)). **Conclusions:** Single mutation of either KRAS or TP53 is associated with better outcomes than co-occurring KRAS/TP53 mutations in metCRC. These data demonstrate use of an extraordinary survivor cohort to identify a molecular profile associated with significant survival differences in an independent cohort of metCRC patients.

3582 Poster Session (Board #205), Sat, 8:00 AM-11:30 AM

Impact of overall severity of adverse events (AEs) on long-term outcomes in metastatic colorectal cancer (mCRC) patients (pts) treated with first line systemic chemotherapy: Findings from 3,971 pts in the ARCAD database. *First Author: John Raymond Zalcberg, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: The prognostic importance of the incidence, severity, type and duration of AEs pts experience during chemotherapy varies between tumor types, and the available evidence across the board is often conflicting. Here we investigated the impact of the overall severity of AEs among pts with mCRC receiving first-line oxaliplatin (Oxa)- and/or irinotecan(Iri)-based regimens. **Methods:** The overall severity of AE data (i.e., max grade (G) of all AEs) were available on 3,971 pts (median age 61; 60% male, 47% ECOG PS 1+; 57% 2+ metastatic sites) enrolled onto 6 1st-line randomized trials. Around 46%, 45%, and 9% of pts had received Oxa-, Iri-, and Oxa+Iri-based regimens, respectively. Pts receiving biologic agents were excluded. Stratified multivariate Cox models were used to assess the associations with overall survival (OS) and progression-free survival (PFS); adjusted hazard ratios (HR_{adj}) and 95% confidence intervals (CIs) are reported. **Results:** Pts who only received Oxa-based treatment reported the lowest rate of G3+ AEs ($p < .0001$) compared to pts treated with Iri- or Oxa+Iri-based regimens. Older age, female gender, and PS 1 or 2+ were associated with higher grade AEs (all $p < .0001$). Considering AEs experienced within 6w after randomization, 10% and 61% of pts experienced G4+ and G2-3 AEs, respectively. G3+ AEs were associated with a shorter OS for both pts receiving Oxa- (HR_{adj}= 1.2, 95% CI, 1.1-1.3, $p_{adj} < .0001$) and Iri-based regimens (HR_{adj}= 1.4, 95% CI, 1.2-1.5, $p_{adj} < .0001$). For the entire treatment course, 19% and 72% of pts experienced G4+ and G2-3 AEs, respectively. For Oxa-based regimens, pts with G3+ AEs had a longer OS (HR_{adj}= 0.86, 95% CI, 0.78-0.94, $p_{adj} = .0016$), whereas G3+ AEs were associated with a shorter OS (HR_{adj}= 1.2, 95% CI, 1.1-1.4, $p_{adj} = .0004$) for pts treated with Iri-based regimens. Similar patterns were seen for PFS. **Conclusions:** Pts who reported higher grade AEs during initial treatment (≤6w) have significantly worse outcome than those who do not. Further analyses with treatment exposure/detailed dose-AE profile and its impact on survival are warranted.

3583 Poster Session (Board #206), Sat, 8:00 AM-11:30 AM

Targeted therapy for HER2 driven colorectal cancer. *First Author: Jeffrey S. Ross, Albany Medical College, Albany, NY*

Background: *ERBB2* (*HER2*) genomic alterations (GA) are evolving therapy taregets in metastatc coorectal cancer (mCRC). **Methods:** Hybrid capture based comprehensive genomic profiling (CGP) was performed on 8874 (9.6%) mCRC including both colonic adenocarcinomas (7587 cases; 85%) and rectal adenocarcinomas (1287 cases, 15%) Tumor mutational burden (TMB) was calculated from a minimum of 1.2 Mb of sequenced DNA. **Results:** *ERBB2* amplifications or a short variant (SV) alterations or both were found in 433 (4.9%) of the total mCRC. 195 (45%) of the *ERBB2* positive mCRC were female and 238 (55%) were male. Median age was 54 years (range 22 to 88 years). The most frequently co-altered genes were SV GA in *TP53* (82%), *APC* (70%), *KRAS* (26%), *SMAD4* (15%) and *PIK3CA* (13%). Clinically relevant GA significantly under-represented in *ERBB2*-altered CRC included significantly reduced GA in *KRAS* at 26% (p = 0.001) and *BRAF* at 4% (p = 0.003) as well as other kinases at 1% including *EGFR*, *KIT*, *MET* and *RET*. The frequency of TMB at > 10 mut/Mb ($p < 0.0001$), but at > 20 mut/Mb mCRC cases demonstrated virtually the same results regardless to *ERBB2* status at a frequency of x%. The overall *ERBB2* GA frequency at 5.3% in rectal mCRC is slightly higher than that seen in colonic mCRC at 4.9%, (p = 0.36). The frequency of TMB > 10 mut/Mb in *ERBB2* WT mCRC is greater in the colonic mCRC than the rectal mCRC ($p < 0.0001$ for both comparisons). When > 20 mut/Mb is used as the cut-off, the greater frequency of TMB in colonic mCRC versus rectal mCRC remains significant ($p < 0.0001$). When the *ERBB2*altered mCRC cases are evaluated, the greater frequency of TMB > 10 mu/Mb in colonic mCRC versus rectal mCRC remains significant (p = 0.009), but the greater frequency in colonic verses rectal mCRC at the > 20 mut/Mb is not significant (p = 0.37). **Conclusions:** Although lower than observed in breast and upper gastrointestinal carcinomas where anti-HER2 therapies are approved indications, the frequency of *ERBB2* GA in CRC at 4.9% is significant. Importantly, nearly half of CRC *ERBB2* alterations are SVs, not detectable by routine IHC and FISH testing. However, the success of anti-HER2 therapies shown here and progress in on-going clinical trials indicates that targeting *ERBB2* has potential to become an approved advance in precision therapy for mCRC patients.

3584 Poster Session (Board #207), Sat, 8:00 AM-11:30 AM

Clinical outcomes and emergent circulating tumor (ct)DNA *RAS* mutations and allele fraction for patients with metastatic colorectal cancer (mCRC) treated with panitumumab from the ASPECCT study. *First Author: Timothy Jay Price, The Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia*

Background: ASPECCT was a phase III clinical trial performed in the chemotherapy-refractory third-line mCRC setting (N = 1010). This analysis explores the relationship between circulating levels of mutations and clinical outcomes for panitumumab-treated subjects using univariate and multivariate models that treat total mutational load as a continuous measure. **Methods:** 238 subjects treated with panitumumab had paired plasma samples at baseline and post-treatment (PT). Samples were analyzed for mutations using the Plasma*Select*-R™ 63-gene panel (0.1% limit of detection). The fraction of mutant *RAS* reads was evaluated for association with tumor response (by RECIST) and overall survival using univariate and multivariate Cox proportional hazards models. **Results:** 52% of the subjects who were *RAS* wild-type by plasma at baseline never developed a *RAS* mutation. For those with mutant *RAS* ctDNA (*KRAS*+*NRAS*) detected at baseline or PT, there was an overall increase in *RAS* mutant DNA fraction at PT compared to baseline. By non-parametric analysis, there was no difference in the distribution of baseline mutant *RAS* fraction between those who achieved stable disease (SD) or those with progression ($P = 0.09$). There was also no difference in the increase in mutant *RAS* fraction on therapy between subjects with SD or progressive disease (PD). In addition, *RAS* mutation was not required for progression: 48% of subjects with PD had no *RAS* mutant DNA detected. **Conclusions:** In this exploratory analysis, baseline plasma mutant *RAS* fraction is an unreliable predictor of subsequent tumor response. Subjects with objective response or SD may have stable or rising levels of mutant *RAS* DNA. Subjects without any detectable *RAS* mutation still experience PD. These findings suggest that detectable plasma ctDNA *RAS* mutations do not necessarily predict response to panitumumab and should be interpreted with caution. Further work is needed to establish clinically relevant and validated thresholds. Clinical trial information: NCT01001377.

3585 Poster Session (Board #208), Sat, 8:00 AM-11:30 AM

Association of genetic variations in genes implicated in the axis with outcome in patients (pts) with metastatic colorectal cancer (mCRC) treated with cetuximab plus chemotherapy. *First Author: Yuji Miyamoto, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Accumulating evidence suggests that right- and left-sided CRCs have different prognoses and different sensitivities to *EGFR* inhibitors in several phase3 trials. These differences might be related to different embryological origins, which are reflected in different molecular profiles of tumors. *LEFTY*, *Nodal* and *ACVR2B*, which are *TGF-beta*superfamily, are key regulators of left-right axis during embryogenesis; these expressions control sidedness. Our aim was to evaluate whether SNPs in these genes are associated with clinical outcomes in mCRC pts enrolled in the FIRE3 trial. **Methods:** Genomic DNA was obtained from mCRC pts receiving cetuximab plus FOLFIRI as first-line treatment and analyzed by using PCR-based direct sequencing. Four functional SNPs in 4 genes (*LEFTY1*, *LEFTY2*, *Nodal*, and *ACVR2B*) were tested in 305 pts in FIRE3 trial cetuximab cohort (NCT00433927). Main characteristics were the following: male/female = 207/98; median age = 64; RAS-wildtype/mutant = 195/95; median PFS = 9.6 months; median OS = 26.5 months, median follow-up time = 41.8 months. **Results:** In patients with left sided tumor (*N*= 237), *LEFTY2* rs3007716 G/G variants (*N*= 14) showed shorter PFS than any A variants (*N*= 222) in univariate (8.0 months (M) vs. 10.3 M, HR = 2.24, 95% CI = 1.27-3.94, P < 0.01) and multivariate analyses (HR = 2.12, 95%CI = 1.20-3.75, P < 0.01). *Nodal* rs1904589 T/T (*N*= 36) showed longer OS than any C variants (*N*= 196) in univariate analysis (50.1 m vs. 29.8 M, HR = 0.61, 95% = 0.37-1.01, P = 0.048) and multivariate analyses (HR = 0.59, 95%CI = 0.35-0.99, P = 0.046). In patients with right sided tumors (*N*= 58), *ACVR2B* rs2268753 C/C (*N*= 12) showed shorter PFS than any T variants (*N*= 43) in univariate analysis (3.7 m vs. 7.7 M, HR = 1.93, 95% = 0.99-3.77, P = 0.038) and multivariate analysis (HR = 2.24, 95%CI = 1.12-4.51, P = 0.023). **Conclusions:** Our study showed for the first time that genetic variations in sidedness related genes are associated with PFS and OS in patients receiving cetuximab based chemotherapy, which may dependent on location.

3586 Poster Session (Board #209), Sat, 8:00 AM-11:30 AM

Right-sided colorectal cancer (RC): Response to first-line chemotherapy in FIRE-3 (AIO KRK-0306) with focus on early tumor shrinkage (ETS) and depth of response (DpR). *First Author: Julian Walter Holch, Department of Medical Oncology, Comprehensive Cancer Center Munich, University Hospital Grosshadern, Ludwig-Maximilians- University Munich, Munich, Germany*

Background: Recent evidence suggests that benefit from anti-EGFR treatment is restricted to RAS wild-type left-sided colorectal cancer (LC) (Holch JW et al. Eur J Cancer 2017). However, these results are preliminary. We therefore investigated patients with RC enrolled in the FIRE-3 trial, which evaluated the efficacy of first-line FOLFIRI plus either cetuximab (cet) or bevacizumab (bev) in RAS wildtype mCRC. New metrics of tumor dynamics were used to characterize the patients. **Methods:** The splenic flexure was used to differentiate LC from RC. Survival analysis was done using Kaplan-Meier estimation and differences were expressed using Log-Rank test, hazard ratios (HR) and corresponding 95% confidence intervals. Central independent radiological data was used to calculate early tumor shrinkage ≥20% (ETS) and depth of response (DpR). **Results:** In total, 330 patients were assessable for central radiological evaluation. In patients with LC (n = 257), treatment with FOLFIRI + cet led to longer overall survival (OS) compared to FOLFIRI + bev (HR = 0.68, p = 0.016). In patients with RC (n = 68), OS was comparable between treatment arms (HR = 1.11, p = 0.715). In patients with RC and ETS < 20%, OS was inferior in patients treated with FOLFIRI + cet. In patients who reached ETS ≥20%, a comparable OS was evident between treatment arms (for further details of efficacy in patients with RC see table). **Conclusions:** Patients with RC do not represent a uniform population. ETS ≥20% defines a subgroup of patients where comparable treatment efficacy was observed with regard to OS, ORR and DpR by addition of cetuximab vs. bevacizumab to FOLFIRI.

	ETS ≥20%			ETS < 20%		
FOLFIRI plus	cet	bev	HR (P-Value)	cet	bev	HR (P-Value)
number of patients	17	16	-	13	22	-
ORR (%)	88.2	93.8	- (0.99)	23.1	18.2	- (0.99)
DpR (%)	57.8	41.3	- (0.30)	-25.5	2.6	- (0.44)
PFS (months)	7.8	13.4	1.72 (0.14)	2.8	5.2	1.74 (0.13)
OS (months)	27.9	23.2	1.05 (0.90)	11.7	15.9	1.90 (0.09)

3587 Poster Session (Board #210), Sat, 8:00 AM-11:30 AM

Factors contributing to the black/white colorectal cancer survival disparity in nonelderly patients. *First Author: Helmneh M. Sineshaw, American Cancer Society, Atlanta, GA*

Background: Previous studies reported that black/white survival disparities among elderly colorectal cancer (CRC) patients largely reflect differences in tumor presentation rather than differences in treatment. We sought to determine the contribution of differences in tumor presentation and receipt of treatment to the black/white survival disparity among nonelderly CRC patients. **Methods:** We selected non-Hispanic black (black) and Non-Hispanic white (white) patients aged 18-64 years, and diagnosed between 2004-2012 with single or first primary invasive stage I-IV CRC in the National Cancer Data Base. Blacks were sequentially matched with three white comparison cohorts, using propensity score and greedy matching algorithm, by demographics (age, sex, diagnosis year, region), tumor presentation (stage, grade, margin, tumor location, node status, comorbidity score), and treatment (surgery, chemotherapy, radiotherapy, metastatectomy) characteristics. We used Kaplan-Meier method to estimate 5-year survival for blacks compared with whites in the entire cohort and in the three sequentially matched cohorts. **Results:** In the entire cohort, 5-year survival was 9.2% lower in nonelderly blacks than whites (57.3% vs 66.5%). The survival difference remained unchanged after demographic matching, but it decreased to 3.3% (5.9% absolute and 64% relative reductions) after tumor presentation matching, and to 2.6% (0.7% absolute and 7.6% relative reductions) after treatment matching. By anatomic subsite, treatment matching reduced the black/white 5-year survival difference by 26% (3%/11.5%) for rectal cancer, only by 5.6% (0.5%/9%) for left colon cancer, and no change for right colon cancer. **Conclusions:** Differences in tumor presentation characteristics explained about two-thirds of the black/white survival disparity in nonelderly CRC patients, while treatment explained less than ten percent of the disparity. Future research should explore the biological mechanisms underlying these observed differences in tumor presentation and implications for treatment.

3588 Poster Session (Board #211), Sat, 8:00 AM-11:30 AM

Prognostic signatures of oligometastasis in colorectal cancer liver metastasis. *First Author: Sajid A. Khan, Yale School of Medicine, New Haven, CT*

Background: Knowledge of molecular differences between limited metastasis (oligometastasis) and widespread metastases may provide biomarkers for selection of patients who will benefit from curative metastasis resection and provide useful prognostic information. In this study, we detect messenger RNA expressional patterns in patients with colorectal cancer liver metastasis (CRCLM) and identify networks of coding and noncoding RNAs corresponding to oligometastatic phenotype. **Methods:** RNA was prepared from frozen tumor tissue of 55 patients with CRCLM patients treated with liver resection and/or biopsy of their metastatic tumors with greater than 15 years of follow-up. Survival was calculated and stratified according to risk of recurrence. Cases were subject to RNA-Sequencing experiments with paired end sequencing. **Results:** RNA analysis with TopHat and Cuffdiff found significant differences in transcript expression according to recurrence for 667 genes (P < 0.05). Of these transcripts, 166 had a greater than 2-fold gene expression between groups when comparing mean Fragments Per Kilobase of transcript per Million mapped reads (FPKM) (P < 0.05). Unsupervised hierarchical clustering revealed distinct genomic patterns based on clinical outcome. A supervised gene expression analysis revealed a differential expression of genes in the Homeobox (*HOX*) family (P < 0.05). Overexpression of individual members of the *HOX* gene family are associated with prognosis. Upregulation of the *HOXD11* gene was associated with cure in 60% of cases while downregulation was associated with 5-year overall survivals of 16% (P = 0.023). Furthermore, when clusters of *HOX* family members were compared, we found that expression correlated with survival, underlining the importance of this gene family in oligometastasis biology. A high ratio of the *HOXD* cluster to *HOXA* cluster was associated with a long recurrence free survival (P = 0.002). **Conclusions:** Common genomic signatures characterize patients with liver oligometastasis from primary colorectal cancer. The *HOX* gene family strongly correlates with prognosis and represents a unique molecular subtype of patients. Further mechanistic studies of the *HOX* gene family in metastases are underway.

3589 Poster Session (Board #212), Sat, 8:00 AM-11:30 AM

Not all *RAS* mutations created equal: Functional and clinical characterization of 80 different *KRAS* and *NRAS* mutations. *First Author: Jonathan M. Loree, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Mutations (mts) in *RAS* predict lack of response to anti-EGFR therapy in colorectal cancer. Outside the "typical *RAS*" mts (*KRAS/NRAS* Codons 12, 13, 59, 61, 117, 146) cited in guidelines and anti-EGFR labeling, clinical impact of other "atypical *RAS*" mts is uncertain. **Methods:** Available literature and databases were surveyed to identify 80 *KRAS/NRAS* mts. We used the NovellusDx Functional Annotation for Cancer Treatment (FACT) to transfect these *RAS* mts (repeated a mean of 5.5 times/mt) in a cell-based assay that quantifies nuclear ERK localization as a measure of MAPK pathway activation, and normalized to wild type (WT) transfection. In 963 metastatic colorectal cancer patients (pts) with *BRAF* WT/*KRAS* mutant tumors, overall survival (OS) was evaluated by level of *RAS* signaling activity. **Results:** Of the surveyed mutations,96% (45/47) of typical mts and 39% (13/33) of atypical mts increased MAPK pathway activation above WT (range: 107%-211% of WT activity). Within the typical RAS mts, mts in *NRAS* or exon 3, 4 of *KRAS* had higher activity than mts in exon 2 (codons 12/13) of *KRAS*, reaffirming the biologic relevance of expanded *RAS* testing (median activity of 130% vs 178%, $P < 0.001$). The median activity of atypical *RAS* mts was lower than typical *RAS* mts (110% vs 159%, $P < 0.001$). Several notable exceptions in atypical *RAS* mts with high activity levels were *KRAS* V14I, Q22K, D33E, N116S, and F156L (all > 165% of WT activity). Conversely, within the typical *RAS* mts in the guidelines, *KRAS* G13C and K117R were not shown to increase activity significantly above WT. Pts with any *RAS* mt with MAPK activity above the median of typical mts had a worse OS compared to pts below the median in univariate (HR 1.45, 95% CI 1.04-2.32, P = 0.033) and multivariate models (HR 1.96, 95% CI 1.13-3.42, P = 0.017) that controlled for age, gender, sidedness, and synchronous vs metachronous presentation. **Conclusions:** Functional characterization confirmed activity of *RAS* mts in the current guidelines, but also suggested that a subset of atypical *RAS* mutations have similar levels of activation of the MAPK pathway. Within the subset of pts with *RAS* mts, those mts resulting in high MAPK activity are associated with notably shorter OS.

3590 Poster Session (Board #213), Sat, 8:00 AM-11:30 AM

Arginine methylation of EGFR in circulating tumor cells: A new biomarker for predicting resistance to anti-EGFR agents. *First Author: Krittiya Korphaisarn, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Arginine methylation of the epidermal growth factor receptor (meEGFR) increases binding affinity of EGF and other EGFR ligands, reduces the efficacy of anti-EGFR agents *in vivo*, and is reported to have a role in predicting response to anti-EGFR agents. This study aimed to investigate the predictive impact of meEGFR in metastatic colorectal cancer (mCRC) patients (pts) treated with anti-EGFR agents using blood-based testing. **Methods:** 15 mL of blood were collected from mCRC pts with documented disease progression following anti-EGFR treatment (Rx). Circulating tumor cells (CTCs) were isolated using antibody (ab)-independent micro-fluidic cassette-based technology (Parsortix system), which separates CTCs on the basis of size and deformability. CTCs were identified based on negative staining for CD45ab and positive staining for EpCAMab. meEGFR was identified based on positive staining for me-R198/200ab on CTCs. Associations between meEGFR-CTCs and total CTCs with progression free survival (PFS) were determined by Kaplan-Meier method and compared by the log-rank test. **Results:** A total of 47 mCRC pts were prospectively included in this study. CTCs were identified in 30 out of 47 cases (64%). Of those 30, meEGFR-CTCs were identified in 19 cases (63%). Mean total CTCs and meEGFR-CTCs counts were 3.6 (range 0-52) and 2.3 (range 0-30) cells per 7.5ml, respectively. There was no association between meEGFR-CTCs and clinic-pathological features (age, sex, tumor site & grade), line of anti-EGFR Rx, previous irinotecan used, or *NRAS, BRAF, PIK3CA*, and MSI status. However, in $RAS^{wt}/BRAF^{wt}$mCRC pts, high levels of meEGFR ratio (defined as > 0.25 meEGFR-CTCs per total CTCs) was associated with significantly inferior PFS with anti-EGFR Rx (median PFS 5.4 mo vs. 8 mo, HR 3.4, 95% CI of 1.5-7.9, P = 0.004). By contrast, high levels of total CTCs (> 3 cells/per 7.5 ml) had no impact on PFS with anti-EGFR Rx. **Conclusions:** We have successfully isolated CTCs from mCRC pts' blood using Parsortix system. Elevated levels of arginine methylated EGFR is associated with a shorter PFS with anti-EGFR-based Rx. Assessment of meEGFR-CTCs may provide a "liquid biopsy" biomarker for reduced efficacy from anti-EGFR Rx.

3591 Poster Session (Board #214), Sat, 8:00 AM-11:30 AM

Early prediction of clinical outcomes in resected stage II and III colorectal cancer (CRC) through deep sequencing of circulating tumor DNA (ctDNA). *First Author: Maximilian Diehn, Stanford University Medical Center, Stanford, CA*

Background: Adjuvant chemotherapy is offered to most pts with Stage III CRC, and to a subset with Stage II disease deemed at high-risk for recurrence. Nevertheless, risk stratification strategies remain suboptimal. Detection of minimal residual disease (MRD) through ctDNA analysis has been shown to identify pts at high recurrence risk in Stage II CRC, but not Stage III disease. **Methods:** The next-generation sequencing based AVENIO ctDNA Surveillance Kit (Research Use Only) was used to identify single nucleotide variants (SNVs) in tumor tissue within a cohort of 145 Stage II and III CRC pts following R0 surgical resection (n = 86 and 59 respectively; median follow-up = 32.1 mo). The same assay was used to monitor ctDNA with a single post-operative blood sample (mean surgery-to-phlebotomy time: 10 days). Regions from 197 genes recurrently mutated in CRC were interrogated, and pts were classified as ctDNA positive (+) or negative (-) in plasma based on the detection of SNVs previously identified in tumor tissue. **Results:** Variants were identified in 99% of tumors (n = 144) with a median of 4 SNVs/sample (range 1-24) and all post-operative plasma samples were successfully profiled. Pts with detectable ctDNA (n = 12) displayed a significantly shorter 2-year relapse-free survival (RFS; 17% vs 88%; HR 10.3; 95% CI 2.3-46.9; $p < 0.00001$), time to recurrence (TTR; HR 20.6; 95% CI 3.1-139.0; $p < 0.00001$) and overall survival (OS; HR 3.4; 95% CI 0.5-25.8; p = 0.041) than ctDNA- pts (n = 132). 11 (92%) of ctDNA+ pts developed recurrence compared to 9 (7%) of ctDNA- pts. Monitoring multiple variants doubled sensitivity of MRD detection compared to tracking a single driver mutation. TTR was shorter in ctDNA+ vs ctDNA- Stage II (HR 23.1, 95% CI 0.28-1900.4; $p < 0.00001$) and stage III pts (HR 17.9; 95% CI 2.7-117.3, $p < 0.00001$). TTR of Stage II and III ctDNA- pts was similar (p = 0.7). **Conclusions:** Our results indicate that ctDNA analysis can detect MRD within days after complete resection of CRC and accurately identifies pts at high risk of recurrence in both Stage II and III CRC. MRD detection via ctDNA sequencing may allow personalization of adjuvant treatment strategies.

3592 Poster Session (Board #215), Sat, 8:00 AM-11:30 AM

Impact of patient age on molecular alterations in left-sided colorectal tumors. *First Author: Benjamin Adam Weinberg, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: The incidence of colorectal cancer (CRC) in younger patients (pts) is rising. This increase is most pronounced in tumors arising from the distal colon and rectum. Since tumor sidedness has emerged as an important prognostic and predictive biomarker in CRC, we aim to explore the impact of age on the tumor biology of left-sided colon cancer (LCC). Herein, we compare profiles of LCC from younger (≤ 45 years) and older pts (≥ 65 years). **Methods:** LCCs (splenic flexure to rectum; n = 1,602) were examined by NextGen sequencing, protein expression, gene amplification, and microsatellite instability fragment analyses. Tumor mutational load (TML) was calculated using only somatic nonsynonymous missense mutations. Chi-square tests were used for comparisons. **Results:** LCCs from younger (median age 40, range 22-45 years, n = 229) and older (median age 71, range 65-89, n = 503) pts were studied. The most frequently mutated genes included *APC*, *TP53*, *KRAS*, *PIK3CA*, *ARID1A, FBXW7*, *SMAD4*, *ATM*, *BRAF*, and *NRAS*. Comparing younger v. older pts, there were no significant differences in the rates of *APC* (75.3% v. 82.9%, P = 0.139), *TP53* (79.5% v. 73.1%, P = 0.261), *KRAS* (37.6% v. 43.0%, P = 0.403), *PIK3CA* (9.4% v. 14.6%, P = 0.234), *ARID1A* (14.3% v. 13.2%, P = 0.884), *FBXW7* (11.4% v. 10.5%, P = 0.830), *SMAD4* (13.1% v. 7.4%, P = 0.129), *BRAF* (4.8% v. 5.7%, P = 0.762), or *NRAS* (3.5% v. 2.6%, P = 0.680) mutations. Additionally there were no significant differences in protein overexpression. However, there was a trend towards increased HER2 amplification in younger pts (5.7% v. 2.1%, P = 0.05). *MSH6* (4.8% v. 0.5%, P = 0.015), *MSH2* (2.4% v. 0%, P = 0.032), *POLE* (2.4% v. 0%, P = 0.032), and *NF1* (7.9% v. 0%, $P < 0.001$) mutations were observed at higher rates in younger pts. High TML (≥ 17 mutations per megabase) was seen more frequently in younger pts (8.2% v. 2.6%, P = 0.02). **Conclusions:** The molecular differences between LCC in younger and older pts are mostly due to mutations in mismatch repair genes. Higher TML may predict a higher response rate to checkpoint inhibitors in younger pts with LCC. The differences in tumor biology observed here warrant further study and may eventually be used to tailor therapy.

3593 Poster Session (Board #216), Sat, 8:00 AM-11:30 AM

Monitoring the effect of first-line treatment in RAS/RAF mutated metastatic colorectal cancer by serial analysis of tumor specific DNA in plasma. *First Author: Caroline Brenner Thomsen, Danish Colorectal Cancer Center South, Vejle, Denmark*

Background: Personalized medicine calls for an early indicator of treatment failure. Circulating tumor DNA (ctDNA) is a promising marker in this setting and our prospective study explored the association between disease control and change of ctDNA during first line chemotherapy in patients with RAS/RAF mutated metastatic colorectal cancer (mCRC). **Methods:** The present study included 138 mCRC patients receiving standard first line combination chemotherapy. In patients with a RAS/RAF mutated tumor the same mutation was quantified in the plasma using droplet digital PCR (ddPCR). The fractional abundance of ctDNA (ctDNA level) was assessed in plasma before treatment start and at every treatment cycle until radiologically defined progressive disease (PD). **Results:** RAS/RAF mutations were detected in the plasma from 77 patients (94% of patients with a tumor mutation). Twenty patients progressed on treatment and 57 stopped treatment without progression. The presence of a RAS/RAF mutation in plasma correlated to overall survival (OS) with a median of 24.2 months for patients with a wild-type tumor compared to 12.7 months for patients with a mution in plasma. A substantial increase in ctDNA level was highly associated with progression on treatment (risk ratio = 4.58, 95%CI = 1.99-10.51, $p < 0.0001$). Furthermore, with a stable ctDNA level the chance of non-progression was 88.2% (range 76.1-95.6%). The first substantial increase in ctDNA level occurred at a median of 51 days (range 14-133 days) before radiologically confirmed PD. **Conclusions:** The results indicate that ctDNA level may be predictive of treatment effect in patients with mCRC. An increase was observed to correlate with high risk of progression with a relevant lead time, whereas an unchanging ctDNA level related to stable disease.

3594 Poster Session (Board #217), Sat, 8:00 AM-11:30 AM

Genetic polymorphisms of CCL5 and CCR5 to predict efficacy of cetuximab-based treatment in metastatic colorectal cancer patients depending on primary tumor location. *First Author: Mitsukuni Suenaga, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: EGFR signaling blockade increases CCL5 expression, which attracts with tumor-infiltrating leukocytes regulating either the host-derived anti-tumor immunity or tumor progression. We tested whether genetic polymorphisms in the CCL5/CCR5 axis could predict efficacy of cetuximab (CET)-based first-line treatment in metastatic colorectal cancer (mCRC) patients (pts). **Methods:** Genomic DNA was extracted from 491 samples of two different cohorts with *KRAS* wild-type mCRC in the FIRE-3 study: an evaluation cohort of 244 pts receiving CET plus FOLFIRI (median age 64 yrs; median follow-up 34.1 mos); and a control cohort of 247 pts receiving bevacizumab plus FOLFIRI (median age 65 yrs; median follow-up 39.4 mos); Single nucleotide polymorphisms (SNPs) of *CCL5* and *CCR5* genes were analyzed by PCR-based direct sequencing. **Results:** Pts in the evaluation cohort with any *CCL5* rs2280789 G allele had shorter OS compared to those with the A/A variant (19.9 vs. 33.4 mos, HR 1.56, 95%CI: 1.05–2.30, $P = 0.024$), which was confirmed in multivariable analysis (HR 1.64, $P = 0.015$). Pts carrying any *CCR5* rs1799988 T allele had a trend lower response rate than those with the C/C variant (68 vs. 81%, $P = 0.078$). Statistically significant differences in efficacy were shown between the groups consisting SNPs and tumor location (Table). The findings were not confirmed in the control cohort. **Conclusions:** Genetic variants of *CCL5* and *CCR5* SNPs may predict outcomes in mCRC pts receiving CET-based first-line treatment depending on tumor location.

	Response rate (%)	*P* value	Median PFS (mos)	HR	*P* value	Median OS (mos)	HR	*P* value
All *KRAS* wt								
Location – *CCR5*		< 0.001			< 0.001			< 0.001
L[a] – C/C	91		10.6	1		38.5	1	
L – Any T	66		10.0	1.30		30.6	1.32	
R[b] – T/T	92		9.0	1.56		27.1	1.66	
R – Any C	48		6.5	3.00		15.8	3.99	
– *CCL5*		0.28			0.001			< 0.001
L – A/A	74		10.5	1		38.3	1	
L – Any G	71		10.0	1.17		21.7	1.43	
R – A/A	68		7.8	1.95		21.9	2.45	
R – Any G	44		3.9	2.13		18.3	3.33	
All *RAS* wt								
Location – *CCR5*		0.002			< 0.001			< 0.001
L – C/C	92		11.5	1		42.8	1	
L – Any T	75		10.5	1.13		38.7	1.13	
R – T/T	88		12.2	1.41		27.1	1.51	
R – Any C	47		6.5	3.12		11.7	4.73	
– *CCL5*		0.059			< 0.001			< 0.001
L – A/A	82		10.9	1		41.2	1	
L – Any G	73		10.0	1.13		20.3	1.79	
R – A/A	65		7.3	2.23		16.5	3.04	
R – Any G	40		3.9	2.10		18.3	5.40	

[a] left, [b] right

3595 Poster Session (Board #218), Sat, 8:00 AM-11:30 AM

Association of high microsatellite instability (MSI-H) with a high immunoscore (IS) compared to PD-L1 expression and increased survival in patients (pts) with metastatic colorectal cancer (mCRC) treated with oxaliplatin (Ox) and fluoropyrimidine (FP): A pooled analysis of the AIO KRK 0207 and RO91 trials. *First Author: Stefanie Noepel-Duennebacke, Ruhr-University Bochum, St. Josef Hospital, Bochum, Germany*

Background: MSI-H is an established prognostic marker in early colon cancer. Moreover, MSI-H, tumor immune cell infiltration and PD-L1 expression are also discussed as potential predictive biomarkers for immunotherapy. However, little is known about the prognostic value of these biomarkers and their association among each other in mCRC. **Methods:** We analyzed samples from pts. with mCRC uniformly treated with a FP and Ox within two randomized AIO trials (KRK 0207 and RO91). MS status was assessed by immunohistochemistry (IHC) of mismatch repair proteins and subsequent fragment length analysis in case of protein loss or incoherent results. PD-L1 expression was determined by IHC (1% expression threshold). Tumor lymphocytic infiltration (CD8 and CD45RO) was scored according to the immunoscore (IS) concept by Galon et al (J Transl Med 2016). **Results:** 41/550 cases (7.5%) displayed MSI-H. The mean IS of the total population was 0.57 (SD 0.97), the IS of MSI-H pts. was significantly higher (mean of 2.4; SD 1.4; $p \leq 0.0001$). 17 cases were PD-L1 positive (pos.) (3 %), only four of these were MSI-H. MSI-H status was significantly correlated with a higher IS, but not with PD-L1 expression (table 1). There was no difference in median overall survival (mOS) between MSI-H and MS stable (MSS) pts. (mOS MSI-H/MSS: 17.6/22.5 months (mos.), log rank: p=0.85), PD-L1 negative (neg.) and pos. pts. (mOS PD-L1 neg./pos.: 22.1/28.9 mos., log rank: p=0.49) and IS high or low pts. (mOS IS high/low: 21.1/22.1mo., log rank: p=0.25). **Conclusions:** In contrast to early stage colon cancer, none of these parameters was prognostic in mCRC patients. Panel-sequencing with a total of 35 genes including RAS, BRAF and POL-E on cases with PD-L1 expression, high IS or MSI-H status to further characterize these cases will be reported. Clinical trial information: AIO-R091, AIO-KRK-0207: EudraCT-Nr: 2008-007974-39.

Correlation of PD-L1 expression, immunoscore (IS) and MS status.

	All	MSI-H (%)	MSS (%)
	550	41 (7.5)	509 (92.5)
PD-L1 neg.	533	37 (6.9)	496 (93.1)
PD-L1 pos.	17	4 (23.5)	13 (76.5)
IS low	503	15 (3)	488 (97)
IS high	47	26 (55.3)	21 (44.7)

3596 Poster Session (Board #219), Sat, 8:00 AM-11:30 AM

Surgeon and hospital variation in adjuvant chemotherapy delivery to patients with stage III colon cancer. *First Author: Zhaomin Xu, University of Rochester Medical Center, Rochester, NY*

Background: It is well established that age and comorbidities have significant impact on adjuvant chemotherapy delivery to stage III colon cancer patients. This study examines differences in the hospital and surgeon-specific probabilities of adjuvant therapy delivery to stage III colon cancer patients by comorbidity burden and age. **Methods:** Patients who underwent surgery for stage III colon cancer from 2004-2013 were included from the New York State Cancer Registry and the Statewide Planning and Research Cooperative System. Comorbidity burden was defined with the Charlson Comorbidity Index (CCI). Multilevel logistic regressions characterized variation in adjuvant chemotherapy delivery among individual hospitals and surgeons by CCI and age. **Results:** 11575 patients met inclusion criteria, of which 59% received adjuvant therapy. Younger age, lower CCI, and high volume surgeons/hospitals were associated with delivery of adjuvant therapy ($p < 0.01$). Median time to chemotherapy was 43 days among CCI = 0 vs 48 among CCI≥2. The risk adjusted hospital and surgeon-specific probabilities of adjuvant delivery decreased with increasing CCI and age. The proportion of variation attributable to surgeons, vs hospitals, increased with CCI and age. Hospital variation between the highest and lowest hospitals increased from a 6-fold difference among CCI = 0 to an 11 fold difference among CCI≥2. Surgeon variation increased from a 14-fold difference among CCI = 0 to a 40 fold difference among CCI≥2. **Conclusions:** Variation in adjuvant chemotherapy delivery to stage III colon cancer patients increased with higher comorbidity burden and age. While a larger proportion of variation is attributable to surgeons among patients with the highest CCI and the most elderly, the vast majority of the variation is related to hospital factors. Even taking into account that some patients may be unfit for adjuvant therapy, this variation in treatment is alarmingly high.

Variation in probability of adjuvant delivery (%).

	CCI = 0	CCI≥2	Age < 60	Age≥80
Hospital Specific (Med, Range)	69 (14-82)	38 (7-71)	83 (72-91)	18 (6-27)
Surgeon Specific (Med, Range)	71 (7-93)	41 (2-89)	84 (33-93)	18 (3-46)
Proportion of Total Variation Attributable to Surgeon	12	39	19	27

3597 Poster Session (Board #220), Sat, 8:00 AM-11:30 AM

Circulating tumor DNA analysis before and after resection for colorectal cancer. *First Author: Erin L. Symonds, Bowel Health Service, Repatriation General Hospital, Daw Park, Australia*

Background: Detection of circulating tumor DNA (ctDNA) has broad clinical utility including disease monitoring, prognostication and response to chemotherapy. ctDNA is commonly detected by targeting tumor-specific features including mutations, insertions, deletions or hypermethylation. The two genes, *BCAT1* and *IKZF1,* are methylated with high frequency in colorectal cancer (CRC). This study aimed to analyze the impact of tumor resection on ctDNA levels by assaying pre- and postoperative blood samples for methylated *BCAT1* and *IKZF1*. **Methods:** 91 people (age 32-86 years, 53% male) with invasive CRC, but without neoadjuvant therapy, had blood collected prior to surgery and within 12 months (1-12 months) after resection. Cancers were clinicopathologically staged. DNA extracted from plasma was assayed for methylated *BCAT1/IKZF1* and detection of either marker was deemed positive for ctDNA. **Results:** 47 (52%) of the 91 CRC patients were ctDNA positive before resection, including 5/30 (17%) stage I, 17/28 (61%) stage II, 23/31 (74%) stage III and 2/2 (100%) stage IV. After resection 75% (35/47) became ctDNA negative (median 2 months after resection), and all had apparent tumour clearance. Of the 35 postoperative ctDNA negative cases 22 had further surveillance CT scans within study timeframe. 86% (20/22) showed no recurrent CRC but 2 of these developed a new cancer (metachronous CRC, prostate). The remaining 2 tested ctDNA positive 14 and 25 months later and recurrence was confirmed. Of the 12 postoperative ctDNA positive cases, two were found to not have complete tumour clearance at surgery (residual disease). Follow-up CT scans were available for a further 8 patients which revealed that 4 later presented with cancer (3 recurrence, 1 thyroid) at a median 15 months after resection. The remaining 4 postoperative positive cases were negative at subsequent blood testing (median 8 months later). **Conclusions:** Methylated *BCAT1/IKZF1* DNA in preoperative blood is dependent on tumor stage, but informs the completeness of resection given the high rate (74.5%) of ctDNA disappearance post-surgery. If cases persistently test ctDNA positive after surgery or become ctDNA positive later, residual or recurrent disease should be suspected, respectively.

3598 Poster Session (Board #221), Sat, 8:00 AM-11:30 AM

Emergence of *KRAS* mutations and acquisition of resistance to EGFR blockade. *First Author: Takeshi Yamada, Department of Digestive Surgery, Nippon Medical School, Tokyo, Japan*

Background: Epidermal growth factor receptor (EGFR) blockade can effectively shrink tumors in patients with metastatic colorectal cancer (CRC). However, most patients who benefit from EGFR blockade acquire resistance. Although *RAS* mutation is established as a main cause of primary resistance, the mechanisms of this acquired resistance remain unclear. Here, we aimed to identify the mechanisms underlying acquired resistance to EGFR blockade by using circulating cell-free (ccf)DNA to track emerging *KRAS, BRAF* and *S492R* mutations during chemotherapy. **Methods:** We enrolled 33 patients with metastatic CRC and no *RAS* mutations in their primary tumors. Patients were treated with first-line systemic chemotherapy that included EGFR blockade. We obtained ccfDNA from each patient before they started chemotherapy, and every 2–3 months during chemotherapy until disease progression. We detected *KRAS* (codons 12, 13, 61, and 146), *BRAF* (V600E) and *S492R* mutations using digital polymerase chain reaction. **Results:** *KRAS* mutations were detected in the ccfDNA of 4 of the 33 patients (12%) before chemotherapy. The response rate was 88% (29/33); all four non-responders had *KRAS* mutations in their ccfDNA and one of the four had both *KRAS* and *BRAF* mutations before starting chemotherapy. A response was detected in all patients (29/29) with no *KRAS* or *BRAF* mutations in their ccfDNA before chemotherapy. Of the 29 initial responders, 14 (48%) acquired resistance. Emerging *KRAS* mutations were detected in the ccfDNA of 13 of these 14 patients (93%); eight of these patients had multiple mutations (e.g. G12D and G12V; G13D and Q61H). *BRAF* mutations were also detected in six patients (43%); none of the patients had solo *BRAF* mutations. Six patients (43%) had *S492R* mutations; none of the patients had solo *S492R* mutations. Only one patient had no *KRAS*, *BRAF* or *S492R* mutations. **Conclusions:** Emergence of *KRAS, BRAF* or *S492R* mutations that were undetectable before the start of chemotherapy may be a mechanism underlying acquisition of resistance to EGFR blockade. Notably, emerging *KRAS* mutations were detected in most of the patients (93%) who acquired resistance. This indicates that *KRAS* mutation emergence may play a major role in the acquisition of resistance to EGFR blockade.

3599 Poster Session (Board #222), Sat, 8:00 AM-11:30 AM

Association of T-cell infiltration assessed in pretherapeutic biopsies (PTB) of patients with locally advanced rectal adenocarcinoma (LARC) with tumor response and relapse after chemoradiotherapy (CRT) and rectal surgery. *First Author: Marc Van Den Eynde, Institut Roi Albert II, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium*

Background: Pre-operative CRT followed by total mesorectal excision (TME) is nowadays the standard of care for patient with LARC (cT3-T4N0 or cTxN+). Currently, pathologic complete response occurs in +/- 15% after CRT. Colorectal cancer T-cell infiltration is a strong prognostic factor for survival after primary tumor resection. Our aim was to determine whether T-cell infiltration in PTB could be predictive of tumor response and relapse after CRT + TME. **Methods:** Between 1999 and 2012, patients with LARC who underwent CRT + TME and with available clinical follow-up and PTB (with sufficient tumor cells density) were identified at the Cliniques universitaires St-Luc. The density of CD3 (T cells) and CD8 (cytotoxic) was quantified on immunostained PTB slides and analyzed with a dedicated image analysis software on whole-slide imaging. Comparisons were made using the Wilcoxon-Mann-Whitney test. Cumulative disease-free survival (DFS) was performed using the Kaplan-Meier estimator and compared by log-rank tests. Cox regression we used for uni- and multi-variate analysis. P value of less than 0.05 was considered statistically significant. **Results:** 154 patients (sex ratio M/F 1.8; mean age 65 years-old; upper (20%), mid (29%) and low rectum (51%), synchronous metastases (11%)) were analyzed. High CD3 and CD8 PTB densities were significantly associated with a higher pathological response (Dworak 3-4) and lower ypTNM stage after CRT +TME ($p < 0,05$). Higher CD3 and CD8 PTB densities were associated with higher patient DFS (CD3: HR = 2,30 (CI95%:1,15-4,59) p = 0,02; CD8: HR = 1,95 (CI95%: 1,01-3,75) p = 0,04). These results were confirmed in uni and multivariate analysis. CD3 and CD8 PTB densities added to pathological response (ypTNM/Dworak) but also clinical response (ycTNM) after CRT + TME increases significantly the accuracy prediction of tumor relapse. **Conclusions:** Pretherapeutic T-cell infiltration of LARC is predictive of tumor response and relapse after CRT +TME. This biomarker could be helpful for patient treatment decision. It must be validated in larger patient cohorts.

3600 Poster Session (Board #223), Sat, 8:00 AM-11:30 AM

Cetuximab (Cet) clearance and survival in patients (pts) with metastatic colorectal cancer (mCRC). *First Author: Di Maria Jiang, The Ottawa Hospital, Ottawa, ON, Canada*

Background: Cet, a monoclonal antibody against EGFR, is a standard therapy for RAS wild-type (WT) mCRC. Limited data suggest a correlation between Cet clearance and progression-free survival (PFS). We performed a population pharmacokinetic (pop-pK) analysis of Cet in pts with KRAS WT mCRC who participated in the randomized phase III NCIC CO.20 trial. **Methods:** Standard Cet doses ± brivanib (Briv) were administered. Intermittent blood samples were obtained, and analyzed by ELISA for Cet. Pop-pK analysis was conducted to estimate Cet clearance. Pts were divided into quartiles according to clearance parameters to evaluate exposure-outcome with overall survival (OS), PFS, response rate (RR), and toxicity. **Results:** Blood samples were available from 703 pts. Cet clearance was best described as a one-compartment model with a saturable elimination (defined by V_{max} and K_m). Mean values (± standard deviation) were 5.6 ± 1.4 L for V, 10.5 ± 2.8 mg/h for V_{max}, and 403.1 ± 2.0 mg/L for K_m. V_{max} and K_m were significantly associated with OS, but not PFS or RR. Median OS for pts in the highest quartile of V_{max} was 7.8 versus (vs.) 11.6 ms for pts in the lowest V_{max} quartile (HR 1.12, 95% confidence interval (CI) 1.05-1.20, $p< 0.001$). In the highest K_m quartile, median OS was 11.6 vs. 7.6 ms in the lowest K_m quartile (HR 0.89, 95% CI 0.83-0.96, $p= 0.001$). Pts with the lowest clearance parameters (lowest V_{max} and highest K_m) had significantly longer OS (11.6 ms) compared to pts with the highest clearance (highest V_{max} and lowest K_m) (7.6 ms) (HR 0.67, 95% CI 0.53-0.83, $p< 0.001$). Overall incidences of grade 3/4 toxicity were not associated with Cet clearance. However, pts with the lowest clearance parameters had more frequent grade 3 diarrhea (OR 0.23, $p= 0.005$). **Conclusions:** For KRAS WT mCRC, standard Cet dosing is not optimal for all pts. Pts with lower Cet clearance have significantly improved OS and increased likelihood of grade 3 diarrhea. Further studies are needed to identify individual patient factors associated with Cet clearance, and to optimize Cet dosing based on individual pk assessments.

3601 Poster Session (Board #224), Sat, 8:00 AM-11:30 AM

Survival prediction in patients treated by FOLFIRI and bevacizumab for metastatic colorectal cancer (PRODIGE 9) using contrast-enhanced CT texture analysis (SPECTRA). *First Author: Anthony Dohan, Lariboisière Hospital, Viscéral and Vascular Radiology Department, INSERM U965, Paris, France*

Background: Quantitative assessment of tumor architecture changes may help to early identify non-responder patients and propose a tailored treatment strategy. Our objective was to build and validate a radiomics signature able to predict early the lack of response to chemotherapy including FOLFIFRI and bevacizumab using baseline and first evaluation CT and to compare it to the RECIST and morphological criteria. **Methods:** For 230 patients of PRODIGE 9 study and treated by FOLFIRI and bevacizumab, a computed analysis (CA) was performed on the dominant liver lesion (DLL) at baseline and 2 months post-chemotherapy. RECIST evaluation was performed at 2 and 6 months. The sum of the target liver lesions (STL), the density of the DLL, CA parameters and their changes rates were correlated with the 2-year survival status. A radiomics signature combining 3 parameters was built in one arm and validated in the second arm. Survival was estimated with the Kaplan-Meier method and compared with log-rank test. **Results:** The strongest predictive factors for 2-year survival status were decrease in STL(AUC = .69±.05[95%CI:.60-.77]), change rate in kurtosis (ssf = 0) (AUC = .66±.05[95%CI:.57-.74]), and the baseline density of the DLL (AUC = .68±.05[95%CI:.59-.77]). Using multivariate analysis, predictive factors of 2-year survival status were the decrease in STL $>$ 15% (HR = 1.92, P= .002), the increase in kurtosis value(ssf = 0) $>$ 93% (HR = 2.16, P= .001), and baseline DLL $>$ 64.3UH (HR = 1.70, P= .02). Then, the SPECTRA-score was built by according 1 point for each of the 3 criteria. Patients with a SPECTRA-score $>$ 1 had a lower overall survival in the training (P= .001) and in the validation cohort (P= .002). Non-response according to RECIST at 6 months had the same prognostic value as SPECTRA-score$>$1 at 2 months. **Conclusions:** A radiomics signature combining STL, density and CA on baseline and first evaluation CT is be able to predict which patient will have a poor outcome with same performances than standard evaluation with RECIST1.1 at 6 months in mCRC patients. Clinical trial information: NCT00952029.

3602 Poster Session (Board #225), Sat, 8:00 AM-11:30 AM

Differences in systemic and surgical therapy between right (R) and left (L) sided metastatic colorectal cancer (mCRC). *First Author: Hagen F. Kennecke, Department of Medical Oncology, BC Cancer Agency, Vancouver, BC, Canada*

Background: Patients (pts) with L sided primary tumors and mCRC have a significantly longer overall survival (mOS) than R sided tumors. Reasons for this remain unclear. The objective of this study was to compare systemic and surgical therapy received by tumor side and correlate this with mOS. **Methods:** Sequential pts with mCRC referred to the British Columbia Cancer Agency in 4 treatment eras were included. Pts with unresected primary tumors were excluded to ensure accurate ascertainment of tumor location. Receipt of systemic therapy includes Òall 3 drugsÓ (irinotecan, oxaliplatin, fluouracil), bevacizumab and epidermal growth factor receptor inhibitors (EGFRi). Cox-regression survival analysis for sidedness was performed controlling for age, sex, tumor grade, lymphovascular/perineural invasion, nodes removed and metastatectomy. **Results:** Among 3242 pts, a progressive improvement in mOS is documented in both L and R sided tumors since 1995. L and R tumors received Òall 3 drugsÓ, bevacizumab and EGFRi therapy with similar frequency which plateaued after the introduction of EGFRiÕs in 2009. Patients with L sided tumors were significantly more likely to have a hepatic or pulmonary resection. In Cox regression analysis, the mOS difference between L and R sided tumors was more pronounced in more recent eras. **Conclusions:** Patients with R sided tumors receive similar systemic therapy compared to L sided tumors, but are significantly less likely to undergo resection of distant disease. Resection of distant metastases may be an important consideration to understand the survival differences between R vs L mCRC.

	1995-2000 N=515		2003-06 N=972		2009-10 N=749		2011-13 N=1006	
Variable	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**
Hepatic Resection	8.1%	6.5%	14%	11%	17% *	11% *	22% *	17% *
Pulmonary Resection	3.6%	0%	6.2% *	0.6% *	6.1%	3.1%	6.6% *	3.3% *
All 3 Drugs	7.8%	5.2%	39%	38%	43%	49%	47%	48%
Bevacizumab	0.6%	0%	23%	22%	53%	58%	57%	57%
EGFRi	0.3%	0%	6% *	2.1% *	22%	19%	19%	22%
Median OS with 95% CI (months)	17 (15,19)	13 (11,15)	22 * (20,24)	17 * (15,19)	26 * (23,28)	19 * (18,22)	28 * (26,30)	21 * (17,23)
HR with 95% CI (R vs L)	0.89 (0.61,1.3)		1.2 (1.0, 1.5)		1.2 (1.0,1.5)		1.2 (1.0,1.4)	
P-value for HR (R vs L)	0.52		0.048		0.034		0.013	

* P-value is significant at 0.05 level

3603 Poster Session (Board #226), Sat, 8:00 AM-11:30 AM

Robotic vs. laparoscopic vs. open abdominoperineal resection for low rectal cancer: Short-term outcomes of a single-center prospective randomized controlled trial. *First Author: Ye Wei, Institute of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Currently, robotic surgery for rectal cancer using da Vinci System is common. However, there is almost no clinical trial reported. This randomized controlled trial aims to compare the safety and efficacy of robotic, laparoscopic and open abdominoperineal resection (APR) for low rectal cancer. **Methods:** From September 2013 to August 2016, patients aged from 18 to 75 years, with low rectal cancer within 5 cm from anal verge, clinical T1 to T3, no distant metastases, were randomly assigned to receive either robotic procedures (RAP), laparoscopic procedures (LAP) or open surgery (OS) for APR in 1:1:1 ratio. The primary endpoint was postoperative complication rate. This study is registered with ClinicalTrials.gov (NCT01985698). **Results:** Totally 406 patients were randomly assigned. Actually, 135 finished RAP, 131 finished LAP, and 137 finished OS (including 4 convert from LAP to OS). RAP had significantly lower postoperative complication rate (11.1%) than both LAP (21.4%, P = 0.023) and OS (27.7%, P = 0.001). Also, RAP reduced intraoperative hemorrhage (median [interquartile range], 100 [90-110] ml) than LAP (130 [100-150] ml, P $<$ 0.001) and OS (150 [120-260] ml, P $<$ 0.001). And RAP promoted postoperative recovery, with shorter days to first flatus (1.0 [1.0-2.0] day) than LAP (2.0 [2.0-3.0] day, P $<$ 0.001) and OS (3.0 [2.0-4.0] day, P $<$ 0.001), shorter days to first automatic urination (2.0 [2.0-3.0] day) than LAP (3.0 [2.0-4.0] day, P $<$ 0.001) and OS (3.0 [2.0-4.0] day, P $<$ 0.001), and shorter days to discharge (5.0 [5.0-6.0] days) than LAP (6.0 [5.0-7.0] days, P $<$ 0.001) and OS (6.0 [5.0-7.0] day, P = 0.005). There was no significant difference in open conversion rate, resection margin involvement (including circumferential resection margin), number of lymph node harvested and pathological tumor stage. **Conclusions:** Robotic APR was safer, and reproduce equivalent surgical quality of conventional laparoscopic and open surgery. Also, it provided less injury and faster functional recovery. Clinical trial information: NCT01985698.

3604 Poster Session (Board #227), Sat, 8:00 AM-11:30 AM

Genetic correlates of therapeutic toxicities of stage III colon carcinoma patients treated with adjuvant FOLFOX+/-cetuximab (NCCTG N0147, Alliance). *First Author: Polly A. Newcomb, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Limited research has investigated the role of variation in the host genome as a determinant of colon carcinoma (CC) outcomes, including toxicity due to therapeutic agents. We examined the relationship between germline genetic factors and treatment-associated serious adverse events (SAEs) in a population of CC patients in which treatment was standardized and follow-up for outcomes was uniformly conducted. **Methods:** Using existing biospecimens from CC patients with resected stage III disease in a phase III randomized trial of FOLFOX adjuvant chemotherapy with and without cetuximab (NCCTG N0147), genome-wide genotyping arrays were conducted for 2200 patients for a total of ~20 million single nucleotide polymorphisms (SNPs). Using logistic regression models we assessed SNP-specific associations with SAEs, utilizing a discovery-based approach to search the genome in an unbiased manner. Detailed information on SAEs was collected using the Common Toxicity Criteria for Adverse Events (CTCAE, v3.0). Analyses evaluating associations with specific classes of common grade ≥3 SAEs were performed, including gastrointestinal toxicities, neutropenia, and paresthesias. A threshold of $P < 5x10^{-8}$was used to denote genome-wide significance. **Results:** Among patients who received FOLFOX, several SNPs on chr 15 near the ANP32A gene and on chr 2 near the CD207 gene were statistically significantly associated with grade ≥3 neuropathy. The strongest SNP-specific associations in these regions were in the range of odds ratio (OR) = 1.3, $P = 2.8\times10^{-10}$ and OR = 1.5, $P = 2.7\times10^{-10}$, respectively. **Conclusions:** Findings from this genome-wide analysis demonstrate the potential importance of germline genetic variation in influencing CC patients' experience of specific toxicities to FOLFOX regimens. These results highlight two genomic regions of potential interest for understanding the biological mechanism for such toxicities, although further evaluation and replication is needed. Support: U10CA180821, U10CA180882, U10CA180820, U10CA180863, U10CA180888, CCSRI 021039, R01CA176272, Eli Lilly & Co, Pfizer, Sanofi. Clinical trial information: NCT00079274.

3605 Poster Session (Board #228), Sat, 8:00 AM-11:30 AM

Association between timing and duration of adjuvant chemotherapy and survival for colorectal cancer in korea, 2011-2014: A nationwide study based on the database of quality assessment and the health insurance. *First Author: In Gyu Hwang, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea*

Background: Few population-based analyses on treatment outcomes of colorectal cancer (CRC) have been conducted in Asian countries. We conducted a nationwide study to assess relationship between timing and duration of adjuvant chemotherapy (AC) and survival for patients with CRC in South Korea. **Methods:** Data from the Health Insurance Review and Assessment Service Database (HIRA) were analyzed for demographics, tumor characteristics, adjuvant chemotherapy, and survival of patients who underwent curative-intent surgical resection for CRC from 2011 to 2014. **Results:** From the HIRA data, a total of 61315 patients were identified: 15620 (25.5%) in stage I, 20525 (33.5%) in Stage II, and 25170 (41.0%) in stage III. Chemotherapy regimens were consisted: 11332 (18.5%) in 5-fluorouracil and leucovorin/capecitabine (FL/CAP), 13183 (21.5%) in FL/CAP plus oxaliplatin (FOLFOX/CAPOX), 357 (0.6%) in uracil and tegafur/doxifluridine (UFT/D) and 36443 (59.4%) in surgery alone. For patients with stage II and III CRC, the initiation of AC $\geq$ 8 weeks after surgery was associated with a significant decrease in overall survival (OS) (FL/CAP: HR, 1.82; 95% CI, 1.53 to 2.17, and FOLFOX/CAPOX: HR, 2.92; 2.47 to 3.45, respectively), however UFT/D regimens were not statistically significant. For patients with stage II and III colon cancer, receiving AC $<$ 3 months had lower OS (FL/CAP: HR, 3.72; 95% CI, 2.80 to 4.94, FOLFOX/CAPOX: HR, 2.15; 1.87 to 2.47, and UFT/D: HR, 1.74; 0.56 to 5.41, respectively). For patients with stage II and III rectal cancer, receiving AC $<$ 3 months regardless of chemotherapy regimens had a significant lower survival (FL/CAP: HR, 1.91; 1.66 to 2.20, FOLFOX/CAPOX: HR, 2.20; 1.75 to 2.77, and UFT/D: HR, 3.71; 1.45 to 9.44, respectively). **Conclusions:** Time to initiation and duration of AC after surgery were associated with survival. Based on our results, starting within 8 weeks and receiving more than 3 months of AC are needed to have an overall survival benefit.

3606 Poster Session (Board #229), Sat, 8:00 AM-11:30 AM

A randomized phase II trial of consolidation chemotherapy after preoperative chemoradiation (preop CRT) versus CRT alone for locally advanced rectal cancer (LARC). *First Author: Sun Young Kim, Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea*

Background: In LARC, preop CRT followed by total mesorectal excision (TME) is a standard of care. Recently consolidation chemotherapy after CRT was shown to be safe and to improve pathologic complete response (pCR) rate in LARC. We aimed to evaluate downstaging (DS) rate (the proportion of ypT0-2N0M0) of CRT followed by consolidation chemotherapy (capecitabine and oxaliplatin: CapOx) compared to that of CRT alone. **Methods:** Patients (pts) with adenocarcinoma of rectum($\leq$ 12cm from anal verge), ECOG PS 0 or 1, and cT3-4NxM0 were enrolled. CRT (50-50.4Gy/25-28fx) with Cap (825mg/m^2/day for 5 days per week throughout CRT) followed by TME was planned in Arm A (control arm). In Arm B, 2 cycles of CapOx was given a week after completion of CRT before TME (Cap 850mg/m^2/day from day 1 to day 14; Ox 100mg/m^{2}on day 1; q 3w). 110 pts (55 per arm) were needed to show improvement of DS rate in per-protocol population (PP set) from 30% to 50% in arm B with one-sided α = 0.15, 1- β = 0.85, and follow-up loss in 5%. **Results:** From 9/2014 Sep to 2/2016, 110 (56 in arm A; 54 in arm B) were enrolled; 108 (55 in arm A; 53 in arm B) were randomized and started study treatment. Median age was 56 years; male/ECOG PS 1/cT4 was 76%/70%/18%. 100 pts (54 in arm A; 46 in arm B) completed CRT $\pm$ CapOx and surgery (R0 or R1 resection), while 8 (1 in arm A, 7 in arm B) dropped out mainly due to consent withdrawal. 2 of each arm underwent non-TME; that leaves 96 (52 in arm A and 44 in arm B) in PP set. Relative dose intensity of CapOx was 96% (Cap) and 95% (Ox). The main treatment outcome is described in table. The mean interval days between completion of CRT and surgery was significantly longer in arm B (52.9 vs 61.3, p $<$ 0.0001). **Conclusions:** 2 cycles of CapOx after completion of CRT was feasible and safe, and it showed improvement in DS rate, even with high dropout rates (13%). Clinical trial information: NCT01952951.

	arm A	arm B	p value
DS	11/52 (21.2%)	15/44 (34.1%)	0.117†
pCR	3/52 (5.8%)	6/44 (13.6%)	0.167†
Diarrhea of any grade*, during CRT$\pm$ CapOx	12/55 (21.8%)	15/53 (28.3%)	0.508
Adverse events (AE) of $\geq$ grade 3, during CRT$\pm$ CapOx	2/55 (3.6%)	4/53 (7.5%)	0.433
AE of $\geq$ grade 3, within 30 days after surgery	1/54 (1.9%)	3/46 (6.5%)	0.331

*All events were grade 1 or 2. †One-sided

3607 Poster Session (Board #230), Sat, 8:00 AM-11:30 AM

Neoadjuvant chemotherapy with mFOLFOXIRI alone for cT4 and fixed cT3 rectal cancer: Results from a single arm phase II study (FORTUNE). *First Author: Jianwei Zhang, Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China*

Background: Although neoadjuvant chemoradiotherapy achieves low local recurrence rates in locally advanced rectal cancer (LARC), it delays administration of systemic chemotherapy. About 30% of patients still developed distant metastases, which is the main obstacle for improving survival of LARC. Besides, preoperative radiation causes lots of concerns about anal and sexual functions. We aimed to explore the efficacy of preoperative chemotherapy with mFOLFOXIRI in LARC rather than consistent use of chemoradiotherapy. **Methods:** Patients with fixed cT3 or cT4 rectal cancer evaluated by pelvic MRI participated in this trial. All candidates were to receive 4-6 cycles of mFOLFOXIRI. MRI will be performed to assess clinical responses. Patients with stable/progressive disease were to have radiation before surgery, whereas responders were to have immediate total mesorectal excision (TME). Postoperative radiation was planned if R0 resection was not achieved. Postoperative FOLFOX was recommended. The primary endpoint is the ratio of tumor downstaging to $ypT_{0\text{-}2}N_0M_0$.The secondary endpoint included pathologic complete response rate, 3-year disease free survival rate and safety. **Results:** Between August 2014 and September 2016, 83 patients were enrolled and 80 participants had received TME. Three refused surgery after chemotherapy, because the tumor location is too low to perform sphincter-preserving operation. Of 80 patients completing at least 4 cycles of preoperative chemotherapy, two received short-term radiation before TME, and 10 patients underwent long-term chemoradiotherapy after MRI evaluation. The pCR rate of the whole group was 15 of 80 (18.8%) and the tumor downstaging rate was 43.8%. Among patients without chemoradiotherapy, the pCR rate and tumor downstaging were 14.3% and 41.4%, respectively. And the chemo-related toxicity was all tolerable. **Conclusions:** Neoadjuvant chemotherapy with mFOLFOXIRI and selective radiation does not seem to compromise outcomes in LARC. The result was promising and further phase III study is warranted to validate this experience. Clinical trial information: NCT02217020.

3608 Poster Session (Board #231), Sat, 8:00 AM-11:30 AM

Pathologic complete response rate after neoadjuvant chemoradiation in patients with locally advanced rectal cancer affects survival in patients with prolonged radiation-surgery interval. *First Author: Benjamin Mitchell Motz, Levine Cancer Institute, Charlotte, NC*

Background: The current standard of care in locally advanced rectal cancer is neoadjuvant chemoradiation and R0 resection. An optimal radiation-surgery interval (RSI) has not been established. A small institutional dataset showed RSI $>$ 49 days improved pathologic complete response (pCR) rates and disease free survival. However, in a national dataset, RSI greater than 60 days was associated with increased rates of positive margins and impaired overall survival. Because pCR is associated with improved survival, we used a national database to evaluate the relationship between RSI, pCR and survival after neoadjuvant therapy for rectal cancer. **Methods:** The NCDB was queried for cases 2004-2013 of AJCC stage II or III rectal adenocarcinoma that underwent neoadjuvant radiation followed by radical resection. We excluded patients with missing and outlier RSI. pCR was defined as ypT0N0M0. Chi-square, univariate, multivariable Cox model, and Cochran-Armitage time trend analyses were performed. **Results:** 23475 patients were identified. 7901 (33.7%) had RSI $\geq$60 days. pCR occurred in 1766 (11.3%) of the $<$ 60 group and 1174 (14.9%) of the $\geq$60 group (p $<$ 0.001). RSI $\geq$60 days has increased over time, from 22.1% in 2004 to 45.4% in 2013 (p $<$ 0.001), as have pCR rates, from 8.4% in 2004 to 14.2% in 2013 (p $<$ 0.001). Multivariable Cox model of the total cohort showed that RSI $\geq$60 days (HR = 1.11, 95% CI = 1.04-1.19) and residual disease (HR = 2.04, 95% CI = 1.78-2.34) were associated with increased mortality. Subgroup analysis of patients with pCR showed RSI $\geq$60 days was not associated with worse survival (HR = 1.07, 95% CI = 0.82-1.41). However, analysis of patients with residual disease showed RSI $\geq$60 days was associated with worse survival (HR = 1.13, 95% CI = 1.06-1.21). **Conclusions:** In a large national database, RSI $\geq$60 days worsens survival in patients who have residual disease after neoadjuvant therapy for locally advanced rectal cancer, while there is no difference in those with pCR. Emphasis should be placed on identifying patients who are unlikely to have pCR and to prioritize resection in these patients within 60 days of completion of chemoradiation.

3609 Poster Session (Board #232), Sat, 8:00 AM-11:30 AM

Prognostic impact of tumor budding in stage II colon cancer: A prospective study (SACURA trial). *First Author: Hideki Ueno, National Defense Medical College, Department of Surgery, Saitama, Japan*

Background: Growing number of studies indicate tumor budding is a significant prognostic factor in colorectal cancer (van Wyk, et al. Cancer Treat Rev 2015), but this has been shown only in retrospective studies. We prospectively evaluated prognostic factors in stage II colon cancer to determine their prognostic value in a multi-institutional phase III study (SACURA trial, ASCO2016 abst#3617). **Methods:** A total of 991 patients with curatively resected stage II colon cancer (2006–2010; 136 institutions) were included in the study. Tumor budding was defined as an isolated cancer cell or a cluster composed of fewer than five cells in the invasive frontal region, and was graded based on its number within a microscopic field of a 20x objective lens (0.785 mm^2) in the hotspot. Tumors with < 5, 5–9, and ≥ 10 budding foci were classified as grades G1, G2, and G3, respectively. All clinical and pathological data including the grade of budding were prospectively recorded and prognostic analyses were performed at 5 years after the completion of registration. **Results:** According to budding grading, 376, 331 and 284 tumors were classified as G1, G2, and G3, and 5-year relapse-free survival (RFS) rate was 90.9%, 85.1%, and 74.4%, respectively ($P < 0.0001$). Budding grade was significantly associated with the incidence of recurrence in the liver, lung, lymph node, and peritoneum ($P < 0.0001$–0.01). Among conventional factors, T stage and the serum CEA levels were associated with RFS, however, tumor grade, lymphatic and venous invasions, and the number of lymph node examined were not significant factors. Multivariate analysis for RFS showed budding, along with T stage, exerted an independent influence on prognostic outcome. Budding grade surpassed T stage and tumor grade in the ability to stratify patients by RFS (Harrell's c-index, 0.63, 0.59, and 0.54, respectively). **Conclusions:** Our prospective study indicates that the grade of tumor budding is more informative for prognostic prediction than conventional prognostic factors in stage II colon cancer. The role of this prognostic factor should be highlighted in the adjuvant treatment setting, and conversely, some of prognostic factors adopted in clinical guidelines may need to be reconsidered. Clinical trial information: NCT00392899.

3610 Poster Session (Board #233), Sat, 8:00 AM-11:30 AM

The feasibility and efficiency of wait and see policy for patients with complete clinical response following neoadjuvant therapy in rectal cancer: A prospective cohort study from China. *First Author: Jin Gu, Peking University Cancer Hospital, Beijing, China*

Background: It has been reported that non-operative treatment (wait and see) is feasible for the selected rectal cancer cases with a complete clinical response (cCR) following neoadjuvant therapy (NT). The aim of this study is to determine whether "wait and see" policy is efficient for the cCR patients in China. **Methods:** We designed a prospective cohort study in China (ChiCTR-TRC-12002488). From Jul 2012 to August 2016, totally 45 patients with locally advanced rectal cancer who were cCR following NT were enrolled in the study; within whom, 32 patients were assigned to wait and see group, and the remaining 13 patients were assigned to surgery group (intent-to-treat grouping). **Results:** The median follow-up time was 24 months (range: 3-51). Of the patients who were followed up more than 12 months (n=37), 8 patients developed tumor progression (7 in wait and see group and 1 in surgery group, respectively). In the wait and see group, the local regrowth took an account of 23.1% (6/26), while the distant metastasis rate was 3.8% (1/26). In the surgery group, there were 23.1% (3/13) of patients who has residual cancer confirmed by postoperative pathological assessment. All the patients with tumor regrowth underwent radical surgery and no body died of cancer. **Conclusions:** Wait and see policy has an acceptable safety and efficiency, it may become an alternative treatment for the patients who were cCR following NT. Clinical trial information: ChiCTR-TRC-12002488.

The criteria of complete clinical response.

Examinations	Presentation
Digital rectal examination	Absence of residual palpable lesion
Colonoscopy	No residual tumor or only a small residual scar, usually accompanied by whitening of the mucosa, and the presence of telangiectasia
Biopsy	No cancer cell
Serum CEA, CA199	Normal
MRI/CT	No massive lesion and suspicious lymph node, normal bowel or diffused edema or fibrosis of bowel wall
Others	No distant metastasis

3611 Poster Session (Board #234), Sat, 8:00 AM-11:30 AM

Recurrence risk factors and outcome stratification in stage II colon cancer patients: A subanalysis of the SACURA trial. *First Author: Megumi Ishiguro, Tokyo Medical and Dental University, Department of Translational Oncology, Tokyo, Japan*

Background: Efficacy of adjuvant chemotherapy for stage II colon cancer is still controversial. We conducted the SACURA trial, a phase III study which evaluated the superiority of 1-year adjuvant treatment with oral tegafur-uracil (UFT) to surgery alone in stage II colon cancer. However, survival benefit of 1-year UFT to surgery alone was not demonstrated (ASCO2016 abst#3617). We herein aimed to identify risk factors for recurrence in the stage II patients "without adjuvant chemotherapy", and to stratify the prognosis by using these factors. **Methods:** Among a total of 982 patients without adjuvant chemotherapy enrolled to the SACURA trial, we extracted the factors correlated to recurrence using a univariate and multivariate Cox proportional hazard model. 943 and 935 patients in the surgery alone group and UFT group were divided to subgroups according to the number of risk factors, and the recurrence rate in each subgroup was evaluated. **Results:** Among the conventional clinicopathological characteristics, the multivariate analysis identified pT4, elevated CEA, and examined lymph nodes less than 12 as significant risk factors for recurrence. The rate of patients with 0, 1, 2, and 3 risk factors were 45.0%, 42.4%, 11.5%, and 1.1%, respectively. The recurrence rate for each subgroup was shown in the table: the recurrence rate increased with number of risk factors, while 10.2% of patients without any risk factors developed recurrence. Difference in the recurrence rate between the treatment groups was significant in patients without risk factor, marginal in patients with 1 risk factor, and none in patients with >1 factors. **Conclusions:** pT4, elevated CEA, and examined lymph nodes less than 12 were identified as risk factors for recurrence in stage II colon cancer patients. The recurrence rate was divided by the number of these risk factors, but we could not extract the very-low risk group in whom adjuvant therapy is unnecessary. Induction of novel risk factors other than conventional clinicopathological characteristics is recommended. Clinical trial information: NCT00392899.

Recurrence rate.

No. of risk factors	Surgery alone group	UFT group	HR (95%CI)
0	10.2%	6.2%	0.60 (0.73-0.98)
1	13.1%	10.3%	0.76 (0.50-1.15)
2-3	27.9%	26.6%	1.00 (0.61-1.63)

3612 Poster Session (Board #235), Sat, 8:00 AM-11:30 AM

Phase I study of trametinib with neoadjuvant chemoradiation (CRT) in patients with locally advanced rectal cancers (LARC). *First Author: Christina Sing-Ying Wu, Emory University, Atlanta, GA*

Background: The RAS/RAF/MEK signal transduction pathway is critical to the development of colorectal cancer, and tumors harboring KRAS, NRAS, and BRAF mutations were shown to be resistant to radiation. Thus, we conducted a phase I study of trametinib, a potent MEK1/2 inhibitor, in combination with CRT in patients with LARC. **Methods:** Phase I trial for patients with Stage II/III rectal cancers with a 3+3 design, and an expansion cohort of 12 patients at the maximum tolerated dose (MTD). Trametinib is given orally at 3 dose levels: 0.5mg, 1mg, and 2mg (Mon-Fri). CRT regimen is infusional 5-flourouracil (5FU) 225mg/m^2/day (Mon-Fri) and daily fractions of 1.8 Gy (total 50.4Gy). There is a 5-day trametinib lead-in followed by trametinib and CRT. Six to 10 weeks after completion of CRT, patients then proceed to their surgery and adjuvant therapy. The primary endpoint is to identify the MTD and recommended phase 2 dose of trametinib with CRT. Immunohistochemistry staining for phosphorylated –ERK (pERK) and genomic profiling is performed on the tumor samples. **Results:** Enrollment is complete at all dose levels with18 patients, and 15 patients evaluable for toxicity and response as of Feb 6. One dose-limiting toxicity of diarrhea was observed at the 2mg dose. Grade 3 and most common toxicities are shown in Table 1. No grade 4/5 toxicities have been observed. At 2mg dose level, 3/9 (33%) patients had pathological complete response (pCR) and 2/9 (22%) had a near pCR. Correlative studies confirm decrease in pERK levels with increasing doses of trametinib. Correlation of genomic mutational status with toxicity, response, and outcomes is being analyzed. **Conclusions:** The combination of trametinib with 5FU CRT is tolerable with promising preliminary activity. Final results will be presented at the meeting. Toxicities. Clinical trial information: NCT01740648.

	Grade 1 (N)	Grade 2 (N)	Grade 3 (N)
Hematological			
Anemia	6	2	1
Lymphocytopenia	2	3	11
Leukopenia	4	2	0
Thrombocytopenia	4	0	0
Hyperglycemia	8	1	0
Non-Hematological			
Generalized rash	8	1	2
Hand-foot syndrome	3	2	0
Rectal Pain	8	3	0
Rectal bleeding	7	2	0
Abdominal pain/distension	5	2	0
Nausea or vomiting	9	1	0
Oral mucositis	4	0	0
Bowel urgency or diarrhea	8	2	1
Fatigue	6	2	0

3613 Poster Session (Board #236), Sat, 8:00 AM-11:30 AM

Impact of adjuvant treatment in elderly patients with locally advanced rectal cancer: A population-based retrospective study. *First Author: Shiru Lucy Liu, Department of Medicine, Dalhousie University, Halifax, NS, Canada*

Background: Little is known about the benefit and use of adjuvant chemotherapy (ADJ) in the elderly population (age ≥ 65) with locally advanced rectal cancer (LARC). We undertook a provincial review of LARC patients to evaluate the potential benefits, including survival and time to relapse (TTR), of ADJ in elderly patients. **Methods:** We performed a retrospective analysis of 286 LARC patients (stage 2 and 3) diagnosed between January 2010 and December 2013 from Nova Scotia, Canada, who underwent curative-intent surgery. Baseline patient, tumor and treatment characteristics were collected. Survival and TTR analysis were performed using Kaplan-Meier and Cox-regression statistics. **Results:** 152 patients were age ≥65, and 92 age ≥70. Median follow-up was 46 months. 178 patients (62%) received neoadjuvant chemo-radiation (NEOADJ). While 109 patients (81%) age < 65 received ADJ, only 68 patients (45%) age ≥ 65 received ADJ. Kaplan-Meier analysis revealed a significant survival and TTR advantage for ADJ irrespective of age (table). In cox-regression multivariate analysis, ECOG status, T stage, and ADJ were significant predictors of survival ($p < 0.04$), while age was not. Similarly, N stage, NEOADJ, and ADJ were significant predictors of TTR ($p < 0.007$). Poor ECOG status was the most common cause of ADJ omission. There was a significantly higher amount of grade≥ 1 chemotherapy-related toxicity experienced by patients age ≥ 65 treated with ADJ compared to no ADJ (77% vs 32%, $p < 0.0001$), which consisted mostly of diarrhea and mucositis. Toxicity was the main reason for non-completion of ADJ in the elderly. **Conclusions:** Elderly patients with LARC have significantly improved overall survival with ADJ, but the use of ADJ is lower than in patients age < 65. However, elderly patients experience more chemotherapy-related toxicities, leading to higher rates of early treatment discontinuation.

Survival and TTR by age with or without ADJ.

	N	5-yr OS (%)	N	Cancer Specific Survival (%)	N	TTR (mo)
<65						
- ADJ	24	71	21	71	25	34
+ ADJ	109	86	103	90	109	50
		p=0.0757		p=0.0276		p=0.0026
65-69						
- ADJ	17	59	16	63	19	36
+ ADJ	41	90	37	95	41	46
		p=0.01		p=0.007		p=0.094
≥70						
- ADJ	65	52	33	45	64	23
+ ADJ	27	89	33	45	64	23
		p=0.008		p=0.009		p<0.001

3614 Poster Session (Board #237), Sat, 8:00 AM-11:30 AM

Comparison of two different neoadjuvant chemoradiatiotherapy regimens for locally advanced rectal cancer: Results of a phase II, multicenter, randomized trial. *First Author: Ji Zhu, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: The aim of this study is to compare clinical outcomes between two groups of different chemoradiation Regimens. **Methods:** Eligible patients were randomly assigned to Patients received either IMRT to the pelvis of 50 Gy/25Fxs concurrent with oxaliplatin 50 mg/m2 weekly and capecitabine 625 mg/m2 bid d1–5 weekly (Arm A), or IMRT to the pelvis of 50 Gy/25Fxs and a concomitant boost of 5 Gy to the primary tumor in 25 fractions, followed by a cycle of XELOX two weeks after the completion of chemoradiotherapy (Arm B). Surgery was scheduled eight weeks after the completion of CRT. All patients were recommended to receive adjuvant CT regardless of pathological stages. A total of six cycles of XELOX chemotherapy was recommended including neoadjuvant and adjuvant period. The primary end point was pCR. **Results:** From February 2010 to December 2011, a total of 120 patients were randomly assigned to Arm A (n = 60) or Arm B (n = 60). One hundred and ten patients (Arm A = 53, Arm B = 57) underwent surgery, the other 10 patients didn't receive surgery because of unresectable disease. Eight and 14 cases were evaluated as pCR in two groups respectively (p= .157). Tumor response was further classified into good response and poor response, the former was defined as ypT0N0, ypT1-2N0 and ypT0N1a. The rate of good responses were 30.0% and 55% (p= .006). No significant differences were found in grade 3 or 4 acute adverse events during the treatment between the two groups. However, number of patients who had delayed incision healing was 13 and 3 patients (p= .007). There were no statistical differences in OS (p= .553), DFS (p= .349) and local-regional control (p= .856) between the two groups. In the univariate analysis, N stage, MRF involvement and tumor response had significant impacts on OS, DFS and LC. In the multivariate analysis, MRF involvement had significant impacts on OS (p= .02), DFS (p= .01) and LC (p= .01). **Conclusions:** A dose-intensified radiotherapy in neoadjuvant chemoradiotherapy demonstrated contribution to tumor regression with acceptable toxicity, but led delayed incision healing after surgery. The impact of MRF involvement on survival merits further investigation. Clinical trial information: NCT01064999.

3615 Poster Session (Board #238), Sat, 8:00 AM-11:30 AM

Microbiota as a new indicator of colorectal cancer (CRC) heterogeneity. *First Author: Iradj Sobhani, Departement of Gastroenterology and Oncology Hopital Henri Mondor, Creteil, France*

Background: Location and somatic gene signature of CRCs may impact prognosis and therapy response. The aim was to characterize colon Microbiota in CRC patients regarding location, gene markers and outcome. **Methods:** Patients (N = 173) signed consent for whole metagenome (shot gun sequencing on Illumina HiSeq2500) analysis of stool DNA: 72 CRC (53 sporadic-S, 19 Lynch-L), 87 asymptomatic subjects (normal colonoscopy), 14 first degree healthy relatives from Lynch families. "MOCAT" pipeline was used, library sorted (Phred quality score ¡20 Alientrimmer v0.4.0) after exclusion of < 35 nt, human genes or phage sequences. Quality sequences were aligned (REFMG.V13) and most abundant genes constructed (MBMA program v0.1). The Shaman program (shaman.c3bi.pasteur.fr) was used. The number of bacteria was estimated (REFMG program). The linear model (GLM) was implemented in the DESeq2 R kit. Dfferences between Control (N = 87) and CRCs (N = 69), between L (N = 19) and S CRCs (N = 50), and between LCRC (N = 19) and Healthy Lynch relatives were obtained after interaction of age, BMI and gender was considered (GLM model). The $P < 0.1$ value was retained after correction (Benjamini and Hochberg). The specific taxonomic composition of the control and CRC groups was subjected to random analysis (Caret's R package) with two optimization parameters (precision and kappa) in the model. **Results:** There was no difference for gender, age ($p = 0.08$) and BMI ($p = 0.187$) in the L and S CRCs. Significant differences were observed between Normal and CRCs, C-CRC and L-CRC, L-CRC and first degree relatives based on the common component (similarity of sequences): 13 species differentiated Normal and CCRs, two were more prevalent in L-CRCs. The panels of bacteria linked with location, MSI, Ras mutations, methylation phenotypes and survival were identified. No significant link was observed with TNM Staging: I (N = 17, 2L and 15S), II (N = 12, 5L and 7S), III (N = 20, 10L, 10S), IV (N = 22.1L, 21S). DFS might be dysbiosis dependent. **Conclusions:** CRC dysbiosis is location-dependent. Several bacteria are associated with Ras mutation, MSI, and methylation status. They may directly or through therapies impact the prognosis. Microbiota signature should be taken in consideration in trials.

3616 Poster Session (Board #239), Sat, 8:00 AM-11:30 AM

Clonal evolution in locally advanced rectal cancers in response to neoadjuvant chemoradiotherapy. *First Author: Sinead Toomey, Department of Molecular Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland*

Background: Locally advanced rectal cancer, LARC (T3/4 and/or N+) is currently treated with neoadjuvant chemoradiotherapy (NACRT), however clinicopathological response is variable. Monitoring clonal evolution in response to NACRT may identify mutations driving therapeutic resistance or tumor growth after treatment. **Methods:** Fresh-frozen pre- and post-NACRT tumor and matched normal tissue from LARC patients were stratified into good (RCPath A), intermediate (RCPath B) and poor (RCPath C) responders. Following histological review, targeted exome capture was performed using an Agilent SureSelect Human all Exome V3 kit. Samples were sequenced to a minimum of 100X coverage on an Illumina HiSeq2000, and clonal evolution was assessed in matched pre- and post-NACRT tumor samples. **Results:** The median somatic mutation burden in pre-treatment samples was 114 (IQR 19-207). Two tumors were microsatellite (MSI) unstable and had elevated mutational burdens. The least evolution occurred in the poor responders, where there was little change in clonal composition after treatment, and driver mutations in genes including TP53 and APC were retained. On average 79% of pre-treatment mutations were retained post-treatment in poor responders and 33% of mutations were retained in intermediate responders. Many of the intermediate responders had loss of driver mutations including TP53 from the pre-treatment sample, but also shared a number of mutations in genes including PIK3CA and BRAF between pre- and post-treatment samples. There was also increased frequency in the post-treatment samples of clones that were not present in the pre-treatment samples. In one intermediate responder, all 47 mutations that were present in the pre-treatment sample including the driver mutations TP53 and APC were absent in the post-treatment sample, while 10 completely new mutations were identified. **Conclusions:** Dynamic mutational processes occur in LARC following selective pressures of exposure to NACRT, including changes in somatic mutation presence or frequency after treatment, owing to persistence or loss of sub-clones. As NACRT can profoundly affect the LARC genome, monitoring molecular changes during treatment may be clinically useful.

TPS3618 **Poster Session (Board #241a), Sat, 8:00 AM-11:30 AM**

Phase 3, open-label, randomized study of first-line pembrolizumab (pembro) vs investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC): KEYNOTE-177. *First Author: Luis A. Diaz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: About 5% of mCRCs are dMMR, leading to high levels of MSI. CRCs with MSI-H have abundant lymphocyte infiltrates and strong expression of immune checkpoints. In the phase 2 KEYNOTE-016 study, the anti-programmed death 1 (PD-1) antibody pembro provided an ORR of 40% in patients (pts) with progressive dMMR mCRC vs 0% in pts with MMR-proficient mCRC. KEYNOTE-177 (ClinicalTrials.gov, NCT02563002) is an international, randomized, open-label, phase 3 study designed to evaluate the efficacy and safety of pembro vs standard-of-care (SOC) chemotherapy in the first-line setting for dMMR or MSI-H mCRC. **Methods:** Key eligibility criteria include age $\geq$ 18 years, locally confirmed dMMR or MSI-H stage IV CRC, measurable disease per RECIST v1.1 by local site assessment, ECOG performance status 0-1, no active autoimmune disease or brain metastases, and no prior therapy for mCRC. Pts are to be randomized 1:1 to receive either pembro 200 mg Q3W or investigator's choice of SOC chemotherapy, which must be chosen prior to randomization; options include mFOLFOX6 or FOLFIRI alone or in combination with bevacizumab or cetuximab. Treatment is to continue until disease progression, unacceptable toxicity, pt/investigator decision, or completion of 35 cycles (pembro only). Response is to be evaluated Q9W per RECIST v1.1 by central imaging vendor review and per RECIST adapted for immunotherapy response patterns. Pts in the SOC arm who have disease progression and meet crossover criteria may be eligible to receive pembro for up to 17 treatment cycles. Eligible pts may continue pembro beyond initial RECIST-defined progression. AEs are to be assessed throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded per NCI CTCAE v4.0. Pts are to be followed for survival Q9W. Primary end point is PFS per RECIST v1.1 by central imaging vendor review. Secondary end points include ORR per RECIST v1.1 by central imaging vendor review, OS, and safety and tolerability. Other end points include DOR and HRQoL. Planned enrollment in KEYNOTE-177 is 270 pts across 21 countries. Clinical trial information: NCT02563002.

TPS3619 **Poster Session (Board #241b), Sat, 8:00 AM-11:30 AM**

CanStem303C trial: A phase III study of napabucasin (BBI-608) in combination with 5-fluorouracil (5-FU), leucovorin, irinotecan (FOLFIRI) in adult patients with previously treated metastatic colorectal cancer (mCRC). *First Author: Axel Grothey, Mayo Clinic Cancer Center, Rochester, MN*

Background: Cancer stem cells are considered to be fundamentally important for resistance to therapy, recurrence and metastasis. Napabucasin is a first-in-class cancer stemness inhibitor in development identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells (Li et al, PNAS 112(6):1839, 2015). Preclinically, napabucasin sensitizes cancer cells to chemotherapeutics, including 5-FU and irinotecan. Encouraging anticancer activity in advanced CRC was observed in a phase Ib/II (Bendell et al, GI ASCO 2017) study of 63 pts with disease control rate (DCR) of 93% (28/30) and overall response rate (ORR) of 33% (10/30) in FOLFIRI-naïve pts who have had an on-study RECIST evaluation. On the basis of these data, a phase III trial is being conducted in North America, Europe, Australia, and Asia. **Methods:** This study (ClinicalTrials.gov NCT02753127) will assess the efficacy of napabucasin+FOLFIRI *vs* FOLFIRI in pts with mCRC (n = 1250). Addition of bevacizumab (bev) is permissible per investigator choice. Pts must have failed 1 prior line of therapy with oxaliplatin and a fluoropyrimidine +/- bev for metastatic disease. Pts are randomized 1:1 to receive napabucasin 240 mg PO BID plus FOLFIRI bi-weekly, or FOLFIRI bi-weekly (bev may be added to FOLFIRI by investigator choice) and stratified by geography, time to progression on 1st-line therapy, RAS mutation status, bev as part of study treatment and primary tumor location. Treatment will continue until disease progression, or another discontinuation criterion. Primary endpoint is overall survival (OS) in the general study population (ITT) (HR 0.80 for OS improvement from 12.54 to 15.68 months); secondary endpoints include OS in the biomarker positive (biomarker+) population, progression free survival (PFS) in the ITT population, PFS in biomarker+ population, ORR and DCR in the ITT and in biomarker+ populations, safety and quality of life. Also, blood and tumor archival tissue will be assessed for PK and biomarker analyses. Global enrollment is underway. Clinical trial information: NCT02753127.

TPS3620 **Poster Session (Board #242a), Sat, 8:00 AM-11:30 AM**

Avelumab and cetuximab in combination with FOLFOX in patients with previously untreated metastatic colorectal cancer (MCRC): The phase II AVETUX-CRC trial (AIO KRK 0216). *First Author: Alexander Stein, Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany*

Background: Inhibition of the PD-1/L1 axis has shown to improve survival as single agent in a variety of tumor types. The efficacy of single agent PD-1/L1 inhibition in patients with treatment refractory MCRC seems to be limited to hypermutated tumors characterized by mismatch repair deficiency. 1st line chemotherapy (e.g. FOLFOX) with cetuximab for patients with RAS/BRAF wildtype MCRC result in objective response rates of about 60%, thus substantial antigen release will likely occur triggering immune control. Furthermore, the induction of immunogenic cell death has been recently shown for cetuximab-based regimen. Thus, the evaluation of FOLFOX and cetuximab in combination with avelumab in 1st line MCRC is of particular interest. **Methods:** AVETUX is a single arm exploratory phase II investigator initiated trial. Patients with RAS/BRAF wildtype MCRC will be included independent of mismatch repair status to receive mFOLFOX6 and cetuximab in combination with avelumab (10mg/kg from day 1 of cycle 2 onwards). Treatment with avelumab is limited to a maximum of 18 months. Primary endpoint is 12month progression-free survival rate, which should be increased from 40% to 57%, with type I error of 10% and 80% power, leading to a sample size of 43 patients. An early stopping rule will be applied in case of an increase in toxicity after the first 15 patients received at least two months of treatment. The trial is flanked by a large translational program including immunoprofiling to determine and correlate the respective immune response signatures with clonal dynamics (RAS/EGFR). Recruitment will start in 11 German sites early 2017. Clinical trial information: EudraCT No 2016-004434-26. **Conclusion:** The AVETUX trial will determine the feasibility and early efficacy of FOLFOX and cetuximab combined with avelumab in 1st line MCRC. The translational research program will shed light on the potential mode of action of this novel combination. Clinical trial information: 2016-004434-26.

TPS3621 **Poster Session (Board #242b), Sat, 8:00 AM-11:30 AM**

The CCTG CO.26 trial: A phase II randomized study of durvalumab plustremelimumab and best supportive care (BSC) vs BSC alone in patients with advanced colorectal carcinoma (CRC) refractory to standard therapies. *First Author: Eric Xueyu Chen, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Durvalumab (D) is a human monoclonal antibody (mAb) that inhibits binding of programmed cell death ligand 1 (PD-L1) to its receptor (PD-1) thereby preventing reduction in the number and efficacy of activated T-cells. Tremelimumab is a mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) thereby resulting in enhanced T-cell activation and anti-tumour activity. Monotherapy with the anti-PD-1 agent pembrolizumab has demonstrated significant activity in CRC pts with tumours demonstrating microsatellite instability (MSI-H). Inhibiting PD-1/PD-L1 alone is likely of limited benefit in advanced CRC as only 5% of pts are MSI-H. Targeting both PD-L1 and CTLA-4 may have additive or synergistic activity as the mechanisms of action of CTLA-4 and PD-L1 inhibition are non-redundant. This study is designed to evaluate whether combining PD-L1 and CTLA-4 inhibition will lead to improved patient survival *vs* BSC alone in advanced CRC, regardless of MSI status. **Methods:** This randomized phase II study (ClinicalTrials.gov NCT02870920) will assess the efficacy and safety of D+T *vs* BSC in pts with metastatic or advanced, unresectable, refractory CRC (n = 180). Pts have failed standard chemotherapy based regimens containing a fluoropyrimidine, irinotecan and oxaliplatin (and an EGFR inhibitor, if *Ras* wild type) and no other therapeutic options. Pts are randomized in a 2:1 ratio to receive D (1500 mg) D1 q 28 days and T (75 mg) D1 for first 4 cycles. Treatment will continue until disease progression, death, intolerable toxicity, or patient/investigator decision to stop. Primary endpoint is overall survival; secondary endpoints include progression free survival, safety, overall response rate and quality of life. Analysis will be according to randomized group stratified by ECOG PS (0 *vs* 1) and site of tumour (right *vs* transverse *vs* left vs rectum). In addition, blood, plasma, and archival tissue will be collected and assessed for potential prognostic and predictive biomarkers, including tumour MSI status. As of February 1 2017, 20 pts have been randomized and recruitment is ongoing. Clinical trial information: NCT02870920.

TPS3622 **Poster Session (Board #243a), Sat, 8:00 AM-11:30 AM**

BEACON CRC (binimetinib [BINI], encorafenib [ENCO], and cetuximab [CTX] combined to treat *BRAF*-mutant metastatic colorectal cancer [mCRC]): A multicenter, randomized, open-label, three-arm phase III study of ENCO plus CTX plus or minus BINI vs irinotecan (IRI)/CTX or infusional 5-fluorouracil/folinic acid/IRI (FOLFIRI)/CTX with a safety lead-in of ENCO + BINI + CTX in patients (Pts) with *BRAF*^{V600E} mCRC. *First Author: Sanne Huijberts, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: *BRAF* mutations are found in ≈10% of mCRC cases. Pts with *BRAF*^{V600E} mCRC have a poor prognosis, with shorter progression-free survival (PFS) and overall survival (OS) than pts with *BRAF*^{wt} mCRC (Van Cutsem et al 2011; Modest et al 2012; Sorbye et al 2015). The benefits of combined BRAF + EGFR inhibition in mCRC have been demonstrated in vitro (Corcoran et al 2012; Prahallad et al 2012; Yang et al 2012), and preclinical evidence suggests that adding MEK signaling inhibition improves antitumor activity. Early clinical data indicate that BRAF + EGFR + MEK inhibition has greater activity than BRAF + EGFR inhibition in pts with *BRAF*^{V600E} mCRC (Van Cutsem et al 2016). Our study will examine the combination of BINI (a MEK inhibitor) + ENCO (a selective BRAF kinase inhibitor) + CTX (an anti-EGFR antibody) and of ENCO + CTX in pts with *BRAF*^{V600E} mCRC. **Methods:** BEACON CRC (NCT02928224) is enrolling pts with *BRAF*^{V600E} mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. A safety lead-in phase (≈30 pts) will determine the safety and tolerability of oral ENCO 300 mg QD + oral BINI 45 mg BID + intravenous CTX 400 mg/m^2 followed by 250 mg/m^2 QW. In the phase 3 portion, ≈615 pts will be randomized 1:1:1 to triplet (ENCO + BINI + CTX), doublet (ENCO + CTX), or control (investigator's choice of IRI/CTX or FOLFIRI/CTX) arms. Pts will be treated in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, or death. The primary endpoint is OS (triplet vs control). Secondary endpoints include OS (doublet vs control), confirmed investigator-assessed objective response rate according to RECIST version 1.1 (triplet or doublet vs control; triplet vs doublet), PFS (triplet or doublet vs control), duration of response, time to response, pharmacokinetics, and pt-reported outcomes. Safety will be summarized using standard adverse event reporting. Clinical trial information: NCT02928224.

TPS3623 **Poster Session (Board #243b), Sat, 8:00 AM-11:30 AM**

Multicenter phase I/II trial of BBI608 and pembrolizumab combination in patients with metastatic colorectal cancer (SCOOP Study): EPOC1503. *First Author: Yasutoshi Kuboki, Department of Gastrointestinal Oncology, National Cancer Center Hospital, Chiba, Japan*

Background: Immune checkpoint inhibitor (ICI) was reported to show durable responses in patients with MSI-H (Microsatellite Instability-High) metastatic colorectal cancer (mCRC). On the other hand, for patients with MSS (Microsatellite Stable) mCRC, ICI monotherapy achieved no response. Recently, WNT/β-catenin signaling has been reported to be involved in the elimination of tumor-infiltrating lymphocytes and the resistance of anti-PD-L1 antibodies. CRC is representative cancer with WNT/β-catenin pathway activation. Furthermore, STAT3 has also been reported to be a key driver of this immune evasion. Considering these rationales, the blocking of these signaling pathways with ICI may enhance antitumor immune response. Therefore, we initiated phase I/II study to assess efficacy and safety for the combination of BBI608, which blocks STAT3 and WNT/β-catenin signaling, with pembrolizumab in patients with mCRC. **Methods:** The eligibility criteria were patients with gastrointestinal cancer not responded to or intolerant of standard chemotherapies (SOC) for phase I part, and MSS mCRC refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, and anti-EGFR antibody (if wild-type *RAS*) for Cohort B in phase II part. For Cohort A, MSI-H mCRC refractory or intolerant to the SOC, irrespective of anti-EGFR antibody are investigated. Phase I part was designed to determine the recommended phase II dose in a "3+3" cohort-based dose escalation design of BBI608 (240mg BID every day on level 1 and 480mg BID every day on level 2) with pembrolizumab (200mg/body q3w). Primary endpoint of the phase II part is Immune-related objective response rate (irORR) determined by their Response Evaluation Criteria In Solid Tumors (irRECIST). A null hypothesis and alternative hypothesis for cohort B are irORR = 5% and 20%, respectively. Required sample size for Cohort B was 40 with a one-sided alpha of 5% and power of 90%. Required sample size for Cohort A (10 patients) was determined in an exploratory manner. We also investigate biomarker study using paired samples of both tumor biopsy and blood. The enrollment to phase I part began in November 2016. Clinical trial information: NCT02851004. Clinical trial information: NCT02851004.

TPS3624 **Poster Session (Board #244a), Sat, 8:00 AM-11:30 AM**

A phase II, open label study of tucatinib (ONT-380) combined with trastuzumab in patients with HER2+ metastatic colorectal cancer (mCRC)(MOUNTAINEER). *First Author: John H. Strickler, Duke Cancer Institute, Duke University Medical Center, Durham, NC*

Background: To improve survival for patients with mCRC, efforts are needed to identify and treat actionable genomic alterations. *HER2* is amplified in approximately 5-8% of patients with *KRAS* and *NRAS (RAS)* wild-type mCRC. *HER2* functions as an oncogenic driver and a mediator of EGFR antibody (Ab) resistance. Although prior studies have shown that anti-HER2 therapies are active in patients with HER2+ (HER2 IHC 3+ or *HER2* amplified) mCRC, there are no HER2-directed therapies approved for these patients. Tucatinib is a potent and highly selective oral small molecule tyrosine kinase inhibitor of HER2, currently being developed to treat metastatic breast cancer. In HER2+ CRC patient derived xenograft models, tucatinib has substantial anti-tumor activity. The addition of the anti-HER2 monoclonal Ab trastuzumab augments tumor growth inhibition. **Methods:** This single-arm phase II study will test the combination of tucatinib and trastuzumab in patients with HER2+ mCRC. Eligible patients include those with RAS wild-type mCRC who have been previously treated with 5-FU, oxaliplatin, irinotecan, and an anti-VEGF monoclonal Ab. Patients must have HER2+ disease by IHC, FISH, or NGS. Prior treatment with anti-HER2 targeting therapy is excluded. The primary objective is to assess the objective response rate for the combination. Secondary objectives are to evaluate the efficacy (PFS, OS, clinical benefit rate), safety, and tolerability of the combination. Correlation between tissue and blood-based biomarkers and clinical outcomes will be explored. Blood will be collected at baseline and each restaging to determine if the combination eliminates *HER2* amplified circulating tumor DNA. Subjects will receive tucatinib at a dose of 300mg by mouth daily, and trastuzumab will be administered every 3 weeks (8 mg/kg IV day 1 of cycle 1, then 6 mg/kg IV Q3 weeks). Response will be assessed every 3 cycles (9 weeks) per RECIST version 1.1. Both agents will be provided by the study. This study was initiated in February 2017. Recruitment is ongoing at 8 sites in the Academic and Community Cancer Research United (ACCRU) network. Clinical trial information: NCT03043313.

TPS3625 **Poster Session (Board #244b), Sat, 8:00 AM-11:30 AM**

LUNA: A randomized phase II trial of liver resection plus chemotherapy or chemotherapy alone in patients with unresectable lung and resectable liver metastases from colorectal adenocarcinoma. *First Author: Yun Shin Chun, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Liver resection for metastatic colorectal cancer is associated with 5-year overall survival (OS) of 58% and accepted as standard of care. However, the role of liver resection with unresectable low-volume lung metastases is unknown. A recent retrospective study showed that resection of liver metastases was associated with statistically improved OS compared to a matched group of patients treated with systemic therapy alone for lung and liver metastases (3-year OS 43% vs. 14%; Mise Y, Ann Surg Oncol 2015). LUNA is a single-institution phase 2 randomized trial designed to determine the overall survival benefit of liver resection in patients with unresectable lung metastases and to integrate biological surrogates to risk stratify patients and optimize patient selection for hepatectomy. **Methods:** Eligibility criteria include resectable liver metastases, defined as sufficient liver remnant volume, adequate vascular inflow and outflow, and preservation of 2 contiguous liver segments. Low-volume lung metastases are defined as solid pulmonary nodules $<$ 2 cm in size and $<$ 15 in number. Chest computed tomography is reviewed by an attending thoracic surgeon, and lung metastases are deemed unresectable due to anatomic location, distribution, or patients' comorbidities. Previous treatment with systemic chemotherapy and/or biologic agents is permitted. After stratification by *KRAS* status and primary tumor location in the colon vs. rectum, patients are randomized 1:1 to liver resection plus chemotherapy or no liver resection with chemotherapy at the discretion of the treating oncologist as routine standard of care. Patients are restaged every 3–6 months until 3 years after randomization or death. The primary endpoint is OS. Secondary endpoints include quality of life and identification of biological surrogates in blood and resected liver tissue associated with response to chemotherapy, time to tumor progression, and survival. Targeting an effect size of extending median OS from 17 to 34 months will provide 80% power with 0.05 one-sided alpha with a sample size of 80 patients. Clinical trial information: NCT02738606.

TPS3626 **Poster Session (Board #245a), Sat, 8:00 AM-11:30 AM**

A phase I dose-escalation of trifluridine/tipiracil in combination with oxaliplatin in metastatic colorectal cancer. *First Author: Antoine Hollebecque, Drug Development Department (DITEP), Gustave Roussy, Villejuif, France*

Background: Trifluridine/tipiracil, also known as TAS-102, is a combination of an antineoplastic thymidine-based nucleoside analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride). The antitumor activity of combined trifluridine/tipiracil and oxaliplatin has been studied in gastrointestinal tumor xenografts, including a 5-FU resistant subline, using a nude mouse model. This study demonstrated increased antitumor activity for the combination compared to trifluridine/tipiracil or oxaliplatin alone ($p < 0.001$) (Nukatsuka et al., Anticancer Res 2015). These data support the rationale for clinical use of the combination. We describe a phase 1, international, dose-escalation study of the combination in metastatic colorectal cancer (mCRC). **Methods:** This trial includes mCRC patients pretreated with at least one line of standard chemotherapy. The 14-day administration schedule of trifluridine/tipiracil differs from current clinical practice to avoid overlapping toxicity, notably decreased neutrophils due to oxaliplatin or trifluridine/tipiracil. Trifluridine/tipiracil is administered orally (cohort 1: 25 mg/m^2 bid; cohort 2: 30 mg/m^2 bid; cohort 3: 35 mg/m^2 bid) from day 1 to 5; and oxaliplatin at 85 mg/m^2 (with a possibility to reduce to 65 mg/m^2) on day 1. The primary objective is to determine the maximum tolerated dose (MTD) through a 3+3 design. Secondary objectives include safety, pharmacokinetics, and preliminary efficacy (overall survival, progression-free survival, overall response rate and biomarkers). As of December 2016, no dose-limiting toxicities had been reported in cohorts 1 or 2. The MTD has not yet been reached and dose-escalation continues with enrollment in cohort 3 at full dose for both drugs (trifluridine/tipiracil 35 mg/m^2 bid and oxaliplatin 85 mg/m^2). Once established, the MTD will be confirmed in 6 additional patients to define the recommended dose to be used in the expansion part of the study planned in the same patient population. The results of the dose-escalation part are expected in 2017. (NCT02848443). Clinical trial information: NCT02848443.

TPS3627 **Poster Session (Board #245b), Sat, 8:00 AM-11:30 AM**

A phase Ib study combining irinotecan with AZD1775, a selective WEE 1 kinase inhibitor, in RAS/RAF mutated metastatic colorectal cancer patients who progressed on first line therapy. *First Author: Deirdre Jill Cohen, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY*

Background: Mutant KRAS tumors show a dependency on WT-H/N-Ras for activation of ATR/Chk1-mediated G2 DNA damage response (Grabocka, Cell, 2015). We have shown in vitro that the Wee1 kinase inhibitor AZD1775, which acts to abrogate the G2 DNA damage checkpoint and induces replication stress during S-phase, selectively sensitizes RAS/RAF mutant cells to the DNA damaging agent irinotecan. Up to 65% of metastatic colorectal cancers harbor RAS or BRAF mutations and these patients have limited treatment options following first line therapy. **Methods:** This is an open label, single-arm, phase Ib study using a modified 3+3 dose-escalation schedule with expansion cohort. Primary objective is to determine the MTD of AZD1775 in combination with irinotecan as 2nd-line therapy in patients with metastatic KRAS, NRAS or BRAF mutated colorectal cancer. Up to 18 patients will be enrolled in the dose escalation portion. Standard dose irinotecan is given on day 1 of every 2 week cycle. AZD1775 is administered PO twice daily for 3 to 5 days of each cycle, starting cycle 2. The maximum tolerated dose (MTD) is defined as the highest dose level at which $\leq$1 of 6 patients experience a dose limiting toxicity. Once the MTD is reached and/or recommended dose for expansion is determined, a dose expansion cohort of 14 patients will be enrolled. Secondary endpoints include characterizing the safety profile at the MTD, obtaining a preliminary estimate of efficacy for the combination (measured by overall response rate, progression-free and overall survival rates), and obtaining pharmacokinetic parameters. Pre- and on-treatment biopsies will be collected from the expansion cohort to determine: adequate target engagement of Wee1, changes in markers of DNA damage, TP53 mutation status, and changes in gene expression profiles in order to identify potential biomarkers of response. At February 2017, 2 patients have been enrolled on this study. Clinical trial information: NCT02906059.

Dose escalation schema.

Dose Level	AZD1775 (q2w)	Irinotecan (q2w)
-1	125 mg bid x 3 days	150mg/m^2
1 (starting dose)	125 mg bid x 3 days	180mg/m^2
2A	150 mg bid x 3 days	180mg/m^2
2B	125 mg bid x 5 days	180mg/m^2
3	150 mg bid x 5 days	180mg/m^2

TPS3628 **Poster Session (Board #246a), Sat, 8:00 AM-11:30 AM**

PRODIGE 34 ADAGE: Adjuvant chemotherapy in elderly patients with resected stage III colon cancer—A randomized phase III trial. *First Author: Thomas Aparicio, Department of Gastroenterology, Saint Louis Hospital, Paris, France*

Background: Colon cancer (CC) occurs in around 50% of the patients after 70 years. Adjuvant chemotherapy (CT) has demonstrated a benefit on disease-free survival (DFS) and overall survival after a stage III CC resection. Nevertheless, adjuvant CT is poorly used in elderly patients. There is still concern about the efficacy of doublet CT with oxaliplatin in fit elderly patients and the usefulness of fluoropyrimidine monotherapy in unfit elderly patients. The selection of patients that should be treated remains a challenge. Geriatric evaluation and tumor biology should be explored to help for patient selection. **Methods:** ADAGE is a multicenter, randomized phase III study comparing 3-years DFS of 2 therapeutic strategies in 2 groups of patients aged over 70 with completely resected stage III CC. Patients are included in one of the 2 groups after a multidisciplinary team evaluation; Group 1 (arm A and B) is defined as "able" to be treated with doublet CT; Group 2 (arm C and D) is defined as "unable" to be treated with doublet CT. In each group, patients are randomized according to a 1:1 ratio. Randomization is stratified according to center, gender, stage (IIIA *vs* IIIB *vs* IIIC), occlusion and/or perforation (yes *vs* no) and independent activity of daily living score (IADL: normal *vs* abnormal). Arm A and D receive LV5FU2 or capecitabine, arm B FOLFOX4 or XELOX and arm C is an observation arm. The treatment is planned for 6 months. Adjuvant CT should start within 12 weeks after surgery. Geriatric questionnaires and Lee score must be completed before randomization. Radiological assessment is performed every 6 months for 3 years after randomization and then annually for 2 years. Hypotheses (α two-sided = 5%, power = 80%) are to improve 3-years DFS from 65% (arm A) to 72% (arm B) in group 1 (756 patients required) and from 40% (arm C) to 55% (arm D) in group 2 (226 patients required). Safety is evaluated based on laboratory and clinical tests before each cycle. Exploratory analysis are planned to determine geriatric prognostic factors for DFS. A biological ancillary study is planned to allow prognostic evaluation of mismatch repair status and other molecular signatures. At the 1stof February 2017 the accrual was 246 patients. Clinical trial information: NCT02355379.

TPS3629 **Poster Session (Board #246b), Sat, 8:00 AM-11:30 AM**

NRG-GI002: A phase II clinical trial platform for total neoadjuvant therapy (TNT) in rectal cancer. *First Author: Thomas J. George, NSABP/NRG Oncology, and The University of Florida, Pittsburgh, PA*

Background: Improvements in outcomes for locally advanced rectal cancer (LARC) have plateaued due to an inability to consistently deliver adjuvant therapy (tx) and thus far ineffective novel therapies. Systematic testing of new chemotherapy and radiation sensitizers are needed to advance treatment outcomes. This randomized phase II modular clinical trial platform utilizes Total Neoadjuvant Therapy (TNT) with parallel experimental arms in LARC. The experimental arms are not intended for direct comparison, but to test a variety of sensitizers or hypotheses in a consistent and relatively homogenous high-risk patient (pt) population with correlative biomarkers. Success of any given experimental arm will be determined by achievement of pathologic endpoints compared to a control arm. **Methods:** This NCTN multi-arm randomized phase II trial serves as a modular platform to assess novel sensitizers to neoadjuvant chemotherapy and/or chemoradiotherapy (chemoRT) in LARC. Eligibility includes LARC as defined by any ONE of the following criteria: distal location (cT3-4 $\leq$5cm from the anal verge, any N); bulky (any cT4 or tumor within 3mm of the mesorectal fascia); high risk for metastatic disease (cN2); or not a candidate for sphincter-sparing surgical resection. After randomization, pts receive neoadjuvant FOLFOX x 4mo $\rightarrow$ chemoRT (capecitabine with 50.4Gy) $\rightarrow$ surgical resection 8-12 wks later. Based on promising phase I results, the first experimental arm will assess the activity of veliparib added to standard chemoRT (capecitabine + RT). Primary endpoint is to demonstrate improvement in Neoadjuvant Rectal Cancer (NAR) score for the experimental arm vs control representing 20% relative risk reduction in DFS HR and 3-4% absolute OS improvement. Secondary endpoints include comparisons of OS, DFS, toxicity, pCR, cCR, tx completion, negative surgical margins, sphincter preservation, sphincter function including quality of life, and exploratory assessments of molecular and radiographic predictors of response and distant failure. Target accrual is 79 evaluable pts per arm with additional arms added through rolling protocol amendments. NCT02921256. Support: U10 CA-180868, -20, 21, -22; UG-189867; AbbVie. Clinical trial information: NCT02921256.

TPS3630 Poster Session (Board #247a), Sat, 8:00 AM-11:30 AM

Randomized trial of FOLFOX alone or combined with atezolizumab as adjuvant therapy for patients with stage III colon cancer and deficient DNA mismatch repair or microsatellite instability (ATOMIC, Alliance A021502). *First Author: Frank A. Sinicrope, Mayo Clinic Cancer Center, Rochester, MN*

Background: In metastatic colorectal cancer with deficient DNA mismatch repair (MMR), anti-PD-1 antibody monotherapy produced high tumor response rates and extended progression-free survival compared to lack of benefit for proficient MMR tumors (Le, M, et al, NEJM 2016). We propose a phase III randomized trial to determine if the addition of the anti-PD-L1 antibody, atezolizumab (Genentech™), to adjuvant FOLFOX can improve patient disease-free survival (DFS) vs FOLFOX alone in patients with stage III colon cancers with dMMR or microsatellite instability (MSI). By blocking the PD-1/PD-L1 interaction, atezolizumab may activate T cells, thereby, restoring their ability to detect and attack tumor cells. Limited data suggest that FOLFOX may increase intratumoral cytotoxic CD8+ T cells that may serve as 'immune priming.' **Methods:** Patients with curatively resected stage III colon carcinomas with evidence of dMMR or MSI will be randomized to modified FOLFOX6 for 6 months (12 cycles) alone or combined with atezolizumab (840 mg IV q2 wk) continued as monotherapy for an additional 6 months (total duration of 12 months). Patients will be stratified by T, N stage and tumor sidedness. Local testing for MSI or MMR proteins is allowed. Atezolizumab must begin by/with cycle 2. The targeted accrual goal of 700 patients provides 90% power to detect an effect size expressed as hazard ratio of 0.6 for the primary endpoint DFS at two-sided alpha of 0.05. Interim analyses are planned at 50% and 75% of events. Secondary endpoints include overall survival, treatment tolerability, and quality of life. This study will be conducted by the Alliance for Clinical Trials in Oncology. The protocol has been approved by NCI CTEP and is expected to be activated in mid 2017. Clinical trial information: NCT02912559.

TPS3631 Poster Session (Board #247b), Sat, 8:00 AM-11:30 AM

Transanal versus laparoscopic total mesorectal excision for low rectal cancer: A multicenter randomized phase III clinical trial (TaLaR trial) protocol. *First Author: Shuangling Luo, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: Since 1982, Total Mesorectum Excision (TME) was regarded as a golden standard for radical resection of rectal cancer. Current evidences have proved that both open and laparoscopic TME could achieve the comparative oncological safety. However, for low rectal cancer, it remains a challenge to achieve complete TME with safe resections margin by the conventional transabdominal approach, especially in cases such as bulky mesorectum, enlarged prostate, narrow pelvic floor, etc. Transanal TME (TaTME) is a new approach for rectal cancer. Several retrospective studies have showed its advantage of providing better resection quality for low rectal cancer compared with transabdominal approach, but its long-term effect still needs to be explored. **Methods:** TaLaR trial is an open-label multicenter randomized controlled phase III trial with a non-inferiority design, aiming to compare the short and long term effect between TaTME and laparoscopic TME (lapTME) for low rectal cancer. Patients diagnosed with clinical stage no more than T3N0 or ycT3N2 rectal cancer, inferior border of the tumor from anal verge less than 7cm, are eligible for the present study. A total of 1114 patients (557 per group) will be randomized to either TaTME or lapTME. The primary end-points are 3-year disease-free survival (DFS) and 5-year overall survival (OS). The secondary endpoints include resection quality, postoperative morbidity and mortality, pelvic function and quality of life. Clinical trial information: NCT 02966483.

TPS3632 Poster Session (Board #248a), Sat, 8:00 AM-11:30 AM

A randomized phase III trial of capecitabine with or without irinotecan driven by UGT1A1 in neoadjuvant chemoradiation of locally advanced rectal cancer (CinClare). *First Author: Ji Zhu, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Irinotecan is an effective drug for rectal cancer. Early small sample size trials have assessed the addition of irinotecan to standard CRT with fluoropyrimidines in neoadjuvant phase of locally advanced rectal cancer, in which pCR rates varied from 13.7 to 37%. ARISTOTLE trial, a multicentre UK-based phase III trial, will complete recruitment in autumn 2016. However, all patients in case group were prescribed with weekly irinotecan dose of 60mg/m^2 guided by UGT1A1*28 6/6 and 6/7 genetypes in neoadjuvant chemoradiation. Therefore, this phase III trial was designed to confirm the potential improvement in outcomes seen with the addition of irinotecan to CRT. **Methods:** Eligible patients are randomly allocated to either radiotherapy 50 Gy with concurrent capecitabine, followed by a cycle of capecitabine and oxaliplatin two weeks after the end of CRT (Control arm) or radiotherapy 50 Gy with concurrent capecitabine and irinotecan, followed by a cycle of capecitabine and irinotecan (Case arm). Capecitabine is prescribed with 825mg/m^2 The primary end point is ypCR. The hypothesis is to increase ypCR from 12% in the control group to 25% in the case group. To detect such a difference, with alpha = 0.05 (two-tailed) and belta = 0.15, 360 randomly assigned patients are required. Secondary end points are toxicities, surgical complications, local control, progression-free survival and overall survival. Clinical trial information: NCT02605265.

TPS3633 Poster Session (Board #248b), Sat, 8:00 AM-11:30 AM

EORTC1527/JCOG1609INT: Diffusion-weighted MRI (DW-MRI) assessment of liver metastasis to improve surgical planning (DREAM). *First Author: Kozo Kataoka, EORTC, Brussels, Belgium*

Background: For patients with initially unresectable colorectal liver metastases (CRLM) with good clinical response to chemotherapy, the presence of disappearing liver metastases (DLMs) diagnosed by CT is a major independent prognostic factor. DW-MRI as well as contrast enhanced (CE)-MRI is recommended to detect and characterize CRLM. However, the correlation between radiological and pathological complete response has not been fully investigated using these latest imaging and pathology techniques. Our main aim is to demonstrate the added value of DW-MRI, CE-MRI to that of CT alone to provide precise assessment of the viability of DLMs. In addition, we aim to optimize the therapeutic management of CRLM patients. No prospective study has been conducted to determine the predictive value of DW-MRI combined with CE-MRI in confirming sites of DLMs and assessing their true status. **Methods:** This is the first collaborative study between EORTC, ESSO and JCOG with an integrated quality assurance program for imaging, surgery and pathology. Patients with unresectable CRLM will receive standard systemic chemotherapy and liver resection if resectable. Both CT and MRI (DW-MRI, CE-MRI and T1/T2) will be used to identify confirmed DLMs (cDLMs). cDLMs will be either resected or, if resection is not possible, followed-up without resection until 2 years after surgery to evaluate the true status of the cDLMs. The primary endpoint is negative predictive value (NPV) of DW-MRI, CE-MRI, T1/T2 and CT in confirming the status of cDLMs using as reference either the histopathological complete response or the absence of a local recurrence at the site of cDLMs during the follow up period of 2 years. The study aims at excluding a NPV$\leq$0.85 and is powered under the alternative that the NPV$\geq$0.95. The planned sample size is 92 evaluable (resected or left behind) cDLMs, with a 1-sided alpha of 5% and a power of 90% adjusting for within-patient correlation between cDLMs of 0.2 and an average number of 2 cDLMs per patient. Approximately 400 patients will be registered from European, Japanese and US sites over 3 years. As of February 2017, 2 patients have been enrolled. Clinical trial information: NCT02781935.

4000 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Second-line tivantinib (ARQ 197) vs placebo in patients (Pts) with MET-high hepatocellular carcinoma (HCC): Results of the METIV-HCC phase III trial. *First Author: Lorenza Rimassa, Humanitas Cancer Center, Humanitas Clinical and Research Center, Rozzano, Italy*

Background: Tivantinib (T), a selective, oral MET inhibitor, improved overall survival (OS) and progression-free survival (PFS) versus placebo (P) in a phase II study in MET-High HCC pts. **Methods:** This randomized, placebo-controlled phase III trial (NCT01755767) enrolled pts with: advanced HCC; Child Pugh A; ECOG PS ≤1; adequate bone marrow, liver, kidney functions; no liver transplant; radiographic disease progression (PD) after or intolerance to sorafenib; tumor MET-High (MET ≥2+ in ≥50% of tumor cells) by centralized immunohistochemistry. Pts were randomly assigned 2:1 to oral T or P, stratified by vascular invasion (VI), extrahepatic spread (ES), AFP (< / > 200ng/mL), treated until PD or unacceptable toxicity. Response (RECIST 1.1) was evaluated by CT / MRI every 8 weeks. Primary endpoint of OS and secondary endpoints including PFS and safety were assessed in the intent-to-treat (ITT) population. **Results:** From Dec 2012 to Dec 2015, 1209 pts were consented in Australia, the Americas, Europe, New Zealand: 589 MET-High, 43 initially randomized at the dose of 240mg BID, then reduced due to high neutropenia rate, 340 randomized at 120mg BID: 226 to T, 114 to P (ITT population). Characteristics of pts were balanced between arms: 306 (90%) male; median age: 67; PS 0: 207 (61%); VI: 117 (34%); ES: 197 (58%); AFP ≤200: 195 (57%); radiographic PD on sorafenib: 275 (81%). Median OS (95% CI) was 8.4 months (m) (6.8-10.0) in T, 9.1 m (7.3-10.4) in P, HR = 0.97 (0.75-1.25), $P = 0.81$. Median PFS (95% CI) was 2.1 m (1.9-3.0) in T, 2.0 m (1.9-3.6) in P, HR = 0.96 (0.75-1.22), $P = 0.72$. No OS difference was seen in pts with VI (HR 1.19, 0.79-1.79), ES (HR 1.09, 0.78-1.52), AFP > 200ng/mL (HR 1.00, 0.71-1.41). Grade (G) > 3 AEs were 55.6% in T, 55.3% in P. In T, most common G > 3 AEs were ascites (7.1%), general deterioration (5.8%), anemia (4.9%); most common serious AE was general deterioration (4.9%). Deaths within 30 days of last dose were 22.1% on T vs 15.8% on P (most common causes: general deterioration 3.5%, hepatic failure 2.6%). **Conclusion:** Tivantinib at the 120mg BID dose did not improve OS or PFS over placebo in patients with advanced MET-High HCC who failed previous treatment with sorafenib. Clinical trial information: NCT01755767.

4001 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). *First Author: Ann-Lii Cheng, National Taiwan University Hospital, Taipei, Taiwan*

Background: SOR is the only approved agent in uHCC and new options are needed. LEN, an inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet derived growth factor receptor α, RET, and KIT, showed activity in uHCC in a phase II trial. We report a phase III trial of LEN vs SOR as first-line therapy for uHCC. **Methods:** In this randomized, open-label, noninferiority (NI) study, pts had uHCC, ≥ 1 measurable target lesion, Barcelona Clinic Liver Cancer stage B or C, Child-Pugh class A, ECOG PS ≤ 1, and no prior systemic therapy. Pts were randomized 1:1 to LEN (body weight ≥ 60 kg: 12 mg/day; < 60 kg: 8 mg/day) or SOR 400 mg twice daily. The primary endpoint was overall survival (OS). The OS hazard ratio (HR) and its 95% CI were estimated with a stratified Cox proportional hazard model. The predefined NI margin was 1.08. Secondary efficacy endpoints were progression-free survival (PFS), time to progression (TTP) and objective response rate (ORR) by modified RECIST. Type I error rates for secondary efficacy endpoints were controlled with a fixed sequence procedure at 2-sided α = 0.05 after OS NI was claimed. **Results:** 954 Pts enrolled (LEN: 478; SOR: 476). Efficacy outcomes are shown in the table. A similar number of pts in both arms had treatment-emergent adverse events (TEAEs). Most common LEN TEAEs were hypertension (42%), diarrhea (39%), decreased appetite (34%), decreased weight (31%), and fatigue (30%). Median (range) treatment duration was 5.7 mos (0−35.0) for LEN and 3.7 mos (0.1−38.7) for SOR. 13% Of LEN-treated and 9% of SOR-treated pts discontinued due to adverse events. 33% Of LEN-treated and 39% of SOR-treated pts received second-line therapy. **Conclusions:** LEN is noninferior in OS, and achieves statistically significant and clinically meaningful improvements in PFS, TTP, and ORR, as first line therapy for uHCC. TEAEs were consistent with the known LEN safety profile. Clinical trial information: NCT01761266.

Outcomes	LEN	SOR	HR
Median OS, mos (95% CI)	13.6 (12.1−14.9)	12.3 (10.4−13.9)	0.92 (0.79−1.06)
Median PFS, mos (95% CI)*	7.4 (6.9−8.8)	3.7 (3.6−4.6)	0.66 (0.57−0.77)
Median TTP, mos (95% CI)*	8.9 (7.4−9.2)	3.7 (3.6−5.4)	0.63 (0.53−0.73)
ORR, n (%)*	115 (24)	44 (9)	

*$P < 0.00001$

4002 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Phase III multi-centre open-label randomized controlled trial of selective internal radiation therapy (SIRT) versus sorafenib in locally advanced hepatocellular carcinoma: The SIRveNIB study. *First Author: Pierce H. W. Chow, National Cancer Center Singapore, Singapore, Singapore*

Background: The optimal therapeutic regime for locally advanced hepatocellular carcinoma (HCC) with and without vascular invasion remains unclear. This study evaluates the efficacy of Selective Internal Radiation Therapy using SIR-Spheres yttrium-90 microspheres (Y90) versus sorafenib in Asian Barcelona Clinic Liver Cancer (BCLC) stage B and C patients without extra-hepatic metastasis. **Methods:** This investigator-initiated multi-center trial randomized eligible patients with locally advanced inoperable HCC to single injection of Y90 or sorafenib (oral 400mg BD) till progressive disease or unacceptable toxicity. The sample size, assuming type I error (two-sided) of 0.05 and power of 90% was 360 patients. Final analysis was planned at 266 reported deaths. **Results:** 360 patients (182 Y90, 178 sorafenib) were enrolled from 27 centers in 11 Asian countries. BCLC C patients without extra-hepatic metastasis comprised 41.4% of patients, 30.6% had portal vein thrombosis (PVT), 88.6% were Child-Pugh A, 57.2% were hepatitis B and 15.0% were hepatitis C. Altogether 28.6% and 9.0% of patients in the Y90 and sorafenib arms respectively failed to receive planned therapy. Intention-to-treat analysis was carried out with the overall survival (OS) in the Y90 and sorafenib arms being 8.54 and 10.58 months respectively (Hazard ratio (HR) 1.17, p =0.203). Tumour response rate (TRR) was 16.5% and 1.7% ($p < 0.001$) respectively. Time-to-tumor -progression (TTP) was 5.88 vs 5.36 (overall) (HR 0.93) and 6.08 vs 5.39 (liver-specific) (HR 0.91) months for Y90 and sorafenib respectively. Progression-free-survival (PFS) was 5.29 vs 5.06 (overall) (HR 0.94) and 5.85 vs 5.06 (liver-specific) (HR 0.92) months respectively. At least one severe adverse event was found in 27.7% and 50.6% of patients in the Y90 and sorafenib arms respectively. **Conclusions:** Asian patients with locally advanced HCC without extra-hepatic metastasis treated with Y90 have statistically significant better TRR, and fewer SAEs when compared with those treated with sorafenib. There were no statistically significant differences in OS between Y90 and sorafenib. Clinical trial information: NCT01135056.

4003 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

KEYNOTE-059 cohort 1: Efficacy and safety of pembrolizumab (pembro) monotherapy in patients with previously treated advanced gastric cancer. *First Author: Charles S. Fuchs, Yale Cancer Center, New Haven, CT*

Background: Pembro has shown promising antitumor activity and manageable safety in a phase 1 study of pts with previously treated advanced gastric cancer. We conducted a global, multicohort, phase 2 study of pembro in pts with advanced gastric or gastroesophageal junction (G/GEJ) cancer (KEYNOTE-059;NCT02335411). **Methods:** Cohort 1 enrolled 259 pts, aged ≥18 y with measurable recurrent or metastatic G/GEJ adenocarcinoma who had progressed on ≥2 prior chemotherapy regimens and had ECOG PS 0-1. Pts received pembro 200 mg Q3W up to 2 y or up to disease progression, investigator/pt decision to withdrawal, or unacceptable toxicity. PD-L1$^+$pts had expression in ≥1% tumor or stromal cells using IHC (22C3 antibody). Primary end points: ORR (RECIST 1.1, by central review), safety, and tolerability. **Results:** Of 259 pts in cohort 1, 76.4% were men; median age was 62.0 y. 51.7% and 48.3% received pembro as 3rd-line (3L) and 4L+ therapy, respectively. 57.1% had PD-L1$^+$ tumors. At data cutoff (Oct 19, 2016), median duration of follow-up was 5.4 mo (range, 0.5 to 18.7). Overall ORR (CR + PR) was 11.2% (95% CI, 7.6-15.7); 1.9% of pts (95% CI, 0.6-4.4) had CR, 9.3% had PR (95% CI, 6.0-13.5), 17% (95% CI, 12.6-22.1) had SD, and 55.6% (95% CI, 49.3-61.7) had PD. Median DOR was 8.1 mo (range, 1.4+ to 15.1+). ORR was 14.9% (95% CI, 9.4-22.1) in 3L pts and 7.2% (95% CI, 3.3-13.2) in 4L+. In PD-L1$^+$ pts, ORR was 15.5% (95% CI, 10.1-22.4) with 2.0% (95% CI, 0.4-5.8) CR and 13.5% (95% CI, 8.5-20.1) PR; in PD-L1$^-$ pts, ORR was 5.5% (95% CI, 2.0-11.6), with 1.8% (95% CI, 0.2-6.5) CR and 3.7% (95% CI, 1.0-9.1) PR. In 3L pts with PD-L1$^+$ tumors, ORR was 21.3% (95% CI, 12.7-32.3), with 4.0% (95% CI, 0.8-11.2) CR; in 3L pts with PD-L1$^-$ tumors, ORR was 6.9% (95% CI, 1.9-16.7), with 3.4% (95% CI, 0.4-11.9) CR. Grade 3-5 treatment-related AEs (TRAEs) occurred in 43 pts (16.6%). TRAEs led to discontinuation in 2 pts (abnormal LFT, bile duct stenosis) and were fatal in 2 pts (acute kidney injury, pleural effusion). **Conclusions:** Pembro showed encouraging efficacy and manageable safety after ≥2 prior lines of therapy in pts with advanced G/GEJ cancer in this large phase 2 trial. Survival and additional biomarker data, including MSI status, will be presented. Clinical trial information: NCT02335411.

4004 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial. *First Author: Salah-Eddin Al-Batran, Institute of Clinical Cancer Research (IKF) at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany*

Background: The MAGIC trial established perioperative (periop) epirubicin, cisplatin, and 5-FU (ECF) as a standard treatment for patients (pts) with operable esophagogastric cancer, but survival continues to remain poor. FLOT4 (NCT01216644) is a multicenter, randomized, investigator-initiated, phase 3 trial. It compares the docetaxel-based triplet FLOT with the anthracycline-based triplet ECF/ECX as a periop treatment for pts with resectable gastric or GEJ adenocarcinoma. **Methods:** Eligible pts of stage ≥cT2 and/or cN+ were randomized to either 3 preoperative and 3 post-operative 3-week cycles of ECF/ECX (epirubicin 50 mg/m2, cisplatin 60 mg/m², both d1, and 5-FU 200 mg/m² as continuous infusion or capecitabine 1250 mg/m2 orally d1-21) or 4 pre-operative and 4 post-operative 2-week cycles of FLOT (docetaxel 50 mg/m2, oxaliplatin 85 mg/m², leucovorin 200 mg/m², and 5-FU 2600 mg/m² as 24-hour infusion, all d1). The primary endpoint was overall survival (OS; 80% power; HR of 0.76; 2-sided log-rank test at 5% type I error). **Results:** Between Aug 2010 and Feb 2015, 716 pts (360 ECF/ECX; 356 FLOT) were randomly allocated. Baseline characteristics were similar between arms (overall, male 74%; median age 62; cT3/T4 81%; cN+ 80%; GEJ 56%). 91% and 37% of pts with ECF/ECX and 90% and 50% with FLOT completed planned pre-operative and post-operative cycles, respectively. Median follow-up was 43 mon. 369 pts died (203 ECF/ECX; 166 FLOT). FLOT improved OS (mOS, 35 mon with ECX/ECF vs. 50 mon with FLOT; HR 0.77 [0.63 - 0.94]; p = 0.012). 3y OS rate was 48% with ECF/ECX and 57% with FLOT. FLOT also improved PFS (mPFS, 18 mon with ECX/ECF vs. 30 mon with FLOT; HR 0.75 [0.62 - 0.91]; p = 0.004). Periop complications were 50% with ECF/ECX and 51% with FLOT. 30- and 90-day mortality was 3% and 8% with ECF/ECX and 2% and 5% with FLOT. There was more G3/4 nausea and vomiting with ECF/ECX and more G3/4 neutropenia with FLOT. **Conclusion:** Periop FLOT improved outcome in patients with resectable gastric and GEJ cancer compared to periop ECF/ECX. Clinical trial information: NCT01216644.

4006 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study. *First Author: John Neil Primrose, University of Southampton, Southampton, United Kingdom*

Background: Despite improvements in multidisciplinary management, BTC has a poor outcome. Approximately 20% of cases are suitable for surgical resection with a 5 year survival of < 10%. BILCAP aimed to determine whether capecitabine (Cape) improves overall survival (OS) compared to observation (Obs) following radical surgery. **Methods:** Patients with completely-resected cholangiocarcinoma (CCA) or gallbladder cancer (including liver and pancreatic resection, as appropriate), with adequate biliary drainage, no ongoing infection, adequate renal, haematological and liver function, and ECOG PS ≤2, were randomized 1:1 to Cape (1250 mg/m^2 D1-14 every 21 days, for 8 cycles) or Obs. Randomization was minimized on tumor site, resection status, ECOG PS and surgical center. The primary outcome was OS in the intention to treat (ITT) population. 410 patients were needed to detect a hazard ratio (HR) of 0.69 (2-sided $\alpha = 0.05$ and 80% power). HR was estimated by Cox survival model with adjustment for the minimization factors. Primary analysis performed with at least 24 months (m) follow-up. **Results:** 447 participants were randomized to Cape (n = 223) or Obs (n = 224) from 44 UK sites between 2006-2014. Median age was 63y (IQR 55, 69) and 201 (45%), 232 (52%), and 14 (3%) patients were ECOG PS 0, 1 and 2 respectively. Primary site: 84 (19%) intrahepatic, 128 (28%) hilar, 156 (35%) extrahepatic CCA and 79 (18%) muscle-invasive gallbladder cancers. Resection margins: R0 in 279 (62%) and R1 in 168 (38%); 207 (46%) were node-negative. Follow up was at least 36m in > 80% of surviving patients. By ITT analysis (n = 447), median OS was 51m (95%CI 35, 59) for Cape and 36m (95%CI 30, 45) for Obs, HR 0.80 (95% CI 0.63, 1.04; p = 0.097). Sensitivity analyses with adjustment for nodal status, grade of disease and gender indicated HR 0.71 (95%CI 0.55, 0.92 p < 0.01). In the per-protocol analysis (Cape n = 210, Obs n = 220) median OS was 53m (95%CI 40, NR) for Cape and 36m (95%CI 30, 44) for Obs, HR 0.75 (95%CI 0.58, 0.97; p = 0.028). Median RFS (ITT) was 25m (95%CI 19, 37) for Cape and 18m (95%CI 13, 28) for Obs. Grade 3-4 toxicity was less than anticipated. **Conclusions:** Cape improves OS in BTC when used as adjuvant and should become standard of care. Clinical trial information: ISRCTN72785446.

4007 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Results of the randomized phase II portion of NRG Oncology/RTOG 0848 evaluating the addition of erlotinib to adjuvant gemcitabine for patients with resected pancreatic head adenocarcinoma. *First Author: Howard Safran, Rhode Island Hospital, Providence, RI*

Background: NRG/RTOG 0848 is a 2-step study designed to determine whether erlotinib (E) added to gemcitabine (G) (randomized Ph II) &/or adjuvant radiation with concurrent 5-FU or capecitabine following 6 months of systemic chemotherapy (Ph III), improve survival in patients (pts) with resected pancreatic head adenocarcinoma. The erlotinib results are reported here. **Methods:** Eligible pts include those with resected pancreatic head adenocarcinoma, pathologic stage T1-T3, N0-1, M0; PS 0-1, & CA19-9 ≤ 180 IU/L. Pts in Arms 1 & 2 received G 1 gm/m^2 weekly for 3 weeks in a 28-day cycle for 6 cycles. Pts in Arm 2 also received E 100 mg/day. The primary hypothesis for the E portion was that G+E would increase overall survival (OS) compared to G alone. With a 1-sided alpha of 0.15, 200 OS events provide 80%/90% power to detect a signal for an increase in median OS from 22 to 28.8/30.6 months (mos). OS was estimated by the Kaplan-Meier method & arms compared using the log rank test. The Cox proportional hazards model was used to analyze treatment effect. **Results:** 336 pts were randomized from 11/17/2009 to 2/28/2014, with 163 pts evaluable for G and 159 for G+E. Median age was 63 years (39-86). Most pts had pathologic T3 disease (78%) & CA19-9 ≤ 90 (93%). There are 32 pts (20%) with grade 4 adverse events (AEs) & 2 pts (1%) with grade 5 AEs on G and 27 (17%) & 3 (2%) on G+E arm, respectively. There are fewer grade ≥ 3 GI AEs on the G arm (22%) as compared to the G+E arm (28%), and 110 (69.2%) & 93 (59.6%) pts received at least 85% of planned G dose for the G & G+E arms, respectively. 58% of E pts received at least 85% of planned E dose. The median follow-up for alive pts is 42.5 mos (min-max: < 1-75). With 203 deaths, median & 3-yr OS (95% CI) are 29.9 mos (21.7-33.4) & 39% (30, 45) for G and 28.1 mos (20.7-30.9) & 39% (31, 47) for G+E; log-rank p = 0.62. The hazard ratio (95% CI) comparing OS of G+E to G is 1.04 (0.79- 1.38). **Conclusions:** The addition of adjuvant E to G did not provide a signal for increased OS in pts with resected pancreatic head cancer compared to G alone. Accrual to the trial is continuing to answer the Ph III radiation question. Clinical trial information: NCT01013649.

4008 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine (PAG) vs AG in patients (Pts) with untreated, metastatic pancreatic ductal adenocarcinoma (mPDA). *First Author: Sunil R. Hingorani, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Hyaluronan (HA) accumulation in the tumor microenvironment produces elevated tumor pressure, vascular compression, and reduced drug delivery. PEGPH20 degrades HA, increasing the access and therapeutic index of anticancer agents. **Methods:** In Stage 1 of this phase II study, pts with untreated mPDA were randomized 1:1 to PAG (P; 3 μg/kg IV 2x/wk x 3 wks in C1, then 1x/wk x 3 wks in C2+, plus AG) vs AG every 28 days. An imbalance in thromboembolic (TE) events in the PAG arm led to a clinical hold (~40% of pts discontinued PEGPH20), exclusion of pts at high risk for TE events and enoxaparin prophylaxis in both study arms. In Stage 2, randomization was 2:1 to PAG vs AG. Tumor HA was tested using a novel assay (VENTANA HA RxDx). Primary endpoints were PFS (evaluable pts) and TE event rate (Stage 2). Secondary endpoints were PFS by HA level and ORR. **Results:** 279 pts were randomized; 231 are evaluable for efficacy. Of 246 pts with HA data, 84 (34%) were HA-High. As of December 16, 2016, the primary PFS endpoint was statistically significant for PAG vs AG (HR 0.73, 95% CI 0.53-1.00; p = 0.048) (Table). PFS in HA-High pts was also statistically significant in the PAG vs AG arm (HR 0.51; 95% CI 0.26-1.00; p = 0.048). ORR in HA-High pts was 46% (PAG) vs 34% (AG). Overall survival in HA-High pts (exploratory) was 11.5 months (mo) (PAG) and 8.5 mo (AG) (HR 0.96, 95% CI 0.57-1.61). TE events were similar (PAG 14% vs AG 10%) following enoxaparin initiation. All grade treatment-related AE included peripheral edema (PAG 63% vs AG 26%), muscle spasms (56% vs 3%), neutropenia (34% vs 19%), and myalgia (26% vs 7%). **Conclusions:** Randomized Phase II study met both primary endpoints (PFS and TE event rate), with the largest improvement in the secondary endpoint of PFS in HA-High pts. These data support HA as a potential predictive biomarker for patient selection of PEGPH20, currently investigated in the ongoing global Phase III HALO 301 study with PFS and OS as co-primary endpoints. Clinical trial information: NCT01839487.

	Events/Total, n Median PFS, months		HR	
Population	PAG	AG	(95% CI)	P value
Efficacy Evaluable (n = 231)	100/139; 6.0	65/92; 5.3	0.73 (0.53, 1.00)	0.048
HA-High (n = 84)	24/49; 9.2	19/35; 5.2	0.51 (0.26-1.00)	0.048

4009 Poster Discussion Session; Displayed in Poster Session (Board #1), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A randomized phase II pilot study prospectively evaluating treatment for patients based on ERCC1 for advanced/ metastatic esophageal, gastric, or gastroesophageal junction cancer: SWOG S1201. *First Author: Syma Iqbal, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Platinum based treatment (tx) is standard in HER2 negative patients (pts) with advanced esophagogastric cancer (AEGC). Retrospective data suggest intratumoral ERCC1 levels may determine platinum sensitivity. A randomized phase II study was performed in pts with AEGC to explore whether the efficacy of a platinum 5-FU/LV/Oxaliplatin (FOLFOX) vs. non-platinum containing regimen irinotecan/taxotere (IT) differed according to ERCC1 levels. **Methods:** 203 untreated pts with AEGC, Her2 -, Zubrod PS 0-1, were randomized to FOLFOX vs. IT, stratified by intratumoral ERCC1 low (<1.7) vs. high (≥1.7). Objectives were to assess PFS and OS in all pts treated with FOLFOX compared with IT, and in those pts with low and high ERCC1 levels and to assess for interactive effects between ERCC1 expression and tx arm. **Results:** 86% of pts had ERCC1 values <1.7. Thus, evaluation of ERCC1 pts in the high subgroup was not feasible. Tx groups were well matched by age, sex, race, ERCC1 level, and site. A series of K-M plots were used to explore whether tx arm differences in PFS varied based on ERCC1 levels; little evidence of such was noted. Grade ≥ 3 anemia, dehydration, diarrhea and fatigue were greater in pts with IT. Grade ≥ 3 neuropathy and decreased neutrophils were greater in pts with FOLFOX. **Conclusions:** In all pts, FOLFOX had a statistically superior PFS and RR, when compared with IT. In pts with ERCC1 <1.7 receiving FOLFOX, PFS and RR was statistically superior, with no difference in OS. There was no significant evidence of differential treatment effect on PFS across ERCC1 levels. Clinical trial information: NCT01498289.

All Patients	FOLFOX (n=99)	IT (n=104)	
ERCC1 <1.7	87%	86%	
ERCC1 ≥1.7	13%	14%	
mPFS	5.7 mos (95% CI 4.4-7.1)	2.9 mos (95% CI 1.9-4.1)	HR 0.70 (95% CI 0.52-0.93, p=0.01)
mOS	11.4 mos (95% CI 9.9-13.3)	8.7 months (95% CI 6.2-10.0)	HR 0.82 (95% CI 0.61-1.10, p=0.19)
RR	33/80 (41%, 95% CI 30-52%)	23/86 (27%, 95% CI 17-36%)	p=0.05
ERCC1<1.7	n=86	n=89	
mPFS	5.9 mos (95% CI 4.4-7.0)	2.8 mos (95% CI 1.9-4.1 mos)	HR 0.67 (95% CI 0.49-0.91, p=0.01)
mOS	10.8 mos (95% CI 9.6-12.4)	8.0 mos (95% CI 5.8-9.9 mos)	HR 0.81 (95% CI 0.59-1.12, p=0.21)
RR	31/71 (44%, 95% CI 32-55%)	20/76 (26%, 95% CI 16-36%)	p=0.04

4010 Poster Discussion Session; Displayed in Poster Session (Board #2), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

ABSOLUTE: A phase 3 trial of nanoparticle albumin-bound paclitaxel (*nab*-PTX) versus solvent-based paclitaxel (*sb*-PTX) in patients with pre-treated advanced gastric cancer (AGC)—Efficacy and QOL results. *First Author: Keisuke Koeda, Department of Surgery, Iwate Medical University School of Medicine, Morioka, Japan*

Background: *Sb*-PTX is a standard second-line treatment for patients (pts) with AGC. *Nab*-PTX was developed to avoid the toxicities with use of solvents in *sb*-PTX and potentially improve efficacy. Based on ABSOLUTE trial, we conducted the additional analysis to evaluate the efficacy and QOL of *nab*-PTX and *sb*-PTX. **Methods:** Pts who were refractory to a fluoropyrimidine-containing first-line treatment were randomly assigned (1:1:1) to receive intravenous q3w *nab*-PTX (260 mg/m^2) on day 1 of a 21-day cycle, and q1w *nab*-PTX (100 mg/m^2) or q1w *sb*-PTX (80 mg/m^2) on days 1, 8, and 15 of a 28-day cycle. The primary objective was to evaluate whether q3w *nab*-PTX and q1w *nab*-PTX were non-inferior to q1w *sb*-PTX in terms of overall survival (OS). Tumor shrinkage at 8 weeks and at the time of the best response were also investigated. For the QOL analysis, EQ-5D score were collected at baseline and every 8 weeks during the first 24 weeks, and thereafter at every 24 weeks. Time to deterioration of EQ-5D score was compared between each arm as a minimally important difference of 0.05. **Results:** 741 pts were randomly assigned to q3w *nab*-PTX, q1w *nab*-PTX, or q1w *sb*-PTX. Median OS (months) were 10.3, 11.1, and 10.9, respectively. Q1w *nab*-PTX was non-inferior to q1w *sb*-PTX (hazard ratio 0.97, 97.5% CI 0.76-1.23; non-inferiority one-sided p = 0.0085), whereas q3w *nab*-PTX was not non-inferior to q1w *sb*-PTX (1.06, 95% CI 0.87-1.31; non-inferiority one-sided p = 0.062).The response rate of target lesions at 8 weeks and at the time of the best response (%) were 22.1 and 27.7 for q3w *nab*-PTX, 28.2 and 34.9 for q1w *nab*-PTX, and 18.0 and 25.6 for q1w *sb*-PTX. Median time to deterioration of EQ-5D score (months) were 2.1 in q3w *nab*-PTX, 3.8 in q1w *nab*-PTX, and 3.7 in q1w *sb*-PTX. **Conclusions:** Q1w *nab*-PTX was non-inferior to q1w *sb*-PTX in terms of OS. In addition, q1w *nab*-PTX showed favorable effect in comparison with q1w *sb*-PTX in terms of response rate of target lesions and time at best response. QOL was similar between q1w *nab*-PTX and q1w *sb*-PTX. These results suggest that q1w *nab*-PTX is a useful second-line treatment for pts with AGC. Clinical trial information: 132059.

4011 Poster Discussion Session; Displayed in Poster Session (Board #3), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Cisplatin/5-FU (CF) +/- panitumumab (P) for patients (pts) with non-resectable, advanced, or metastatic esophageal squamous cell cancer (ESCC): An open-label, randomized AIO/TTD/BDGO/EORTC phase III trial (POWER). *First Author: Markus H. Moehler, University Medical Center Mainz, Mainz, Germany*

Background: Most ESCC pts have advanced disease at time of diagnosis. Chemotherapy (CTX) is used to improve quality of life (QoL) and overall survival (OS), but still with limited impact. Prior studies suggested increased efficacy of EGFR antibodies (AB) combined with CF (Lorenzen, *Ann Oncol* 2009). **Methods:** This open-label, randomized (1:1), multicenter, multinational phase III included pts with non-resectable, advanced or metastatic ESCC (RECIST1.1), not radiochemotherapy (RCTX) eligible and ECOG 0-1. Previous CTX in metastatic setting, concurrent RCTX and exposure to EGFR-AB were excluded. Pts received CF (C 100 mg/m² d1 + F 1000 mg/m²/d, d1-4) or CFP (9 mg/kg d1) q3 weeks until disease progression. Due to more Gr3-4 SAEs in the first 60 Pts with CFP, C was reduced to 80mg/m²d1 Tumor assessment was performed q9 weeks. Primary objective was OS: superiority of CFP (9 months [mo]) over CF (6 mo) with 300 pts (90% power). **Results:** Between 6.2012-5.2015, 146/155 pts were randomized. After interim analysis for futility, the trial was stopped. 60(83%) of CFP and 55 (79%) of CF pts had any AE, mostly diarrhea, hypokalemia, hypomagnesaemia, rash, and hand-foot syndrome. Main Gr≥3 AEs were low neutrophils 21/ 24% and anemia 13/16 % for CFP vs CF, respectively. Gr 3-4 skin reactions and rash were higher in CFP (10%) vs CF (0%). Overall, 51/72 (71%) of CFP and 36/70 (51%) of CF had SAE. Main SAE were dysphagia, acute kidney injury, diarrhea, fevers and febrile neutropenia in 6/6%, 7/4%, 7/3%, 3/6% and 6/1% for CFP vs CF, respectively. For all CFP vs CF pts, median OS was 9.4 vs. 10.2 mo (hazard ratio (HR) 1.17, 95%CI 0.79-1.75; P=0.43). For 56 pts treated with cisplatin 100mg/m²d1, OS was 9.4 vs. 12.9 mo (HR 1.83, 95 % CI 0.98-3.42; P=0.06). After C was reduced (80mg/m²), OS (85 pts) favored CFP vs CF, with 9.8 vs. 8.3 mo (HR 0.84, 95%CI 0.49-1.43; P=0.51). Median PFS for all CFP vs CF pts, was 5.3 vs. 5.8 mo. (HR 1.21, 95%CI 0.85-1.73; P=0.29) respectively. **Conclusions:** Addition of Panitumumab to CF provided no additional benefit to chemotherapy alone as first-line treatment of ESCC. Biomarker program is going on for further analyses. Clinical trial information: NCT1627379.

4012 Poster Discussion Session; Displayed in Poster Session (Board #4), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

KEYNOTE-059 cohort 2: Safety and efficacy of pembrolizumab (pembro) plus 5-fluorouracil (5-FU) and cisplatin for first-line (1L) treatment of advanced gastric cancer. *First Author: Yung-Jue Bang, Seoul National University Hospital, Seoul, Republic of Korea*

Background: Preliminary analyses from the global, multicohort, phase 2 KEYNOTE-059 (NCT02335411) study suggested that safety of pembro + 5-FU + cisplatin is manageable as 1L therapy in pts with advanced gastric or gastroesophageal junction (G/GEJ) cancer (cohort 2). We present efficacy and updated safety data from KEYNOTE-059 cohort 2. **Methods:** Cohort 2 enrolled pts ≥18 y with HER2$^-$ recurrent or metastatic G/GEJ adenocarcinoma, measurable disease, no prior therapy for metastatic/advanced disease, and ECOG PS 0-1. Pts received pembro 200 mg on day 1 of each 21-day cycle + cisplatin 80 mg/m^2 for 6 cycles + 5-FU 800 mg/m^2 (or capecitabine 1000 mg/m^2 in Japan) Q3W for up to 2 y or until disease progression, investigator/pt decision to withdrawal, or unacceptable toxicity. PD-L1$^+$pts had expression in ≥1% tumor or stromal cells using IHC (22C3 antibody). End points were safety and tolerability (primary), ORR (RECIST v1.1, by central review), DOR, PFS, and OS (secondary). **Results:** Of 25 enrolled pts, 64% were men, 68% were Asian, and 64% had PD-L1$^+$ tumors. Median age was 64 y. At data cutoff (Oct 19, 2016), median duration of follow-up was 12.2 mo (range, 1.8 to 19.6) and 84% of pts had discontinued treatment, mainly owing to clinical or radiologic disease progression (64%). ORR (CR + PR) was 60% (95% CI, 38.7-78.9) in all pts. Overall, 32% of pts had SD (95% CI, 14.9-53.5), 4% had PD (95% CI, 0.1-20.4), and 4% were not evaluable (95% CI, 0.1-20.4). ORR was 68.8% (95% CI, 41.3-89.0) in PD-L1$^+$ pts and 37.5% (95% CI, 8.5-75.5) in PD-L1$^-$ pts. Median DOR (range) was 4.6 mo (2.6 to 14.4+) in all pts, 4.6 mo (3.2 to 14.4+) in PD-L1$^+$ pts, and 5.4 mo (2.8 to 8.3+) in PD-L1$^-$pts. Median PFS was 6.6 mo (95% CI, 5.9-10.6); median OS was 13.8 mo (95% CI, 7.3-not estimable). Grade 3-4 treatment-related adverse events (TRAEs) occurred in 76% of pts. TRAEs led to discontinuation in 3 pts (grade 3 stomatitis, grade 2 hypoacusis, and grade 1 creatinine increase). No TRAEs were fatal. **Conclusions:** Pembro + 5-FU + cisplatin showed manageable safety and encouraging antitumor activity as 1L therapy for pts with advanced G/GEJ cancer. Further exploration of pembro + 5-FU + cisplatin in this setting is warranted. Clinical trial information: NCT02335411.

4013 Poster Discussion Session; Displayed in Poster Session (Board #5), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (HCC): CheckMate 040 study. *First Author: Todd S. Crocenzi, Providence Cancer Center, Portland, OR*

Background: Many pts with advanced HCC progress on SOC therapy. Nivo is a fully human anti–PD-1 IgG4 mAb that demonstrated durable responses (20% ORR with a median DOR of 9.9 mo; 9-mo OS rate was 74%) in pts with advanced HCC in the dose-expansion (EXP) phase of the CheckMate 040 study (NCT01658878; Melero et al. 2017). Here we present survival and durability of response data in both sor-naive and -experienced pts with advanced HCC in CheckMate 040. **Methods:** Pts naive to or previously treated with sor received nivo in phase 1/2 dose-escalation (ESC; 0.1–10 mg/kg) and -EXP (3 mg/kg) cohorts Q2W regardless of PD-L1 status. Primary endpoints were safety/tolerability (ESC) and ORR (EXP; ORR by investigator [INV] and blinded independent central review [BICR]) using RECIST v1.1. Secondary endpoints included DOR, DCR, and OS. Biomarkers were assessed using pre-treatment tumor samples. **Results:** Overall, pts (N=262) had a median follow-up of 12.9 mo, and 98% had Child-Pugh scores 5–6. In sor-naive pts (n=80), the ORR (INV) was 23%, with 44% of responses (8/18) ongoing (Table). The DCR was 63%; 40% of pts had stable disease ≥6 mo. In sor-experienced pts (n=182; 91% progressed on sor), the ORRs (INV) were 16%–19%. Overall, responses occurred regardless of etiology or tumor cell PD-L1 expression. Nivo had a manageable safety profile consistent with that reported in other tumor types. Updated data with additional 4 mo of follow-up will be presented. **Conclusions:** Nivo demonstrated durable responses with long-term survival and favorable safety in both sor-naive and -experienced pts with advanced HCC. Clinical trial information: NCT01658878.

	Sor Naive		Sor Experienced			
	ESC + EXP (n=80)		ESC (n=37)		EXP (n=145)	
	INV	BICR	INV	BICR	INV	BICR
ORR, n (%)[a]	18 (23)	16 (20)	6 (16)	7 (19)	28 (19)	21 (14)
CR	1 (1)	1 (1)	3 (8)	1 (3)	3 (2)	2 (1)
PR	17 (21)	15 (19)	3 (8)	6 (16)	25 (17)	19 (13)
SD	32 (40)	25 (31)	16 (43)	12 (32)	64 (44)	60 (41)
PD	26 (33)	32 (40)	12 (32)	13 (35)	47 (32)	56 (39)
Not evaluable	4 (5)	5 (6)	3 (8)	4 (11)	6 (4)	8 (6)
DOR, median (95% CI), mo[a]	NR (6–NE)	17 (NE–NE)	17 (7–NE)	19 (3–NE)	12 (7–NE)	NR (11–NE)
12-mo OS rate (95% CI), %	73 (61–81)		58 (40–72)		60 (51–67)	

NR, not reached; NE, not estimable. [a]RECIST v1.1; mRECIST ORRs (BICR): sor naive, 24%; sor experienced, 22% (ESC), 19% (EXP).

4014 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study. *First Author: Yelena Yuriy Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the phase 3 ONO-12 study, 3rd- or later-line nivolumab (N) monotherapy prolonged OS vs placebo in Asian pts with adv G/GEJ cancer (median OS, 5.3 vs 4.1 mo; HR, 0.63; $P < 0.0001$; ASCO-GI 2017, Kang YK et al. *J Clin Oncol.* 2017;35 (suppl 4S) [abstract 2]). The phase 1/2 CheckMate 032 study showed favorable clinical activity of N ± ipilimumab (I) in Western pts with adv CTx-R G/E/GEJ cancer (NCT01928394). We report updated long-term follow-up data of G/E/GEJ pts in CheckMate 032. **Methods:** Pts received N 3 mg/kg Q2W (N3), N 1 mg/kg + I 3 mg/kg Q3W (N1+I3), or N 3 mg/kg + I 1 mg/kg Q3W (N3+I1). Primary endpoint was ORR. Secondary endpoints included DOR, OS, PFS, and safety. Efficacy in pts by PD-L1 status was assessed. **Results:** 160 heavily pretreated pts (79% had ≥ 2 prior Tx) were enrolled (N3, n = 59; N1+I3, n = 49; N3+I1, n = 52); 24% had PD-L1$^+$ (≥ 1%) tumors. ORR was 12% in N3, 24% in N1+I3, and 8% in N3+I1. In pts with PD-L1 ≥ 1%, ORR was 19% (3/16) in N3, 40% (4/10) in N1+I3, and 23% (3/13) in N3+I1; in pts with PD-L1 < 1%, ORR was 12% (3/26), 22% (7/32), and 0% (0/30), respectively. Median DOR was 7.1 mo in N3, 7.9 mo in N1+I3, and NA in N3+I1. OS in all pts and in pts with PD-L1 ≥ 1% is in the Table. Grade 3–4 treatment-related AEs reported in ≥ 10% of pts in any treatment arm were diarrhea (N3, 2%; N1+I3, 14%; N3+I1, 2%), ALT increased (N3, 3%; N1+I3, 14%; N3+I1, 4%), and AST increased (N3, 5%; N1+I3, 10%; N3+I1, 2%). **Conclusions:** N ± I led to durable responses and long-term OS in heavily pretreated Western pts with adv G/E/GEJ cancer, which is consistent with the clinical activity observed in Asian pts in the ONO-12 study. Safety was consistent with prior reports. These data support ongoing investigation of N ± I in pts with adv G/E/GEJ cancer. Clinical trial information: NCT01928394.

OS in all pts and pts with PD-L1 ≥ 1%.

All pts	N3 n = 59	N1+I3 n = 49	N3+I1 n = 52
Median (95% CI), mo	6.2 (3.4, 12.4)	6.9 (3.7, 11.5)	4.8 (3.0, 8.4)
Rate (95% CI), %			
12 mo	39 (26, 52)	35 (22, 49)	24 (13, 37)
18 mo	25 (14, 37)	28 (15, 41)	13 (5, 24)
24 mo	22 (12, 35)	22 (10, 37)	–
Pts with PD-L1 ≥ 1%	n = 16	n = 10	n = 13
Median (95% CI), mo	6.2 (1.9, 12.4)	NA (1.2, NA)	5.6 (2.4, 10.9)
Rate (95% CI), %			
12 mo	34 (12, 57)	50 (18, 75)	23 (6, 47)
18 mo	13 (2, 35)	50 (18, 75)	15 (2, 39)

4015 Poster Discussion Session; Displayed in Poster Session (Board #7), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase I study of AG-120, an IDH1 mutant enzyme inhibitor: Results from the cholangiocarcinoma dose escalation and expansion cohorts. *First Author: Maeve Aine Lowery, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: Mutations in the metabolic enzyme isocitrate dehydrogenase 1 (mIDH1) occur in patients (pts) with cholangiocarcinoma (CC) and are detected in up to 25% of intrahepatic CC. mIDH1 produce the oncometabolite, D-2-hydroxyglutarate (2-HG), resulting in epigenetic and genetic dysregulation and oncogenesis. AG-120 is a first-in-class, potent, oral inhibitor of mIDH1 tested in this phase I study in mIDH1 solid tumors, including CC. **Methods:** AG-120 was escalated in a 3+3 design from 100 mg twice daily to 1200 mg once daily (QD) in 28-day cycles (N = 60, mIDH1 advanced solid tumors). Key eligibility for CC: recurrence of progressive mIDH1 CC following standard therapy (dose escalation) or at least a prior gemcitabine-based regimen (expansion cohort). Response (RECIST 1.1) was assessed every 8 weeks. Plasma and tumor tissue were collected for exploratory analyses. **Results:** Based on the safety, pharmacokinetic, and pharmacodynamic data from dose escalation, the 500 mg QD dose was selected for expansion in mIDH1 CC and other mIDH1 solid tumors. As of Dec 16, 2016, 73 pts with mIDH1 CC had been dosed in the dose escalation (n = 24) and expansion (n = 49) cohorts. Demographics: M/F = 24/49, median number of prior therapies = 2 (range 1–5), ECOG 0–1 = 26/47. There were no dose-limiting toxicities. Treatment-related adverse events (AEs) in ≥5% pts: fatigue (21%), nausea (18%), vomiting (12%), diarrhea (10%), decreased appetite (8%), dysgeusia (5%), QT prolongation (5%). Two (3%) pts experienced related grade 3 AEs: fatigue and low phosphorus. There were no AG-120-related AEs leading to discontinuation. Among the 72 efficacy evaluable (≥1 post baseline response assessment or discontinued prematurely) mIDH1 CC pts (24 in escalation and 48 in expansion cohort), 6% (n = 4) had a confirmed partial response and 56% (n = 40) experienced stable disease. The progression-free survival rate at 6 months was 40%, and 8 pts have been treated with AG-120 for ≥1 year. **Conclusions:** In this pretreated mIDH1 CC population, AG-120 was associated with a favorable safety profile and prolonged stable disease. A global, phase III, randomized, placebo-controlled study of AG-120 in mIDH1 CC has been initiated (ClarIDHy). Clinical trial information: NCT02073994.

4016 Poster Discussion Session; Displayed in Poster Session (Board #8), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

SWOG S1310: Randomized phase II trial of single agent MEK inhibitor trametinib vs. 5-fluorouracil or capecitabine in refractory advanced biliary cancer. *First Author: Richard D. Kim, H. Lee Moffitt Cancer Center, Tampa, FL*

Background: No standard treatment options are available for patients with advanced BC who fail gemcitabine/platinum therapy. The rationale for evaluation of trametinib was based on the presence of MAPK alterations and on earlier promising results with other MEK inhibitors in BC. **Methods:** Pts with histologically proven BC who progressed on gemcitabine/platinum were randomized to trametinib (2mg qd) (Arm A) vs infusional 5FU at 2400 mg/m2 over 46 hours or capecitabine (1000 mg/m^{2}PO days 1-14 BID) (Arm B). Patients were stratified by planned chemotherapy 5FU/LV vs capecitabine; and disease site: cholangiocarcinoma vs gallbladder. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS) and response rate (RR). 80 eligible patients (40 for each arm) were needed to detect an improvement in median OS from 5 months to 8.25 months (1.65 HR). A planned interim futility analysis of objective response was performed on the first 14 pts registered to the trametinib arm. **Results:** The study was stopped early based on the lack of measurable response in the trametinib arm. 53 pts were randomized (27 pts in Arm A vs 26 pts in Arm B). Median age was 62 years and the primary sites of tumor were cholangiocarcinoma (77%) and gallbladder (23%). Median OS was 4.3 months (95% CI 3.1-5.1) for Arm A, and 8.0 months (95% CI 3.2-14.6) for Arm B with a HR of 2.02 (95% CI 1.01-4.03, p=0.05). The median PFS was 1.3 months (95% CI 1.2-1.5) for arm A and 2.8 months (95% CI 1.4-6.9) for arm B with a HR of 2.95 (95% CI 1.38-6.30, p=0.01). Overall RR was 8% (95% CI 0%, 19%) in Arm A vs 10% (95% CI 0%, 23%) in Arm B (p>0.99), and 8% vs 45% had stable disease. Eight pts in Arm A experienced treatment-related ≥ grade 3 toxicities, including one death due to vomiting/dehydration. Seven pts in Arm B experienced treatment-related grade 3 toxicities; no higher grade toxicities were reported. **Conclusions:** To our knowledge, this is the first prospective randomized study of a targeted agent versus chemotherapy for the second line treatment of BC. In this unselected population, the lack of response to trametinib resulted in early closure. The PFS and OS for trametinib were inferior to 5FU. Clinical trial information: 02042443.

4017 Poster Discussion Session; Displayed in Poster Session (Board #9), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

ARQ 087, an oral pan-fibroblast growth factor receptor (FGFR) inhibitor, in patients (pts) with advanced intrahepatic cholangiocarcinoma (iCCA) with FGFR2 genetic aberrations. *First Author: Vincenzo Mazzaferro, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: FGFR genetic aberrations have been implicated in the development and progression of a number of solid tumor types, including iCCA. Pts with unresectable advanced iCCA who relapse after first-line chemotherapy have limited treatment options with poor prognosis. Recently, FGFR2 fusions, observed in up to 20% of pts, have been recognized as a potential therapeutic target. ARQ 087 is a multi-kinase inhibitor with a potent pan-FGFR activity. **Methods:** 119 cancer pts were enrolled in the phase 1/2, open-label study of ARQ 087. Study design and results of the phase 1were reported previously. Assessments included response by RECIST v1.1 every 8 wks, safety (physical examination, vital signs, ECOG PS, laboratory tests), plasma concentrations of phosphate and FGF19, 21 and 23 (potential biomarkers). **Results:** As of 1Feb17, 35 iCCA pts with FGFR2 genetic aberrations were treated with ARQ 087 300 (n = 33) or 400 mg (n = 2) daily. FGFR2 status was identified by FISH or NGS, 29/35 pts were FGFR2 fusion positive (FISH n = 15/18; NGS n = 14/17). Pts were all white, female (60%) with ECOG PS 0 (69%) and median age 58 yrs (31-82). Median number of prior systemic therapies was 1(0-6). Drug-related AEs (all grades) were reported in 89% of pts; the most common (≥10%) included nausea (37%), dry mouth (29%), asthenia (26%), fatigue, vomiting (23%, each), abnormal LFTs, dysgeusia (20%, each), alopecia, diarrhea, vision blurred (14%, each), and conjunctivitis (11%). Grade 3/4 AEs occurring in ≥2 pts were asthenia and abnormal LFTs (6%, each). AEs were mostly (71%) of mild to moderate intensity, manageable and reversible. Median time on treatment was 183 days (95%CI: 166-289). 19 pts were on treatment for > 16 wks, nine are ongoing. 30 pts had at least one post-treatment radiographic assessment: 6 (20%) had PR (32-47% tumor reduction, all FGFR2 fusion positive), 17 SD (7 had tumor reduction between 10 to 25%), and 7 had PD. One pt died prior to scheduled assessment and assessment in 4 pts is pending. **Conclusions:** ARQ 087 demonstrated encouraging antitumor activity and manageable safety profile. Updated data, including safety, efficacy and biomarkers will be presented. Clinical trial information: NCT01752920.

4018 Poster Discussion Session; Displayed in Poster Session (Board #10), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase II trial of gemcitabine (G), cisplatin (C), and nab-paclitaxel (N) in advanced biliary tract cancers (aBTCs). *First Author: Rachna T. Shroff, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BTCs are often diagnosed at an advanced stage and have a poor prognosis. The standard therapy for aBTCs is the combination of GC. However, the median overall survival (mOS) is dismal at 11.7 months (mos) with a median progression free survival (mPFS) of 8 mos. **Methods:** A single arm, phase II study was conducted at MD Anderson and Mayo Clinic Arizona. Patients (pts) with aBTC were treated at initial dose level of G/C/N (in mg/m^2) at 1000/25/125 (n = 27) which was reduced to lower doses due to grade 3/4 hematological (heme) toxicity (tox) - G/C/N: 800/25/100 (n = 33). Cycles were q21 days with restaging q3 cycles until progression. PFS was the primary endpoint (endpt). Using a Bayesian hypothesis test-based design, we assumed mPFS of 8 mos under the null hypothesis (H0), 10 mos under the alternative (H1). Secondary endpts included mOS, RECIST v1.1 response rate (RR), safety and CA19-9 response. **Results:** 60 pts were enrolled with data on 51 available as of the time of this abstract (age: median 60 yrs [range 31-77], ECOG PS 0/1 (17/34), M/F (30/21), intrahepatic cholangiocarcinoma/extrahepatic/gallbladder (32/8/11). Median follow-up was 11.5 mos and median number of treatment (trmt) cycles = 5. Pts at initial dose level had significant grade 3/4 heme tox: neutropenia, febrile neutropenia, anemia, and thrombocytopenia leading to trmt discontinuation in 6/27 pts. After dose reduction to G/C/N (in mg/m^2) at 800/25/100, trmt was better tolerated with only 4 pts experiencing grade 4 heme tox. Non-heme tox were grade 3 in 10 pts: nausea/vomiting, diarrhea, thromboembolic event/CVA, hypokalemia, constipation, cystitis, LFT elevations. In the initial 51 pts, mPFS = 11.4 mos (95% CI: 6.1, not reached) and mOS not reached (estimated > 20 mos, 1-year survival rate 66.7%; 95%CI: 65.9-92.2%). 34 pts evaluable for response: disease control rate (PR+CR+SD)-82.3% and RR-32.3%. 3 unresectable cases were operated post trmt with 1 pathologic CR. **Conclusions:** The combination of GCN was well tolerated at adjusted doses and demonstrates encouraging preliminary efficacy having met its mPFS endpt and a 1-year survival rate higher than historical control. These results merit evaluating GC +/-N in a randomized controlled study. Clinical trial information: NCT02392637.

4019 Poster Discussion Session; Displayed in Poster Session (Board #11), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Intergroup phase III trial of neo-adjuvant chemotherapy, followed by chemoradiation and surgery with and without cetuximab in locally advanced esophageal carcinoma: First results from the SAKK 75/08 trial. *First Author: Thomas Ruhstaller, Kantonsspital, St. Gallen, Switzerland*

Background: We compared chemoradiotherapy followed by surgery with the addition of neoadjuvant and adjuvant cetuximab (cetux) in patients with esophageal carcinoma. **Methods:** Pts with resectable esophageal cancer (T2N1-3;T3-4aNx) received two cycles of induction chemotherapy (docetaxel 75mg/m2, cisplatin 75mg/m2) followed by chemoradiation (45 Gy, docetaxel 20mg/m2 and cisplatin 25mg/m2 weekly) and surgery or the same treatment with addition of neoadjuvant cetux 250mg/m^2 weekly and adjuvant cetux 500mg/m2 bi-weekly for three months. Primary endpoint was progression-free survival (PFS). After a median follow-up of 4y 166 of the planned 180 events occurred (plateau reached). **Results:** 300 pts were treated between 2010-13: 88% male, median age 61y, 63% adenocarcinoma, 85% cT3/4a, 90% cN+. 84% completed neoadjuvant therapy, 87% were operated (cetux: 89%, control: 86%), 67% started and 50% completed adjuvant cetux-therapy. The R0 resection rate was 95% in the cetux-arm and 97% in the control-arm, there were 10 and 14 treatment-related deaths and 9 and 4 postoperative in-hospital deaths, respectively. Major differences in adverse events (grade >2) with addition of cetux were higher rate of allergic reactions and hypomagnesemia, but lower rate of dysphagia (-15%) and esophagitis (-4%) during chemoradiation. **Conclusions:** The addition of cetuximab to a multimodal therapy showed a statistically significant reduction of loco-regional recurrences which led to a statistically non-significant, but clinically relevant improvement of PFS and OS. Clinical trial information: NCT01107639.

	Control-arm	Cetux-arm	Log-rank test p-value	Hazard ratio (HR)
Progression-Free Survival				
Median PFS (mo)	24 (18 – 34)	35 (24 – nr)	p = 0.13	HR = 0.79 (0.58 - 1.07)
- 3y	41%	50%		
- 4y	37%	48%		
Overall Survival (OS)				
Median OS (mo)	36 (26 – 50)	61 (44 – nr)	p = 0.055	HR = 0.73 (0.52 - 1.01)
- 3y	51%	62%		
- 4y	43%	56%		
Loco-regional failure (LRF)				
Median time to LRF	nr	nr	p = 0.017	HR = 0.53 (0.31 - 0.90)
Rates free of LRF				
- 3y	63%	79%		
- 4y	61%	79%		
Distant failure (DF)				
Median time to DF	nr	nr	p = 0.97	HR = 1.01 (0.64 - 1.59)
Rates free of DF				
- 3y	67%	65%		
- 4y	64%	64%		

nr = not reached, mo = months, y = years

4020 Poster Discussion Session; Displayed in Poster Session (Board #12), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A randomized phase III trial on the role of esophagectomy in complete responders to preoperative chemoradiotherapy (CRT) for esophageal squamous cell carcinoma (ESCC). *First Author: Sook Ryun Park, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*

Background: To investigate the role of esophagectomy in pts who achieved clinical complete response (cCR) with CRT for locally advanced ESCC. **Methods:** Pts with resectable cT3-T4a anyN M0 or anyT N+ M0 thoracic ESCC, 20-75 yrs, and ECOG PS ≤2 received 2 cycles of induction XP (capecitabine 1000 mg/m^2 bid D1-14 + cisplatin 60 mg/m^2 D1 q3w) followed by CRT (50.4 Gy/28 fx, X 800 mg/m^2 bid x 5 d/w and P 30 mg/m^2 weekly). Pts with cCR were randomized to surgery (S) or observation (O). The primary endpoint was disease-free survival (DFS). **Results:** From Nov 2012 to March 2016, 86 pts (17.7% of the target number) were enrolled. The slow accrual caused early closure of the study. 81 pts completed CRT, and 38 pts (44.2%) achieved cCR among whom 37 pts were randomized to S (n=19) or O (n=18). The compliance rates differed between the allocated arms (68.4% in the S arm vs 100% in the O arm; *P*=0.020). In both Intent-to-treat (ITT) and as-treated analysis, there were no significant differences in DFS, PFS, TTP, and OS in both arms although the S arm tended to have better DFS, PFS and TTP than the O arm (Table 1). In the as-treated analysis, the relapse rate was 23.1% (3/13) in the S arm and 45.8% (11/24) in the O arm (*P*=0.288). All 10 locoregional only relapse in the O arm were considered resectable, of whom 8 pts underwent surgery (n=7) or endoscopic dissection (n=1). In the as-treated analysis, the S arm had a higher R0 resection rate (92.3% vs 42.9%; *P*=0.031) and lower pTNM stages (*P*=0.0005) than the O arm. **Conclusions:** Watchful waiting might be a valuable option in pts with thoracic ESCC who have cCR to CRT. Further large-scale studies are necessary to confirm our results and to optimize treatment decision in the individual pt. Clinical trial information: NCT01740375.

Survival outcomes between the surgery and observation arms.

	ITT Analysis			As-Treated Analysis		
	S (n=19)	O (n=18)	P	S (n=13)	O (n=24)	P
DFS median	Not reached (NR)	21.7 mo (95% CI 0–45.9)	0.262	NR	27.7 mo (95% CI 0–61.2)	0.273
2-yr DFS	66.7% ± 11.1%	42.7% ± 13.1%		66.7% ± 13.6%	50.2% ± 10.9%	
PFS, median	NR	25.0 mo (95% CI 2.4–48.8)	0.282	NR	25.6 mo (95% CI 0–55.9)	0.300
TTP, median	NR	25.6 mo (95% CI 2.7–48.5)	0.257	NR	31.9 mo (95% CI 0.6–63.2)	0.203
OS, median	NR	NR	0.560	NR	NR	0.903

4021 Poster Session (Board #13), Sat, 8:00 AM-11:30 AM

Phase III study of individualized intraperitoneal/intravenous/oral chemotherapy compared with standard intravenous/oral chemotherapy in patients with advanced gastric cancer. *First Author: Yang Yang, The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University and Clinical Cancer Institute of Nanjing University, Nanjing, China*

Background: Tumor mRNA expression levels may have a promising role as potential predictive biomarkers for chemotherapy. Intraperitoneal (IP) chemotherapy provides sustained high local concentrations, and its efficacy has been shown in ovarian cancer and gastric cancer patients with peritoneal metastasis. We developed a regimen combining IP/intravenous(IV)/oral chemotherapy for the treatment of advanced gastric cancer patients with individualized chemotherapeutics according to mRNA expression. This multicenter phase III study evaluated the efficacy of individualized multi-route chemotherapy compared to standard systemic chemotherapy. **Methods:** Eligibility criteria included pathologically confirmed advanced gastric adenocarcinoma, and no prior chemotherapy. Patients were randomized 3:1 to an individualized arm (IN) and standard arm (ST). Randomization was stratified by center. Patients in individualized arm first underwent mRNA expression (BRCA1/TOPO1/TS) to choose sensltive chemotherapeutics from oxaliplatin/cisplatin/docetaxel/irinotecan/S-1 and then received individualized IP/IV/oral chemotherapy. The primary endpoint was overall survival (OS). Secondary endpoints were response rate, progression-free survival (PFS), and safety. **Results:** Between April 2013 and December 2015, 231 patients were enrolled, and 218 patients were included in the efficacy analysis. Baseline patient characteristics were balanced between the two arms. The median OS for IN and ST were 16.3 and 14.1 months, respectively (adjusted hazard ratio [aHR] 0.77, 95% confidence interval [CI] 0.61-0.98, $p < 0.05$). The overall response rate was 44.0% in the IN arm, and 33.9% in the ST arm ($p < 0.05$). Both regimens were tolerable. **Conclusions:** The primary analysis showed the statistical superiority of the individualized multi-route regimen. It suggested clinical efficacy of this regimen in patients with advanced gastric cancer. Clinical trial information: ChiCTR-IPR-15006201.

4022 Poster Session (Board #14), Sat, 8:00 AM-11:30 AM

Clinical impact of microsatellite instability in patients with stage II and III gastric cancer: Results from the CLASSIC trial. *First Author: Yoon Young Choi, Yonsei University Health System, Seoul, Republic of Korea*

Background: The clinical implications of microsatellite instability (MSI) in gastric cancer are unclear. We investigated the usefulness of MSI status as a predictor of prognosis and responsiveness to adjuvant chemotherapy in patients with stage II and III gastric cancer. **Methods:** Tumor specimens and clinical information were collected from patients enrolled in the CLASSIC trial, a randomized controlled study of capecitabine plus oxaliplatin-based adjuvant chemotherapy. Five mononucleotide markers were used to assess tumor MSI status. **Results:** Of 592 specimens, 36 (6.1%) were MSI-high (MSI-H), whereas others were MSI-low or microsatellite-stable (MSS). Among 286 patients not treated with adjuvant therapy, those with MSI-H tumors had a better 5-year disease-free survival rate than did those with MSI-low/MSS tumors (hazard ratio adjusted by age, sex, tumor grade, disease stage, tumor location: 0.244 [95% confidence interval, 0.069–0.867]; $p = 0.0292$). Among 306 patients who received adjuvant chemotherapy, MSI-H status did not correlate with better disease-free survival (adjusted hazard ratio: 0.561 [95% confidence interval, 0.190–1.654]; $p = 0.2946$). Benefits from adjuvant chemotherapy differed by MSI status; although adjuvant chemotherapy improved disease-free survival among patients with MSI-low/MSS (adjusted hazard ratio: 0.634 [95% confidence interval, 0.485–0.828]; $p = 0.0008$), no benefit was observed in the MSI-H group (adjusted hazard ratio: 1.877 [95% confidence interval, 0.284–12.390]; $p = 0.5130$). **Conclusions:** Among patients with stage II and III gastric cancer, a MSI-H status correlated with a favorable prognosis, and adjuvant chemotherapy benefited those with MSI-L/MSS tumors but not those with MSI-H tumors.

4023 Poster Session (Board #15), Sat, 8:00 AM-11:30 AM

PD-L1 expression and response to neo-adjuvant chemotherapy in esophageal adenocarcinoma. *First Author: Eileen E. Parkes, Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, United Kingdom*

Background: Programmed Death-1 Receptor (PD-1) and its ligand (PD-L1) downregulate T cell activation and suppress tumor killing. This study investigated the role of PD-L1 and tumor infiltrating lymphocytes (TILs) in response to neo-adjuvant therapy and prognosis in esophageal adenocarcinoma (EAC). **Methods:** Transcriptional profiling of 273 formalin fixed paraffin embedded pre-treatment endoscopic EAC biopsies was carried out using the Almac Diagnostics Xcel array and the expression levels of PD-L1 probesets corresponding to protein encoding extracted. Response was assessed by tumor regression grade (TRG; score ≤ 2 = response). Immunohistochemistry (IHC) for PD-L1 and CD8 was performed in matched resection specimens from 135 patients. All EAC patients were treated with cisplatin-based neo-adjuvant chemotherapy followed by surgical resection between 2003 and 2014 at four UK centers as part of the OCCAMS consortium. Associations between expression, protein levels and TRG were assessed by Kruskal-Wallis, Mann-Whitney Unpaired, Spearman rank correlation or chi-squared tests. Survival analysis was performed using Cox Proportional Hazards regression. **Results:** High PD-L1 gene expression in the pre-chemotherapy biopsies was associated with pathological response (TRG ≤ 2; $p = 0.02$) following neo-adjuvant chemotherapy. PD-L1 ($> 5\%$) was expressed in the tumor or stromal cells in 4% and 15% of resection specimens respectively. PD-L1 gene and IHC expression ($> 5\%$) were closely associated between the biopsies and both the tumor ($p = 0.032$) and stroma ($p = 0.019$) of the matched resection specimens. Patients with PD-L1 IHC positivity in tumor cells demonstrated improved relapse-free survival (HR 0.314; 95% CI 0.099-0.997; $p = 0.049$) and positive stromal PD-L1 IHC staining correlated with pathological response ($p = 0.05$). Biopsy gene expression of PD-L1 and CD8 was closely associated ($p = 0.024$) and the presence of CD8+ TILs in the microenvironment strongly correlated with tumor ($p < 0.001$) and stromal ($p < 0.001$) PD-L1 positivity. **Conclusions:** High PD-L1 expression in the pre-treatment biopsies in EAC is predictive of response to neo-adjuvant chemotherapy and may aid selection of conventional and immune-targeted agents.

4024 Poster Session (Board #16), Sat, 8:00 AM-11:30 AM

VIKTORY trial: Report on AZD1775/paclitaxel in TP53 mutation (+) GC, selumetinib/paclitaxel in ras aberrant GC, AZD5363/paclitaxel in PIK3CA mt and biomarker negative, savolitinib/docetaxel in met (+), and vistusertib/paclitaxel in RICTOR(+) GC. *First Author: Jeeyun Lee, Samsung Medical Center, Seoul, Republic of Korea*

Background: The VIKTORY trial is a biomarker-based umbrella trial in GC. **Methods:** See table below. **Results:** From June 2014 to Jan 2017, 432 metastatic gastric cancer patients were enrolled. 124 (28.7%) were treated on one of the associated study protocols. At January 2017, 25 pts were allocated to selumetinib/paclitaxel arm, 25 to AZD1775/paclitaxel arm, 16 to AZD5363/paclitaxel arm, 16 to vistusertib/paclitaxel arm, 4 to savolitinib monotherapy, 19 to savolitinib/docetaxel arm, 19 to phase I AZD6738/paclitaxel arm. Initial efficacy signals have been seen in several arms (selumetinib/paclitaxel, 6 of 21 evaluable patients in PR). Correlative analyses between molecular signatures and treatment response are ongoing and will be presented at the meeting. For vistusertib/paclitaxel in the biomarker negative arm, we found RICTOR amplification as a promising predictive biomarker for response. Two (of three) GC patients with RICTOR amplification achieved PR to vistusertib/paclitaxel. **Conclusions:** This is one of the first attempts to undertake a biomarker-driven trial in metastatic GC. 28.7% of the patients were guided to one of the parallel arms based on molecular screening outcomes. We were able to identify potential molecular targets in the biomarker-negative arm, for further assessment in new protocols. Clinical trial information: 02299648.

Biomarker	Treatment arm
RAS amp/mt or MEK signature	selumetinib(AZD6244, ARRY-142886, licensed from Array BioPharma), 75 mg bd continuous/docetaxel 60mg/m^2 q 3 wks
PIK3CA amp/mt	AZD5363, 400 mg bd 4d on 3d off/paclitaxel 80 mg/m^2 D1,8,15 q28d
MET amp or MET overexpression	1) savolitinib (AZD6094, HMPL504), 600 mg qd/docetaxel 60 mg/m^2 q 3wk; 2) savolitinib 800mg OD q 3 wks
TP53 mt	AZD1775, 225 mg BD (x 5 doses) days 1~3 q3w paclitaxel 80 mg/m^2 D1,8,15
Biomarker negative (non-actionable)	vistusertib 50 mg bd 3 d on 4 d off, of a 7 d/paclitaxel 80 mg/m^2 D1,D8, D15 q 28 d
RICTOR amplification	vistusertib 50 mg bd 3 d on 4 d off, of a 7 d / paclitaxel 80 mg/m^2 D1,D8,D15 q 28 d
TSC1 TSC2 null	vistusertib 50 mg bd 3 d on 4 d off, of a 7 d/paclitaxel 80 mg/m^2 D1,D8, D15 q 28 d

4025 Poster Session (Board #17), Sat, 8:00 AM-11:30 AM

Correlation of benefit from immune checkpoint inhibitors with next gen sequencing (NGS) profiles in esophagogastric cancer (EGC) patients. *First Author: Geoffrey Yuyat Ku, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Immuno-oncology (IO) with anti-PD-1 and –PD-L1 antibodies (Abs) is active in EGC but only benefits a minority of Pts. Biomarkers are needed to identify responders. **Methods:** We reviewed our experience of Pts treated with anti-PD-1/PD-L1 Abs and correlated their outcomes with PD-L1 and mismatch repair protein (MMR) status by immunohistochemistry (IHC), as well as MSK-IMPACT (≥340-gene) NGS profile. MSIsensor from IMPACT assesses microsatellite instability phenotype, while ≥20 mutations (or 17 mutations/Mb) strongly correlates with MMR-deficiency (dMMR) by IHC (J Clin Oncol 2016;34:2141). Progression-free (PFS) and overall survival (OS) were analyzed from the start of IO. **Results:** 71 Pts were identified, with 3 Pts receiving 2 IO regimens. 66 had adenoCAs and 5 had squamous CAs. Median age 58, 77% male, 96% had received ≥2 prior chemo regimens. 39 (55%), 18 (25%) and 17 Pts (24%) respectively received anti-PD-1, anti-PD-L1 and anti-CTLA-4 plus anti-PD-1/PD-L1 Abs. 6 Pts (8%) had objective response (2 complete responses or CRs) and the median PFS and OS are 1.6 and 4.7 mos; 2-yr OS is 17%. PD-L1 IHC was performed in 16 Pts (23%; 7 +ve), MMR was tested in 20 Pts (28%; 4 dMMR) and IMPACT was obtained in 44 Pts (62%). All 4 dMMR tumors were also MSI by MSIsensor and had a median of 46 mutations (range, 29-63) or, equivalently, 33 mutations/Mb (range, 21-46); 2 of 2 dMMR tumors tested PD-L1 +ve. 3 of the 4 Pts with dMMR/MSI tumors had a response (including 1 CR) and the median OS of these 4 Pts is not reached with 23+ months of follow-up. Finally, a patient whose tumor is MMR-proficient, not MSI but has 15 mutations (including in *POLD1*), achieved an ongoing CR at 37+ mos. For the 44 Pts with IMPACT testing, there appeared to be improved OS for tumors with ≥10 vs. <10 mutations/Mb (2-yr OS 80% vs. 12%, p=0.03). **Conclusions:** Pts with tumors that are MSI or have ≥10 mutations/Mb on MSK-IMPACT appear to derive significant benefit from IO. MSK-IMPACT can offer novel information, identify novel mutations (e.g. *POLD1*) and may be used to help select Pts for IO. We are seeking to define a mutation no. cut-off that can serve as a biomarker and updated data will be presented.

4026 Poster Session (Board #18), Sat, 8:00 AM-11:30 AM

Association of a DNA damage response deficiency (DDRD) assay with prognosis in resected esophageal and gastric adenocarcinoma. *First Author: Richard C. Turkington, Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, United Kingdom*

Background: Current strategies to guide the selection of neo-adjuvant or adjuvant therapy in esophageal and gastric adenocarcinomas (EAC/GAC) are inadequate. We assessed a clinically validated 44 gene DNA Damage Response Deficiency (DDRD) assay to predict prognosis following neo-adjuvant DNA damaging chemotherapy (CT) in EAC and adjuvant CT or chemoradiotherapy (CRT) in GAC. **Methods:** Transcriptional profiling of 273 formalin fixed paraffin embedded pre-treatment endoscopic EAC biopsies was performed using the Almac Diagnostics Xcel array. All EAC patients were treated with cisplatin-based neo-adjuvant chemotherapy followed by surgical resection between 2003 and 2014 at four UK centers in the OCCAMS consortium. Further validation was performed using a publically available dataset of 270 resected gastric cancers treated with adjuvant platinum-based CT, CRT or surgery alone at the Samsung Medical Centre, Seoul, Korea. The association between the DDRD score and prognosis was assessed by Kaplan-Meier analysis and Cox Proportional Hazards regression. **Results:** A total of 66 EAC samples (24%) were characterized as DDRD positive with the remaining 207 samples (76%) being DDRD negative. DDRD assay positivity was associated with improved DFS (HR 0.58; 95% CI 0.36-0.93; p = 0.024) and OS (HR 0.56; 95% CI 0.34-0.92; p = 0.023) following multivariate analysis. DDRD positive patients had a higher pathological response rate (p = 0.033) and a higher rate of loco-regional versus distant relapse (30% vs 20%; p = 0.013). For GAC, 132 samples (49%) were characterized as DDRD positive with the remaining 138 (51%) being DDRD negative. DDRD positivity was associated with improved DFS (HR 0.48; 95% CI 0.25-0.96; p = 0.037) following D2 gastrectomy and adjuvant CT or CRT. DDRD status was not associated with DFS in the surgery alone cohort (HR 0.87; 95% CI 0.55-1.38; p = 0.562). **Conclusions:** The DDRD assay is strongly predictive of benefit from DNA damaging neo-adjuvant CT and esophagectomy in EAC and gastrectomy and CT/CRT in GAC and can be applied to routine diagnostic material.

4027 Poster Session (Board #19), Sat, 8:00 AM-11:30 AM

A randomized, double-blind, multi-center phase III study evaluating paclitaxel with and without RAD001 in patients with gastric or esophagogastric junction carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (RADPAC). *First Author: Sylvie Lorenzen, Third Department of Internal Medicine (Hematology/Medical Oncology), Klinikum rechts der Isar, Technische Universitat Munchen, Munich, Germany*

Background: There is a need for effective treatments in the second- or further line setting in advanced gastric cancer, especially for new agents. In the current trial we evaluated paclitaxel with RAD001 (everolimus) in patients with gastric carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen. **Methods:** This is a randomized, double-blind, multi-center phase III study. Patients with gastric carcinoma or adenocarcinoma of the esophagogastric junction (EGJ) who have progressed after treatment with a fluoropyrimidine/platinum-containing regimen were randomly assigned to receive Paclitaxel (80 mg/m2) on day 1, 8 and 15 plus placebo (arm A) or RAD001 (10mg daily, arm B) d1-d28, repeated every 28 days as 2nd, 3rd or 4th line therapy. Primary end point was overall survival (OS), secondary endpoints were best overall response, disease control rate, progression free survival (PFS) and toxicity. **Results:** 300 patients (median age: 62 years; median lines prior therapy: 2; 47.7% of patients had prior taxane therapy) were randomly assigned (Arm A, 150, Arm B, 150). In the intention to treat population, there was no significant difference in median PFS (placebo, 2.07 vs. RAD001, 2.2 months, HR 0.88, p = 0.3) or median OS (placebo, 5.0 vs. RAD001, 6.1 months, HR 0.93, p = 0.54). For patients with prior taxane use, RAD001 improved PFS (placebo 1.8 vs. RAD001, 2.7 months, HR 0.69, p = 0.03) and OS (placebo 3.9 vs. RAD001, 5.8 months, HR 0.73, p = 0.07). Combination of paclitaxel and RAD001 was tolerable, but the RAD001 arm was associated with significantly more grade 3-5 mucositis (13.3% vs. 0.7%; p < 0.001). **Conclusions:** The addition of RAD001 to paclitaxel/RAD001 did not improve outcomes in pretreated metastatic gastric/EGJ cancer. Of note, activity was seen in the taxane pretreated group. Additional biomarker studies are planned to look for subgroups that may have a benefit. Clinical trial information: 2009-018092-14.

4028 Poster Session (Board #20), Sat, 8:00 AM-11:30 AM

Results of interim analysis of the multicenter randomized phase III SENORITA trial of laparoscopic sentinel node oriented, stomach-preserving surgery versus laparoscopic standard gastrectomy with lymph node dissection in early gastric cancer. *First Author: Keun Won Ryu, Gastric Cancer Branch, Research Institute and Hospital, National Cancer Center, Goyang, South Korea*

Background: The benefits and hazards of laparoscopic sentinel node oriented stomach-preserving surgery, compared to those of laparoscopic standard gastrectomy with lymph node dissection in early gastric cancer (EGC), are unknown. The SENORITA trial investigated the clinical impact of laparoscopic sentinel node oriented stomach-preserving surgery in EGC. **Methods:** Other than those with absolute indication for endoscopic resection, eligible patients had EGC confined to the mucosa and submucosa, with diameter ≤ 3cm, regardless of histology on preoperative evaluation. Patients were randomized for laparoscopic standard gastrectomy or laparoscopic stomach-preserving surgery. Patients were stratified based on depth (mucosa vs. submucosa) and size (≤ 2cm vs. 2 < ≤ 3cm) of the EGC and by participating institution. The primary endpoint was 3-year disease-free survival (3yDFS). The expected 3yDFS was 97% and non-inferior margin was 5%. 580 patients and 24 events were needed to show non-inferiority with 80% power. One interim analysis was planned after 12 events (50%) occurred. Using the O'Brien-Fleming error spending function, the two-sided nominal significance level for the interim analysis would be 0.0054. **Results:** From March 2013 to May 2016 462 patients were randomized; analysis was performed in 421 after a dropout of 41 patients. Laparoscopic stomach-preserving surgery was possible in 75.6% by study protocol. Interim analysis was conducted based on 12 events (median follow-up: 15.89 months). The 3yDFS in the laparoscopic standard gastrectomy arm was 96%; the 3yDFS in the laparoscopic stomach-preserving surgery arm was 93%, (99.46% CI: -3.18%, 9.18%). The postoperative complication rates were 15.0% and 12.9%, respectively (p = 0.542). **Conclusions:** In this interim analysis, laparoscopic sentinel node oriented stomach-preserving surgery did not show non-inferiority for 3yDFS. The follow-up time was not mature enough to evaluate non-inferiority. Further follow-up will elucidate the role of laparoscopic sentinel node oriented stomach-preserving surgery. Clinical trial information: NCT01804998.

4029 Poster Session (Board #21), Sat, 8:00 AM-11:30 AM

Short-term outcomes from a multi-institutional, phase III study of laparoscopic versus open distal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer (JLSSG0901). *First Author: Sang-Woong Lee, Osaka Medical College, Osaka, Japan*

Background: The safety of laparoscopic gastrectomy for advanced gastric cancer is controversial. We conducted a multi-institutional, randomized controlled trial to compare short- and long-term outcomes of laparoscopic distal gastrectomy (LAP) with D2 lymph node dissection for advanced gastric cancer in comparison to open distal gastrectomy (OP) in Japan (UMIN000003420). We herein demonstrate short-term outcomes of this trial. **Methods:** Patients with potentially curable gastric cancer (T2-T4, N0-2 and M0) by distal gastrectomy were eligible for inclusion. Between November 2009 and July 2016, 507 patients were randomly assigned to either the LAP group (n = 252) or the OP group (n = 255). Only credentialed surgeons in both the procedures from 37 Japanese institutions participated in the study. The primary endpoint was 5-year relapse free survival. Secondary endpoints were 5-year overall survival, adverse events and short-term clinical outcomes. **Results:** According to study protocol, 47 patients among the total eligible patients were excluded because of distant metastasis or tumor extension intraoperatively. The remaining 460 patients underwent distal gastrectomy with D2 lymph node dissection and were analyzed as per protocol. Estimated blood loss was lower in LAP than in OP (30 vs. 150 ml, $P < 0.001$) and operative time was longer in LAP than in OP (291 vs. 205 min, $P < 0.001$). Post-operative analgesics use was less in LAP than in OP (38.3 vs. 53.6 %, $P = 0.001$), and first day of flatus was shorter in LAP than in OP (2 vs. 3 days, $P < 0.001$). There were no significant differences in all grade intra-operative complications (LAP 0.9% vs. OP 2.6%, $P = 0.285$). In addition, there were no significant differences in grade 3 and higher post-operative complications between the two groups (LAP 3.1% vs. OP 4.7%, $P = 0.473$). Hospital mortality was 0.4 % in each group. **Conclusions:** Credentialed surgeons could safely perform laparoscopic distal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer. The laparoscopic approach could be accepted without increasing major surgical complications in this setting. Clinical trial information: 000003420.

4030 Poster Session (Board #22), Sat, 8:00 AM-11:30 AM

Assessment of conditional survival probability in resected esophageal adenocarcinoma. *First Author: Donna M. Graham, Queens University of Belfast, Belfast, United Kingdom*

Background: Prognostication for cancer patients is based upon factors determined at baseline and becomes less relevant over time. Conditional survival (CS) estimates future prognosis based upon survival to a specific time point after treatment. We analyzed CS for patients in the United Kingdom (UK) undergoing surgery and neoadjuvant chemotherapy (NAC) for gastro-esophageal junction (GEJ) or esophageal adenocarcinoma (EAC). **Methods:** 1409 patients with GEJ/EAC treated with NAC and surgical resection at 7 centers across the UK from 2002-2014 were identified. Clinicopathological and survival data was collected as part of the Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) consortium. A multivariable Cox survival model was used to analyze the association of factors such as node positivity (N+), lymphovascular invasion (LVI+), tumor differentiation, circumferential resection margin involvement (CRM+) and pathological response by tumor regression grade (TRG ≤ 2) with risk of relapse (RR) or death from time of surgery. **Results:** Of 1409 patients, 726 (51.5%) were aged <65 years, and 1195 (84.8%) were male. Hazard ratios (HR) for RR conditional on recurrence-free (RF) years to date are detailed below. N+ was the most robust predictor of relapse and mortality over time. LVI+ and moderate to poor differentiation influenced relapse in the first 2 years whereas CRM+ and TRG≤ 2 had their greatest effect in the year following surgery. Age, sex, and year of surgery had no association with RR or mortality. Similar patterns were observed for risk of death. **Conclusions:** CS provides a more dynamic estimate of future RR and survival among patients who have accrued survival time, especially in patients with high-risk features. CRM+ and LVI+ govern early survival events but as time from surgery increases these factors become less relevant.

Probability of relapse within timeframe conditional on RF status.

	0-1yr		1-2yr		2-3yr		3-5yr	
	HR	p-value	HR	p-value	HR	p-value	HR	p-value
N+	2.06	<0.001	2.76	<0.001	2.91	0.002	2.81	0.012
LVI+	1.80	0.001	1.63	0.009	0.62	0.242	0.85	0.722
Mod/poor diff	1.73	0.001	1.50	0.033	0.91	0.826	1.97	0.187
CRM+	1.68	<0.001	1.00	0.986	1.14	0.664	1.41	0.432
TRG ≤2	2.38	0.015	1.22	0.488	1.47	0.447	4.20	0.058

4031 Poster Session (Board #23), Sat, 8:00 AM-11:30 AM

Impact of chemoradiotherapy on PD1/PDL1 expression and clinical outcomes in gastroesophageal cancers. *First Author: Arsen Osipov, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Expression of the immune modulating proteins, programmed death receptor-1 (PD1) and its ligand (PDL1), in gastrointestinal malignancies is associated with poor prognosis. PD1/PDL1 expression levels have also been identified as predictors of response to checkpoint inhibition. Minimal data is available on how expression of PD1 and PDL1 is influenced by chemoradiotherapy (CRT). In this study, we investigated the relationship between PDL1/PD1 expression, CRT, and clinical outcomes in gastro-esophageal (GE) cancer. **Methods:** With IRB approval, we identified 28 patients with gastric cardia or GE junction tumors who underwent neoadjuvant standard CRT followed by surgical resection. Pre-CRT biopsies and post-CRT surgical specimens were analyzed using quantitative immunohistochemistry for the expression of PDL1 and PD1. Samples were categorized as trace-low (TL) or moderate-high (MH) expressors of PDL1 and PD1. The impact of these and other clinical and pathologic variables on overall survival (OS) was assessed using multivariate cox proportional hazards modeling. Co-expression of PDL1 and PD1 in matched samples was determined by regression analysis. **Results:** Following CRT, PDL1 and PD1 expression increased in 54% and 32% of patients, respectively. On multivariate analysis, patients with MH expression of PD1 after CRT irrespective of pre-CRT expression levels had a significant decrease in OS compared to those with TL expression (median survival 23.1 vs 74.1 months; HR,3.31; CI,1.05-10.35; $p = 0.039$). In patients with gastric confined tumors, an increase in PD1 expression from TL to MH after CRT was associated with significantly lower OS rates ($p = 0.003$). Regression analysis of PD1 to PDL1 was significant ($p < 0.01$) both before and after CRT, with a correlation coefficient of 0.34 in pre-CRT and 0.49 in post-CRT specimens. **Conclusions:** Elevated expression of PD1 is associated with poor OS in patients with GE cancer. Neoadjuvant CRT upregulates both PDL1 and PD1. In gastric cancer patients, this led to significantly worse survival. These data identify potential mechanisms of resistance and suggest a role for checkpoint inhibitors in combination with CRT.

4032 Poster Session (Board #24), Sat, 8:00 AM-11:30 AM

Current trends and survival in patients with esophageal squamous cell carcinoma: An analysis of the National Cancer Database from 2007 to 2013. *First Author: Brandon C. Chapman, University of Colorado School of Medicine, Aurora, CO*

Background: Although surgical resection is the treatment of choice for patients with esophageal squamous cell carcinoma (ESCC), some evidence suggests that definitive chemoradiation (CR) may have equivalent survival compared to surgery alone. The objective of this study was to evaluate current trends in the treatment of ESCC and its impact on overall survival (OS). **Methods:** Using the NCDB (2004-2013), patients with non-metastatic/loco-regional ESCC were categorized into definitive CR, neoadjuvant CR/surgery, surgery alone, and surgery/adjuvant therapy. Multivariate Cox proportional hazard models by stepwise selection were applied to estimate hazard ratios (HR) of predictors of OS. **Results:** We identified 11,229 patients with ESCC undergoing definitive CR (n = 8855, 78.9%), neoadjuvant therapy/surgery (n = 953, 8.5%), surgery alone (n = 1130, 10.1%), and surgery/adjuvant therapy (n = 291, 2.6%). The distance of primary tumor from incisors was comparable for all four groups. On multivariable analysis, treatment modality had the largest impact on OS followed by AJCC stage, age and annual surgical volume. Compared to neoadjuvant therapy/surgery, both surgery only (HR 1.17, 95% CI 1.04-1.32) and definitive CR (HR 1.51, 95% CI 1.37-1.66) were associated with increased long-term mortality. However, there was no difference in mortality in the surgery/adjuvant therapy group (HR 1.10, 95% CI 0.94-1.30) compared to the neoadjuvant therapy/surgery group. Patients treated at facilities performing more than 20 esophagectomies per year, regardless of whether they underwent surgical resection, had improved OS compared to facilities performing 10-19 per year (HR 1.47, 95% CI 1.29-1.68), 5-9 per year (HR 1.44, 95% CI 1.29-1.62), and < 5 per year (HR 1.53, 95% CI 1.38-1.70). **Conclusions:** Patients receiving either neoadjuvant therapy or adjuvant therapy and esophagectomy for ESCC have improved OS compared to patients undergoing esophagectomy alone and definitive CR. These findings suggest that patients with ESCC should be considered for multimodality treatment at high-volume centers and surgery should be included in the treatment plan whenever possible.

4033 Poster Session (Board #25), Sat, 8:00 AM-11:30 AM

Enteral nutrition to improve nutritional status, treatment tolerance, and outcomes in patients with esophageal cancer undergoing concurrent chemoradiotherapy (CCRT): Results of a prospective, randomized, controlled, multicenter trial (NCT 02399306). *First Author: Tao Li, Department of Radiation Oncology, Sichuan Cancer Hospital and Institution, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*

Background: Patients with esophageal cancer undergoing CCRT are at high risk of malnutrition. The aim of this study was to investigate the influence of enteral nutrition on nutritional status, treatment tolerance and outcomes in esophageal cancer patients undergoing CCRT. **Methods:** Patients with inoperable esophageal cancer were randomly assigned (2:1 ratio) to the enteral nutrition group (EN group) or the control group. Patients in the EN group were supported with individual enteral nutrition intervention according to the nutritional status assessment results. The control group was treated with conventional diet guidance. The primary endpoint was the change in body weight from baseline after treatment. Secondary endpoints were nutrition related blood parameter changes, treatment tolerance and outcomes. **Results:** Between Mar. 2015 and Jan. 2017, 158 patients from ten hospitals were randomised into the EN group (n = 106) and the control group (n = 52). Following CCRT, patients in EN group lost only 0.72±3.27 kg of body weight compared with 2.10±2.89 kg in the control group ($P < 0.001$). Participants who received EN had less decline than controls in serum albumin (2.66±5.05 g/L and 4.75±4.94 g/L, $P < 0.001$) and hemoglobin (10.29±15.78 g/L and 18.48±14.66 g/L, $P < 0.001$). Grade 3/4 leukopenia in the control group was significantly more frequent than the EN group (33.3% vs. 20.0 %, P = 0.011). Patients supported on EN experienced greater chemoradiotherapy completion rates (92.5% vs. 67.3%, P = 0.001) and lower infection rates (18.8% vs 31.7%, P = 0.021). There was significant difference in tumor response between two groups (EN group: 81.1%, control group: 67.3%, P = 0.004). The 1- and 2-year OS rates in the EN group were significantly greater (89.6% and 75.4%, respectively) compared with the control group (78.5% and 57.9%, respectively). **Conclusions:** Enteral nutrition may be advantageous in patients with esophageal cancer undergoing CCRT by improving nutritional status, treatment tolerance and outcomes. Clinical trial information: NCT 02399306.

4034 Poster Session (Board #26), Sat, 8:00 AM-11:30 AM

How many lymph nodes is enough? Defining the optimal lymph node dissection in stage I-III gastric cancer using the National Cancer Database. *First Author: Karna Tushar Sura, Beaumont Health, Department of Radiation Oncology, Oakland University William Beaumont School of Medicine, Royal Oak, MI*

Background: Gastric cancer is one of the most causes of cancer-related death worldwide. Surgical resection with lymph node dissection is the primary therapeutic modality. However, the appropriate extent of lymph node dissection remains controversial. Herein, the National Cancer Database (NCDB) was used to determine the optimal number of lymph nodes (LNs) to be dissected for resectable gastric cancer. **Methods:** The NCDB was queried from 2004-2013 for patients with invasive gastric cancer who underwent surgical resection with negative margins. The optimal number of LNs dissected was determined using a univariate $\chi 2$ cut-point analysis. Actuarial survival was determined using the Kaplan Meier method, and comparisons of survival estimates were completed with log-rank tests. Multiple sensitivity analyses were utilized to decrease bias. **Results:** 17,851 patients were included. The mean (±SD) number of LNs examined was 16 ± 11. For all patients, the optimal number of LNs needed to be examined was 20+ nodes. When correcting for stage migration (< 7 LNs removed), the optimal cut-off value was 20+ LNs. When stratifying by pathologic nodal stage, the cutpoint was 10+ LNs for pN1 and pN2. The 5-year survival was 30.6 ± 1.6% for 0-9 removed LNs compared to 48.2 ± 1.2% for 10+ removed LNs ($p < 0.001$) in pN1 disease and 18.3 ± 1.7% for 0-9 removed LNs compared to 32.6 ± 1.2% for 10+ removed LNs ($p < 0.001$) in pN2 disease. For pN3 disease, the optimal cut-off point was 20+ LNs; the 5-year survival was 17.2 ± 1.3% for 0-19 removed LNs compared to 28.5 ± 1.7% for 20+ removed LNs ($p < 0.001$). Moreover, the outcome was inferior among patients who had > 10% positive dissected LNs ($p < 0.05$). **Conclusions:** The optimal number of dissected LNs of 20+ LNs was associated with superior survival. Extended LN dissection is to be considered especially in patients with > 10% positive dissected LNs.

4035 Poster Session (Board #27), Sat, 8:00 AM-11:30 AM

Patterns of care and treatment outcomes of patients with stage I esophageal cancer: A National Cancer Database analysis. *First Author: Amy Catherine Moreno, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The aim of this study was to examine current patterns of care and associated outcomes for patients with stage I esophageal cancer (EC) treated in the United States. **Methods:** The National Cancer Data Base (NCDB) was queried for patients diagnosed with clinical stage T1-2N0 EC from 2004-2012. Patients were categorized into four treatment groups: observation without definitive therapy (Obs), chemoradiotherapy (CRT), local excision (LE), and esophagectomy (Eso). Patient, tumor, and treatment parameters were compared between groups. Kaplan-Meier 5-year overall survival (OS) estimates, postoperative 30- and 90-day mortality comparisons, and multivariate Cox proportional hazards modeling are reported. **Results:** A total of 5,460 patients met the criteria. Of these, 21% were observed, 14% underwent CRT, 23% LE, and 42% Eso. Median age and follow up were 67 years and 28 months, respectively. Eso was the primary treatment for patients of age ≤ 80 while 48% of patients age > 80 were observed. Age, race, comorbidity score, tumor location within the esophagus, type of medical insurance, median income, type of facility (academic vs. non-academic), and distance from treating facility were significant factors for predicting receipt of local therapy over observation. Postoperative 30-day mortality between the LE and Eso groups was 0.5% and 2.9%, respectively ($P < .001$), which increased to 1.4% and 5.5% at 90 days ($P < .001$). Five-year OS was 21% for Obs, 26% CRT, 64% LE, and 63% Eso ($P < .001$). Multivariate analyses demonstrated improved OS with any form of local definitive therapy: CRT (*HR*: 0.54, 95% CI [0.48 - 0.61], $P < .001$), LE (*HR*: 0.24, [0.20 - 0.27], $P < .001$), Eso (HR: 0.31, [0.28 - 0.35], $P < .001$). Age, comorbidity score, facility type, distance, median income quartile, and insurance status were also independently associated with OS. **Conclusions:** Management of stage I EC is influenced by several demographic and socioeconomic factors. Clinical observation yields suboptimal outcomes compared to any local therapy, and a surgical approach should be considered over CRT whenever feasible.

4036 Poster Session (Board #28), Sat, 8:00 AM-11:30 AM

Three-field versus two-field lymphadenectomy for carcinoma of the middle and lower esophagus: Short-term results of a randomized controlled trial. *First Author: Bin Li, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: The safety and efficacy of esophagectomy with 3-field lymphadenectomy remain controversial. **Methods:** We did this randomized trial in Fudan University Shanghai Cancer Center in China. Between March 2013 and November 2016, 400 patients with cancer located in the middle and lower esophagus were recruited and randomly assigned to receive 3-field or 2-field lymphadenectomy at a 1:1 ratio. Postoperative complications between the 3-field group (n = 200) and 2-field group (n = 200) were compared on the basis of the intention-to-treatment principle. **Results:** There was no significant difference between the two arms in terms of gender, age, BMI, FEV1, and tumor location. Median operative time was 183 minutes (range 125 to 331) in 3-field group versus 168 minutes (range 116 to 375) in 2-field group, $P < 0.001$. Overall morbidity was 28% (56/200) in the 3-field group and 30.5% (61/200) in the 2-field group, $P = 0.583$. The mortality rate was 0% (0/200) for the 3-field group and 0.5% (1/200) for the 2-field group, $P = 1.000$. Although more reintubation occurred in the 3-field group than in the 2-field group (3% [6/200] vs. 0% [0/200], $P = 0.030$), the distribution of severity (stratified according to the Clavien-Dindo classification) and hospital stay were similar between the two groups. A significantly higher number of lymph nodes were retrieved in the 3-field group (median 37, range 3 to 85) compared to those in the 2-field group (median 24, range 7 to 61) ($P < 0.001$). 44 patients (22%) had positive cervical nodes in the 3-field group. **Conclusions:** Morbidity after esophagectomy with 3-field lymphadenectomy is comparable with that after 2-field lymphadenectomy. Cervical lymphatic involvement is common in patients with middle and lower esophageal cancer. 3-field lymphadenectomy may offer more accurate tumor staging related to cervical lymphatic metastasis. TABLE. Regions of lymph nodes metastases Clinical trial information: NCT01807936.

	2-field arm (n = 200)		3-field arm (n = 200)		
	No.	%	No.	%	P
None	106	53.0%	98	49.0%	0.424
Neck			7	3.5%	-
Mediastinum	37	18.5%	18	9.0%	0.006
Abdomen	21	10.5%	20	10.0%	0.869
Mediastinum & neck			14	7.0%	
Abdomen & neck			5	2.5%	
Mediastinum & abdomen	36	18.0%	20	10.0%	0.021
Neck & mediastinum &abdomen			18	9.0%	

4037 Poster Session (Board #29), Sat, 8:00 AM-11:30 AM

Exclusive chemoradiotherapy with or without dose escalation in locally advanced esophageal carcinoma: The CONCORDE study (PRODIGE 26). *First Author: Gilles Crehange, Georges-François Leclerc Center, Dijon, France*

Background: In esophageal cancer (EC), 20 to 45% of patients suffer from local failure after 50Gy concomitant chemoradiation (cCRT). Improvements in staging together with target definitions led us to test dose escalation in the modern era of new technologies. **Methods:** Patients were randomly assigned cCRT to 40Gy elective nodal irradiation with either a 10Gy boost (Arm A) or 26Gy boost (Arm B) combined with FOLFOX-4. The primary endpoint of this phase II was acute toxicity according to the NCIC-CTCAE (version 4.0). Quality of life according to the EORTC QLQ-C30 and OG25 was a secondary endpoint. All analyses were performed in intent-to-treat. **Results:** 160 patients were randomized between Jun 2011 and Feb 2016: 81 patients in arm A and 79 patients in arm B. The mean age at diagnosis was 61.9 (7.9) years and 62.1 (7.8) years, respectively. Seventy patients in each arm had squamous cell carcinoma (86.4% in arm A and 88.6% in arm B) and 59 patients (72.8%) and 58 patients (73.4%) had stage III disease in arms A and B, respectively. IMRT was performed in 57 (70.4%) and 55 (69.6%) patients in arms A and B. The rates of grade ≥3 (G3+) non-hematological toxicity were not significantly different between arms A and B (76.5% vs 86.0%, p = 0.12). The rates of G3+ hematological toxicity were not significantly different between arms A and B (82.7% vs 88.6%, p = 0.29). The rates of G3+ non-hematological toxicity were not significantly different between patients treated with 3DRT (83.3%) and IMRT (81.3%) (p = 0.77). The mean global health scores at baseline and 3 months were 63.9 (sd = 21.4) vs 69.6 (sd = 23.1) in arm A (p = 0.10) and 65.27 (sd = 19.54) vs 58.8 (sd = 19.9) in arm B (p = 0.16). The presence of dysphagia was neither significantly different between arm A (89.23%) and arm B (86.21%) (p = 0.61) at baseline nor at 3 months (77.78% vs 86.84%, p = 0.29). Odynophagia was present at baseline in 78.46% in arm A and 75.86% in arm B (p = 0.73) while the rates observed at 3 months were 68.18% and 73.68%, respectively (p = 0.59). **Conclusions:** Dose escalated cCRT in patients with EC is feasible with no increased acute toxicity and no deterioration of QOL. A phase III trial is on-going to conclusively address the issue of local control with cCRT. Clinical trial information: NCT01348217.

4038 Poster Session (Board #30), Sat, 8:00 AM-11:30 AM

Expression of Claudin 18.2 and HER2 in gastric, gastroesophageal junction, and esophageal cancers: Results from the FAST study. *First Author: Martin H. Schuler, University Hospital Essen, Essen, Germany*

Background: Claudin 18.2 (CLDN18.2), a gastric mucosa tight junction protein, is aberrantly expressed in various cancers. In the FAST Phase 2 trial (NCT01630083), IMAB362, an anti-CLDN18.2 monoclonal antibody, administered in combination with EOX chemotherapy, prolonged survival compared to EOX alone in patients with advanced/recurrent gastric, gastroesophageal junction (GEJ), and esophageal cancers ineligible for trastuzumab. The aim of the present analysis was to assess tumor CLDN18.2 expression and co-expression with HER2 in the FAST population. **Methods:** Tumor tissue samples from patients screened for inclusion into the FAST trial were analyzed for CLDN18.2 expression using a CE-marked, validated immunohistochemistry (IHC) assay. CLDN18.2 expression was centrally scored based on staining intensity and percentage of stained tumor cells. In a subset of tissue samples with known HER2 status, overall HER2 expression and co-expression with CLDN18.2 were determined. **Results:** Tissue samples from 730 patients with gastric, GEJ, and esophageal cancer were screened for the FAST study. Of these 730 samples, 685 (94%) were assessed by central IHC; 49% (n=333/685) met the FAST CLDN18.2 expression criterion (≥2+ intensity in ≥40% of tumor cells) for inclusion. Across the 154 tissue samples with known HER2 status, the majority (84%; n=129/154) were $HER2^-$. Furthermore, 94 of these 154 samples (61%) met the FAST CLDN18.2 expression criterion, of which 14% (n=13/94) co-expressed HER2 (Table). **Conclusions:** In tissue samples from patients screened for the FAST trial, nearly half met CLDN18.2 expression inclusion criterion. In samples with known HER2 status, co-expression of CLDN18.2 and HER2 occurred in 14% of the samples that met study eligibility. These data suggest CLDN18.2 may serve as a non-HER2 overlapping targetable alteration in a distinct subpopulation of patients with gastric, GEJ, or esophageal cancers. Clinical trial information: NCT01630083.

	Eligible for FAST* (n=94)	Not eligible for FAST* (n=60)	Total (N=154)
$HER2^+$, n (%)	13 (13.8)	12 (20.0)	25 (16.2)
$HER2^-$, n (%)	81 (86.2)	48 (80.0)	129 (83.8)

*Based on CLDN18.2 expression criterion.

4039 Poster Session (Board #31), Sat, 8:00 AM-11:30 AM

Phase II study of intraperitoneal docetaxel plus capecitabine/cisplatin for gastric cancer with peritoneal metastasis: XP+IP DOC trial. *First Author: Ryoji Fukushima, Teikyo University, School of Medicine, Tokyo, Japan*

Background: Intraperitoneal (IP) chemotherapy with taxanes provides sustained high local concentrations, and the efficacy of IP paclitaxel (PTX) has been shown in ovarian cancer. We previously reported the safety and efficacy of IP PTX plus systemic chemotherapy in clinical trials. Capecitabine/cisplatin (XP) is one of the standard regimens for the first-line treatment of advanced gastric cancer worldwide. We designed a new regimen combining IP docetaxel (DOC) with XP, and the recommended dose of IP DOC was determined to be 10 mg/m^2 in a phase I study. A phase II study of XP plus IP DOC was performed in gastric cancer patients with peritoneal metastasis. **Methods:** Gastric cancer patients with peritoneal metastasis confirmed by diagnostic imaging, laparoscopy or laparotomy were enrolled. DOC was administered intraperitoneally at 10 mg/m^2 on days 1 and 8. Cisplatin was administered intravenously at 80 mg/m^2 on day 1, and capecitabine was administered at 1000 mg/m^2 bid for 14 consecutive days, repeated every 21 days. The primary endpoint was the 1-year overall survival (OS) rate. Secondary endpoints were response rate, negative conversion rate on peritoneal cytology and safety. **Results:** Out of 50 patients enrolled, 48 patients received protocol treatment, and were evaluated for OS and toxicity. The median number of courses was 6 (range 1-15). The 1-year OS rate was 75% (95% confidence interval, 60-85%). The best overall response was stable disease in all the three patients with target lesions. Cancer cells ceased to be detected by peritoneal cytology in 28 (76%) of 37 patients. Nineteen patients underwent gastrectomy after response to chemotherapy. The incidences of grade 3/4 hematological and non-hematological toxicities were 42% and 48%, respectively. The frequent grade 3/4 toxicities included neutropenia (21%), leukopenia (8%), anemia (29%), anorexia (25%) and nausea (17%). Infection of the intraperitoneal port was observed in one patient. There were no treatment-related deaths. **Conclusions:** Combination chemotherapy of XP plus IP DOC regimen is well tolerated and active in gastric cancer patients with peritoneal metastasis. Clinical trial information: UMIN000016469.

4040 Poster Session (Board #32), Sat, 8:00 AM-11:30 AM

Clinicopathological features of program death ligand-1 expression with mismatch repair, Epstein-Barr virus status, and cancer genome alterations in metastatic gastric cancer. *First Author: Akihito Kawazoe, Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Chiba, Japan*

Background: Recently, anti-programmed death 1 (PD-1) or its ligand (PD-L1) antibodies have shown promising activities in metastatic gastric cancer (MGC). However, little is known about detailed clinicopathological features of PD-L1 expression in patients (pts) with MGC. **Methods:** Pts with histologically confirmed MGC were eligible for this prospective observational study. PD-L1 expression on tumor cell (TC) or inflammatory cell (IC) and mismatch repair (MMR) were analyzed by immunohistochemistry (IHC). Epstein–Barr virus (EBV) was detected by in situ hybridization. The expressions of tyrosine kinase receptors (RTKs) such as HER2, EGFR and MET and cancer genome alterations were also evaluated by IHC or next generation sequencing. **Results:** A total of 237 pts were enrolled from September 2015 to December 2016. Samples of 199 (84.0%) pts were obtained from biopsy. PD-L1 expression on TC and IC was positive in 27 (11.4%) and 167 pts (70.5%), respectively. One hundred and seventy-one pts (72.2%) had positive PD-L1 expression on either TC or IC. MMR deficient (D-MMR) and EBV was detected in 14 (6.9%, n = 203) and 14 pts (5.9%, n = 237), respectively. PD-L1 expression on TC was more frequently observed in pts with D-MMR ($P < 0.001$) and KRAS mutation ($P < 0.001$), while that on IC was more frequently observed in pts with EBV+ (P = 0.045), lymph node metastasis (P = 0.001), and lung metastasis (P = 0.045). In contrast, pts with peritoneal metastasis were associated with less frequent PD-L1 expression in IC (P = 0.003). A significant association was not observed between PD-L1 expression and RTKs expression or presence of other gene alterations. D-MMR was significantly associated with intestinal type (P = 0.026) and absence of liver metastasis (P = 0.022). PD-L1 expression on either TC or IC was not prognostic factor (hazard ratio ; 0.92, P = 0.741). Seven pts with D-MMR and seven pts with EBV+ MGC were enrolled in clinical trials of anti-PD-1/PD-L1 antibodies. **Conclusions:** PD-L1 expression in MGC was associated with some clinicopathological features. Impact of these characteristics on efficacy of anti-PD-1/PD-L1 antibody warrants further evaluation.

4041 Poster Session (Board #33), Sat, 8:00 AM-11:30 AM

The Nationwide Cancer Genome Screening Project in Japan SCRUM-Japan, GI-screen: Efficient identification of cancer genome alterations in advanced gastric cancer. *First Author: Shigenori Kadowaki, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*

Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in advanced non-colorectal gastrointestinal (GI) cancer (aNon-CRC), called as the SCRUM-Japan GI-SCREEN. **Methods:** This study is ongoing with 20 major cancer centers. Patients with aNon-CRC, who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect gene mutation, copy number variant (CNV) and fusions across 143 genes in a CLIA certified CAP accredited laboratory. The detected genomic variant data were classified according to whether genetic drivers of cancer including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase. In this presentation, we show the results of advanced gastric cancer (aGC) cohort. **Results:** As of October 31st in 2016, a total of 565 aGC samples were analyzed. The sequence with the OCP was successfully performed in 425 (75.2%). Out of 475 patients except for the 90 patients in which precise data is not collected, the proportion of histology type is followed; intestinal type 44.6%, diffuse type 54.5%, other 0.6%, unknown 0.2%. Out of 406 samples of which results were available, the frequently detected mutations were *TP53* (47.8%), *PIK3CA* (8.6%), *KRAS* (5.4%), *SMAD4* (4.9%), *TET2* (4.4%), *APC* (3.9%), *ERBB2* (3.7%) and CNVs were *ERBB2* (10.8%), *CCNE1* (9.4%), *KRAS* (3.7%), *ZNF217* (3.2%), *FGFR2* (2.7%), and *MET* (2.5%). *FGFR3-TACC3* fusion, *WIPF2-ERBB2* fusion and *EGFR* vIII were detected in 2, 1, and 2 cases, respectively. **Conclusions:** This nationwide screening system is efficient to detect rare gene alterations in aGC. This novel knowledge provides an intriguing background to investigate new target approaches and represents a progress toward more precision medicine. Clinical trial information: UMIN000016344.

4042 Poster Session (Board #34), Sat, 8:00 AM-11:30 AM

A phase II study of early FDG-PET evaluation after one-cycle chemotherapy in patients with locally advanced esophageal squamous cell carcinoma treated with neoadjuvant chemoradiotherapy: Final report. *First Author: Ta-Chen Huang, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

Background: The optimal use of the metabolic tumor response measured by ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET) in the treatment of esophageal cancer is currently unknown. We launched a phase II clinical trial to evaluate the early metabolic response to one-cycle chemotherapy in locally advanced esophageal squamous cell carcinoma (ESCC) patients, who subsequently received neoadjuvant chemoradiation (neo-CRT) followed by surgery. **Methods:** ESCC patients with stage T3 or N1M0 or M1a (AJCC, 6th edition) were enrolled to receive one-cycle chemotherapy, day 1 and 8 doses of paclitaxel, cisplatin, and 24-hour infusional 5-fluorouracil and leucovorin, followed by paclitaxel/cisplatin- based 40Gy neo-CRT and surgery. FDG-PET was performed at baseline and day 14 of the one-cycle chemotherapy. The primary endpoint is pathological complete response (pCR) to neo-CRT. We hypothesized that early PET responders, defined as $>$ 35% reduction of maximum standardized uptake value (SUV_{max}) from the baseline, would significantly improve pCR. **Results:** Between Feb 2008 and Mar 2012, 66 patients (M: F = 61: 5) were enrolled. Their clinical stages were: II or III, 56; IVA, 10. Forty seven received surgery. The pCR rate per surgical population was 34.0%. The median progression-free survival (PFS) and overall survival (OS) for the whole study group was 16 months (95% CI 9-27) and 22 months (95% CI 16-40), respectively. A total of53 patients were evaluable for PET response. The early PET response was not associated with high pCR rate or better survivals. However, in an exploratory analysis, the post-chemotherapy SUV_{max} was an independent prognostic factor for pCR, PFS and OS. A predictive model for pCR composed of weight loss and the post-chemotherapy $SUV_{max}$was established with an AUC of 0.84. **Conclusions:** Our study failed to validate the predictive value of predefined early PET response to one-cycle chemotherapy for pCR to neo-CRT in locally advanced ESCC patients. However, the FDG-PET SUV_{max} after one-cycle chemotherapy may have prognostic and predictive significance, and may be explored in further studies. Clinical trial information: NCT01034332.

4043 Poster Session (Board #35), Sat, 8:00 AM-11:30 AM

Is surgical resection beneficial in recurrent or metastatic gastric cancer? *First Author: Yong Won Choi, Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, South Korea*

Background: Although chemotherapy is currently established as a standard treatment in recurrent or metastatic gastric cancer, the role of palliative surgical resection is still controversial. We investigated the survival benefit of surgical resection in patients (pts) with recurrent or metastatic gastric cancer who received systemic chemotherapy. **Methods:** A retrospective review was conducted on 698 pts who received palliative chemotherapy for recurrent (n = 307) or primary metastatic (n = 391) gastric cancer. Overall survival (OS) of pts who underwent surgical resection followed by chemotherapy was compared to that of pts who received chemotherapy alone. **Results:** Among 140 pts (primary metastatic: 97, recurrent: 43) with surgical resection, gastrectomy, metastasectomy, and gastrectomy with metastasectomy were performed in 83 (primary metastatic: 81), 44, and 13 pts, respectively. Higher surgical resection rate was observed in pts with young age ($<$ 70) (p = 0.010), ECOG PS 0 or 1 (p = 0.010), primary metastatic ($p < 0.0001$), absence of liver metastasis (p = 0.002), and signet ring cell histology (p = 0.002). The median OS of pts who underwent surgical resection before chemotherapy was significantly longer than that of pts who received chemotherapy alone (19 vs. 9 months, $p < 0.0001$). The OS benefit of surgical resection was consistent across subgroups in terms of baseline characteristics including age, ECOG PS, disease status (primary metastatic vs. recurrent), peritoneal metastasis, and first-line chemotherapy regimen (single vs. combination). In multivariate analysis, surgical resection was independently associated with favorable OS (hazard ratio = 0.41, $p < 0.0001$) along with ≥second-line chemotherapy ($p < 0.0001$), whereas ECOG PS 2 or 3 (p = 0.013), signet ring cell histology ($p < 0.0001$), and peritoneal metastasis (p = 0.046) were independent prognostic factors of poor OS. **Conclusions:** The present study suggests that judicious use of surgical resection before chemotherapy in recurrent or metastatic gastric cancer pts may result in favorable outcome, although large scale phase III trials are essential to establish this treatment approach as a standard practice.

4044 Poster Session (Board #36), Sat, 8:00 AM-11:30 AM

The prognostic role of metastatic lymph node ratio-staging system in gastric cancer patients: Analysis of the National Cancer Database. *First Author: Rand Naffouje, Weiss Memorial Hospital, Chicago, IL*

Background: The NCCN recommends retrieval of at least 15 lymph nodes for adequate nodal staging in gastric cancer. There is an ongoing debate about the accuracy of the classification systems for nodal involvement based on the absolute number of positive nodes (AJCC-N) vs. the ratio of positive nodes (rN). In this study, we aim to assess the accuracy of each system in the prediction of 5-year survival using the National Cancer Data Base (NCDB) for gastric cancer. **Methods:** The database included 168,377 gastric cancer patients between 2004-2014. Patients who were approached with palliative intent, or had metastatic disease were excluded from the analysis. Only patients who had at least one regional node examined were included. A univariate and multivariate regression analysis were conducted to identify significant predictors of the 5-year survival among the perioperative patients' characteristics. Bayesian Information Criterion (BIC) was used to compare the model fitting when the AJCC nodal staging is applied to that of the ratio nodal staging. **Results:** 48,126 patients were included in the final analysis. 23,102 (48%) patients had ≥15 nodes examined. The univariate and multivariate regression analysis identified age, male gender, Caucasian race, and presence of comorbidities as significant demographic predictors. TNM T-stage, N-stage, and rN-stage were significant predictors with worsening prognosis as the stage increases. Overall, BIC demonstrated that the model using rN had a better fit (rN = 30321 vs. AJCC-N = 30619). However, subgroup analysis showed that the AJCC-N functioned better when $<$ 15 nodes were examined (rN = 17367 vs. AJCC-N = 17311), whereas rN functioned better when ≥15 nodes were collected (rN = 16776 vs. AJCC-N = 16831). **Conclusions:** Both AJCC-N and rN are valid systems for nodal staging in terms of survival prediction in gastric cancer. When at least 15 nodes are resected in line with the current NCCN guidelines, the rN staging system for nodal metastasis appears to function more accurately in survival prediction. It might be advisable to consider the ratio of positive lymph nodes when a large number of nodes are collected to avoid over-staging and stage migration.

4045 Poster Session (Board #37), Sat, 8:00 AM-11:30 AM

Nomogram for lymph node metastasis prediction with early gastric cancer patients: To decide additional gastrectomy after endoscopic dissection. *First Author: Su Mi Kim, Samsung Medical Center, Seoul, Republic of Korea*

Background: Accurate prediction of metastatic lymph node is critical to avoid unnecessary gastrectomy and improve quality of life for patients with early gastric cancer. The aim of this study was to develop and validate a nomogram for prediction of lymph node metastasis in early gastric cancer patients. **Methods:** We reviewed the clinicopathological data of 10595 patients who underwent curative resection for early gastric cancer from 2001 to 2015 at Samsung Medical Center. This model was externally validated by 2100 patients who underwent curative resection for gastric cancer in National Cancer Center. Multivariate analysis using the Cox proportional hazard regression model was performed to develop the nomogram, and discrimination and calibration were evaluated by external validation. Overall survival, disease free survival, and recurrence free survival were compared between gastrectomy groups of 6641 patients and endoscopic dissection group of 999 patients who was performed the treatment in Samsung Medical Center for early gastric cancer by risk on nomogram to demonstrate the efficacy of nomogram. **Results:** Multivariate analyses revealed that age, tumor size, lymphatic invasion, depth of invasion, and histologic differentiation were significant prognostic factors for lymph node metastasis. The nomogram had good discrimination with a concordance index of 0.845 [95% confidence interval 0.832-0.858], supported by an external validation point of 0.813 [95% confidence interval 0.786-0.84]. In low risk on nomogram, endoscopic dissection group had similar overall survival (P = 0.319), disease free survival (P = 0.469) and recurrence free survival (P = 0.091) compared to gastrectomy group. **Conclusions:** We developed and validated a nomogram predicting lymph node metastasis for early gastric cancer based on a large database. This personalized nomogram is useful to avoid unnecessary gastrectomy after endoscopic dissection resulting in improved quality of life for early gastric cancer patients.

4046 Poster Session (Board #38), Sat, 8:00 AM-11:30 AM

Ramucirumab (R) plus pembrolizumab (P) in treatment naive and previously treated advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: A multi-disease phase I study. *First Author: Ian Chau, Royal Marsden Hospital, Sutton, United Kingdom*

Background: Angiogenesis and immunosuppression are hallmarks of tumor growth. This is the first study to combine R (anti-VEGFR2) with P (anti-PD-1) to simultaneously target both processes in the tumor microenvironment. **Methods:** Ongoing, multi-cohort, phase 1a/b trial enrolled pts with G/GEJ adenocarcinoma, measurable disease, ECOG PS 0-1, previously treated (Cohorts A and B) or untreated (Cohort A2) for advanced disease. PD-L1 was positive (tumor proportion score [TPS] $\geq$1%) or negative (TPS $<$ 1%) using the DAKO PD-L1 22C3 IHC pharmDx assay. R was administered at 8 mg/kg on Days 1&8 (Cohorts A and A2) or 10 mg/kg on Day 1 (Cohort B) with P 200 mg on Day 1 q3W. Primary objective- assess safety and tolerability of R+P; preliminary efficacy will be examined. **Results:** As of 21-Nov-2016, 41 previously treated G/GEJ pts were enrolled. Median age was 58 y, 76% male, 66% had ECOG PS of 1, 46% were PD-L1+, and 59% received study treatment as third or subsequent line. Median duration on therapy was 2.8 mo and 4.1 mo for A and B, respectively. Overall, 33 (80%) pts experienced a treatment-related AE (TRAE) and similar between cohorts A and B. Ten (24%) pts experienced grade 3-4 TRAEs, most commonly colitis (7%) and hypertension (7%). One treatment-related death occurred (pneumonitis and pulmonary sepsis). Responses occurred in 3 (7%) pts with 46% disease control rate (DCR). Progression-free and overall survival rates at 6 mo were 22.4 % (95% CI, 9.8-38.0) and 51.2% (95% CI, 33.9-66.1) respectively. Nine (22%) pts remain on treatment. Eighteen of 25 planned treatment naïve G/GEJ pts were enrolled. Median age was 70 yr, 83% male, 56% had ECOG PS of 0, and PD-L1 status is pending. Median duration on therapy was 2.1 mo. Twelve (67%) pts experienced a TRAE. Grade 3 TRAEs occurred in 5 (28%) pts (hypertension [n = 3], diarrhea, and acute kidney injury). No grade 4-5 events occurred. Preliminary efficacy data showed 3 (17%) pts responded with 50% DCR. Median PFS is immature and 89% of pts remain on treatment. **Conclusions:** R+P generated no new safety signals and demonstrated encouraging antitumor activity in treatment naïve and previously treatedadvanced G/GEJ adenocarcinoma. Clinical trial information: NCT02443324.

4047 Poster Session (Board #39), Sat, 8:00 AM-11:30 AM

Meaningful changes in quality of life (QoL) in patients with gastric cancer: Exploratory analyses from RAINBOW and REGARD. *First Author: Ian Chau, Royal Marsden Hospital, London, United Kingdom*

Background: EORTC QLQ-C30 is a well-established QoL instrument for cancer patients (pts), but there is limited information for gastric cancer. To identify priority domains and describe meaningful changes, we explored data from 2 randomized ramucirumab phase 3 trials in pts with previously treated gastric or gastroesophageal junction cancer. **Methods:** Pts completed QLQ-C30 v3.0 at baseline and Q6W while on study. Data from all treatment arms were pooled (N=1020). Changes from baseline in QoL domains were compared by best overall response (BOR) and ECOG performance status (PS) using analysis of covariance. Odds ratios (ORs) for BOR and PS outcome groups per QoL unit (point) change were estimated by cumulative logit regression modeling, with OR$\leq$0.85 considered meaningful. **Results:** Changes from baseline in QoL domains were significantly associated with BOR and PS outcomes (Table). ORs for BOR and PS outcomes for these domains were statistically significant ($p<0.05$) and suggested changes of 10-15 points predict clinical outcomes. **Conclusions:** QLQ-C30 is sensitive to clinical outcomes in advanced gastric cancer patients, particularly in global QoL, functional status and disease symptoms of fatigue, pain, and appetite loss. These analyses can inform trial designs and interpretation of results.

Mean (std dev) change from baseline at Wk 6 (0-100 scale with positive change reflecting improvement).

	BOR				PS			
Domains w/ most consistent changes	Complete/partial response (n=149)	Stable disease (n=398)	Progressive disease or other (n=100)	p-value	Improved by ≥1 (n=33)	No change (n=541)	Worsened by ≥1 (n=72)	p-value
Global QoL	2.5 (19.1)	-1.9 (20.3)	-7.3 (22.4)	0.0011	5.1 (20.4)	-0.8 (20.1)	-11.0 (20.3)	<0.0001
Physical functioning	-3.7 (15.4)	-3.6 (16.9)	-13.3 (21.0)	<0.0001	4.4 (16.3)	-4.4 (16.4)	-14.4 (21.9)	<0.0001
Role functioning	-2.6 (22.1)	-4.1 (24.8)	-17.7 (35.0)	<0.0001	6.1 (28.5)	-5.1 (25.0)	-16.0 (33.0)	0.0001
Fatigue	-1.0 (20.8)	-2.3 (21.2)	-12.4 (26.5)	<0.0001	8.1 (23.8)	-2.6 (20.8)	-14.8 (27.2)	<0.0001
Pain	2.5 (24.5)	1.5 (24.4)	-7.2 (29.8)	0.0052	11.6 (32.4)	1.0 (24.0)	-9.0 (29.5)	0.0002
Appetite loss	6.5 (29.4)	3.7 (32.5)	-6.3 (35.0)	0.0061	13.1 (26.3)	3.3 (31.5)	-4.6 (39.3)	0.0261

4048 Poster Session (Board #40), Sat, 8:00 AM-11:30 AM

Prognostic and predictive factors for overall survival (OS) in metastatic esophagogastric cancer (EGC): A meta-analysis. *First Author: Emil ter Veer, Department of Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands*

Background: Prognostic and predictive factors for metastatic EGC are important to estimate prognosis, inform clinical decision-making and design future trials. We performed a systematic review with meta-analysis to identify these factors. **Methods:** We searched Medline, EMBASE and CENTRAL for phase 2/3 randomized controlled trials (RCTs) until January 2016 on palliative chemotherapy and targeted therapy for metastatic EGC. Prognostic and predictive factors were identified from respectively multivariate cox regressions and stratified treatment comparisons. Hazard Ratio's (HR) for OS were extracted and pooled with meta-analysis if possible. Prognostic factors were considered independent if the multivariate HR was significant (P$\leq$0.05). Predictive factors were clinically relevant if P for subgroup interaction was $\leq$0.20 and the HR in one of the subgroups was significant (P$\leq$0.05). **Results:** We identified 47 RCTs (14,853 patients), wherein 54 potential prognostic and 40 predictive factors were reported. Eight independent prognostic factors for poor OS reported in $\geq$2 RCTs based on $\geq$300 patients were: performance status of $\geq$1 vs 0 (pooled HR, 95% confidence interval: 1.47, 1.25-1.73) or 2 vs 0-1 (1.52, 1.32-1.76); metastatic vs locally advanced disease (1.55, 1.39-1.72); diffuse vs intestinal/other histology (1.38, 1.12-1.71); $\geq$3 vs $<$ 2 metastatic sites (1.35, 1.07-1.70); presence of metastases in peritoneum (1.24, 1.01-1.51) or liver (1.45 (1.28-1.64); measurable vs non-measurable disease (1.31, 1.04-1.66); and no prior vs prior surgery (1.33, 1.16-1.53). Predictive factors for specific treatment comparisons based on $\geq$300 patients were: age ($\geq$65 vs $<$ 65); performance status; tumor location (GEJ vs stomach); disease stage; number of metastatic sites; peritoneal metastasis; measurable disease; histology; HER2; KRAS; VEGF A; and Neuropilin-1 for first line treatments; and time to progression on first line therapy ($<$ 3, 3-6 or $\geq$6 months) for second-line treatments. **Conclusions:** Eight independent prognostic factors for OS and thirteen clinically relevant predictive factors for treatment efficacy of EGC were found.

4049 Poster Session (Board #41), Sat, 8:00 AM-11:30 AM

Cardiac death rates after irradiation for esophageal cancer: An epidemiologic study among esophageal cancer survivors. *First Author: Remco Jurriaan Molenaar, Academic Medical Center, Amsterdam, Netherlands*

Background: Esophageal cancer is frequently treated with radiation in addition to surgery and/or chemotherapy. Long-term survivors that received radiation may be at risk for radiation-induced cardiotoxicity. **Methods:** Esophageal cancer survivors (defined as surviving > 5 yrs after diagnosis) from all 18 Surveillance Epidemiology and End Results (SEER) registries from 1973 to 2013 were queried for irradiation status, cause of death and survival using SEERaBomb, a package for the R statistical programming language. **Results:** 6,514 esophageal cancer survivors were identified, of whom 2,892 (44%) received no radiation therapy and 3,448 (53%) received external beam radiotherapy. Mean age at the time of esophageal cancer diagnosis was 64.0 yrs in the no radiation group and 63.0 yrs in the radiation group. Median person years of follow up after esophageal cancer diagnosis was 8.6 yrs (interquartile range [IQR]: 7-12) in pts receiving no radiation and 7.9 yrs (6-11) in pts receiving radiation. A total of 590 esophageal cancer survivors died of cardiac disease; 254 received no radiation and 336 did receive radiation. Median time to cardiac death after esophageal cancer diagnosis was 32.2 yrs (IQR: 19-38) in pts that received no radiation and 25.3 years (15-30) in pts that received radiation (log-rank $P< 0.001$). Compared with unirradiated pts, irradiated pts had an increased risk of dying of cardiac disease (hazard ratio [HR] = 1.47; 95% confidence interval [CI]: 1.2-1.7, Cox regression $P< 0.001$). The association between radiation and cardiac death was the strongest in esophageal cancer pts diagnosed before 1995 (HR = 1.75; 95% CI: 1.4-2.2, $P< 0.001$) and in squamous cell carcinoma of the esophagus (HR = 1.9; 95% CI: 1.4-2.6, $P< 0.001$) but not in adenocarcinoma (HR = 1.04; 95% CI: 0.8-1.4, $P= 0.8$). **Conclusions:** 5-year esophageal cancer survivors that were treated with radiotherapy have an increased risk of dying of cardiac disease, compared with unirradiated counterparts. This association was strongest in pts treated before 1995 and in squamous cell carcinoma pts. This may be due to late radiation-induced cardiotoxicity, decreasing with the use of heart-sparing radiation techniques after 1995.

4050 Poster Session (Board #42), Sat, 8:00 AM-11:30 AM

Pathophysiology and therapeutic strategies for peritoneal recurrence after gastric cancer surgery. *First Author: Satoshi Murata, Department of Surgery, Shiga University of Medical Science, Otsu, Japan*

Background: We recently showed that cancer cells, with proliferative and tumorigenic potential, can spill into the peritoneal cavity during curative (R0) gastric cancer (GC) surgery, which is associated with peritoneal recurrence (PM). To elucidate the pathophysiology of PM, the relationship between spilled cancer cells and cancer stem cells was evaluated. Furthermore, to identify a therapeutic strategy for PM, the prognostic impact of hyperthermic intraperitoneal chemotherapy (HIPEC) following GC surgery with spillage of cancer cells was evaluated. **Methods:** Patients with advanced GC (≥pT2 [MP]) who underwent R0 gastrectomy between 2010 and 2015 were enrolled. Ninety-four consecutive patients with negative results in peritoneal cytology and cancer cell culture (CCC [-]) following peritoneal washing (PW) before GC surgery were included. Spilled cancer cells in PW after GC surgery (PW-Post) were examined to identify any CD44-positive cancer stem-like cells associated with cancer metastasis. Based on the PW-Post CCC results, associations between HIPEC and recurrence-free survival (RFS), or overall survival (OS) were evaluated. HIPEC was performed following GC surgery using CDDP, MMC, and 5-FU in 5 L saline maintained at 42˚C for 30 min. **Results:** Spilled cancer cells included $CD44^+$ cancer stem-like cells. In 48 patients with PW-Post positive CCC (CCC [+]), the number of patients with pStage I, II, and III were 4, 7, and 15, respectively, in those who received HIPEC (n = 26), and 3, 9, and 10, respectively, in those who did not (n = 22). Among patients with CCC (+), the 5-year peritoneal RFS, hepatic RFS, and lymph node RFS rates were 93.3%, 100%, and 68.5%, respectively, in patients who received HIPEC, and 56.7%, 35.6%, and 66.7%, respectively, in those who did not (P = 0.008, P = 0.008, and P= 0.24, respectively). Among patients with PW-Post CCC (-), none developed recurrence, regardless of whether they received HIPEC (n = 28) or not (n = 18). **Conclusions:** The results show that PW-Post CCC is a promising predictive biomarker for recurrence after R0 GC surgery. Adjuvant HIPEC performed with R0 GC surgery showed preventive effects on peritoneal and hepatic recurrence and survival benefits for patients with PW-Post CCC (+).

4051 Poster Session (Board #43), Sat, 8:00 AM-11:30 AM

Phase II study of afatinib in recurrent and/or metastatic esophageal squamous cell carcinoma (R/M ESCC) (KCSG HN14-18). *First Author: Min Hee Hong, Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Republic of Korea*

Background: Afatinib, an irreversible pan-ErbB kinase inhibitor showed anti-tumor activity against esophageal cancer in phase I trial. In this multicenter, open-label, single arm phase II study, we aimed to evaluate the activity and safety of afatinib in R/M ESCC. **Methods:** Patients (pts) who had ECOG PS 0-2 and had progressed on platinum-based chemotherapy for R/M ESCC were enrolled. Pts were treated with afatinib 40mg/day until disease progression, unacceptable toxicity, or patient's refusal. Primary endpoint was objective response rate (ORR) per RECIST 1.1. The estimated sample size was 49, using a two-stage minimax design to evaluate incremental response rate from 5 to 15%. Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety profile. Additionally, we try to identify biomarker to predict efficacy of afatinib with target capture sequencing and gene expression profile as exploratory endpoints. **Results:** In a total of 49 enrolled pts (median age 60; range 44 -84), ORR and DCR were 14.3 % and 73.3%, respectively. With a median follow-up of 6.6 months, median PFS and OS was 3.4 months (95% CI 2.2-4.6) and 6.6 months (95% CI 5.2-8.0). Median treatment duration and duration of response were 2.8 months (range, 0.4-15.3) and 7.1 months (range, 2.5-13.9), respectively. Dose reduction and interruption occurred in 19 (38.8%) and 15 (30.6 %) pts. Treatment-related adverse events (TRAE) occurred in 33 pts (67.3%) with most common TRAEs being diarrhea (n=22, 44.9%) and acneiform rash (n=12, 24.5%). G3-4 TRAEs were rare, occurring in 7 pts (14.3 %). **Conclusions:** Afatinib demonstrated modest efficacy with manageable toxicity in platinum-resistant R/M ESCC patients. Given the modest response rate, identification of predictive biomarkers is essential for further clinical investigation of afatinib in R/M ESCC. Those biomarkers are being analyzed and will be presented in the conference (NCT02353936). Clinical trial information: NCT02353936.

Efficacy	Total (n=49)	%
Best response		
Complete response	0	0.0
Partial response (confirmed)	7	14.2
Stable disease	29	59.1
Progressive disease	11	22.4
Not evaluable	2	4.0
ORR (95% CI)		14.2 (4.4 – 24.0)
DCR (95% CI)		73.3 (61.1 – 85.9)

4052 Poster Session (Board #44), Sat, 8:00 AM-11:30 AM

Early presence of antiangiogenesis-related adverse events as a potential biomarker of antitumor efficacy in patients with metastatic gastric cancer treated with apatinib. *First Author: Xinyang Liu, Harvard T.H. Chan School of Public Health, Boston, MA*

Background: Reliable biomarkers of apatinib response in gastric cancer (GC) are lacking. We investigated the association between early presence of common adverse events (AEs) and clinical outcomes in metastatic GC patients. **Methods:** We conducted a retrospective cohort study using data on 269 apatinib-treated GC patients in two clinical trials. AEs were assessed at baseline until 28 days after the last dose of apatinib. Clinical outcomes were compared between patients with and without hypertension (HTN), proteinuria or hand and foot syndrome (HFS) in the first 4 weeks using Kaplan–Meier methods, Cox proportional hazard regression and logistic regression models. Landmark analyses were performed as sensitivity analyses. Predictive model and risk scores were analyzed to predict overall survival (OS). **Results:** Presence of AEs in the first 4 weeks was associated with prolonged median OS (169 vs. 103 days, log-rank p=0.0039; adjusted hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.64-0.84, p=0.001), prolonged median progression-free survival (PFS, 87 vs. 62 days, log-rank p=0.0309; adjusted HR 0.69, 95%CI 0.53-0.91, p=0.007), and increased disease control rate (54.67% vs. 32.77%; adjusted odds ratio 2.67, p<0.001). Results remained significant in landmark analyses. An AE-based prediction model and subsequently derived scoring system showed high calibration and discrimination in predicting OS. **Conclusions:** Presence of HTN, proteinuria or HFS during the first cycle of apatinib treatment was a viable biomarker of antitumor efficacy in metastatic GC patients.

Correlation between presence of at least one antiangiogenesis-related adverse event (AE) and antitumor efficacy of apatinib.

Clinical outcomes	With AE (n=150)	Without AE (n=119)	Unadjusted analysis		Multi-adjusted analysis[a]	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Median OS (IQR), days	169 (96-255)	103 (58-201)	0.67 (0.51,0.88)	0.0039	0.64 (0.48,0.84)	0.001
Median PFS (IQR), days	87 (57-150)	62 (41-121)	0.75 (0.58,0.98)	0.0309	0.79 (0.53,0.91)	0.007

[a]Adjusted for sex, age, number of metastatic sites and ECOG PS. IQR: interquartile range.

4053 Poster Session (Board #45), Sat, 8:00 AM-11:30 AM

Comparison of chemoradiotherapy (CRT) using carboplatin/paclitaxel (CP) versus cisplatin/5-FU (CF) for esophageal or gastroesophageal junctional (GEJ) cancer. *First Author: Hao-Wen Sim, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: For resectable esophageal or GEJ cancer, trimodality therapy improves survival compared to surgery alone and represents the current standard of care. The optimal CRT regimen for neoadjuvant or definitive treatment of locoregional esophageal or GEJ cancer remains uncertain. **Methods:** A retrospective comparison of CF and CP for locoregional esophageal or GEJ cancer (2011-2015) was performed. Overall survival (OS) and disease-free survival (DFS) were assessed using multivariable Cox proportional hazards regression, controlling for age, performance status and Charlson comorbidity index. **Results:** 101 patients (pts) were identified (61 CF, 40 CP). 75% were male. Median age was 62 years (range 30-84). Primary sites were esophageal (52%, with 65% squamous histology) and GEJ (48%). Surgery was undertaken in 34 (56%) CF and 27 (68%) CP pts. Median follow-up was 43 months. Overall, there was a non-significant trend for improved OS with CF compared to CP (HR 0.61, 95% CI 0.33-1.14, p = 0.12). In the subgroup having surgery (N = 61), we found no significant difference in OS (HR 0.99, 95% CI 0.39-2.55, p = 0.99). In the subgroup without surgery (N = 40), CF was significantly superior to CP (HR 0.21, 95% CI 0.08-0.53, $p < 0.001$). Comparing only pts in this subgroup who received equitable radiation doses (N = 33), CF was still significantly superior to CP (HR 0.09, 95% CI 0.03-0.32, $p < 0.001$). OS was similar by histology (adenocarcinoma/squamous) in all-comers (p = 0.54), and in CF (p = 0.90) and CP subgroups (p = 0.63). DFS results corresponded with OS. There was a non-significant numerical difference in pCR rates between CF (31%) and CP (18%) (p = 0.35), which were lower than previously reported. **Conclusions:** Survival is similar for CF and CP CRT regimens in pts undergoing trimodality therapy, but for those who do not proceed to surgery, it appears that CF is more effective than CP. Clinicians may prefer CP for surgical candidates given its favourable toxicity profile. However, when treating with definitive CRT, CF may be preferable to CP as a standard regimen.

4054 Poster Session (Board #46), Sat, 8:00 AM-11:30 AM

A multicentre, phase II study with cabazitaxel in previously treated patients with advanced or metastatic adenocarcinoma of the oesophagogastric junction and stomach (CABAGAST). *First Author: Harald Schmalenberg, Krankenhaus Dresden-Friedrichstadt, IV. Medizinische Klinik, Dresden, Germany*

Background: This is a single-arm study to determine prolonged (> = 4 months) disease control rate with cabazitaxel administered in second- (or later) setting for patients with advanced or metastatic adenocarcinoma of the esophagogastric junction (EGJ) and stomach. **Methods:** 65 patients with advanced EGJ and stomach cancer were treated with 20mg/m^2 Cabazitaxel every 3 weeks for a maximum of 6 cycles. Main objective of the study was a prolonged Disease Control Rate (pDCR: CR, PR or SD lasting at least 4 months). Secondary Outcome Measures were overall survival (OS), progression-free survival (PFS), response rate by subgroup (with vs without previous treatment with a taxane) and toxicity. Patients were assessed for tumor response every 6 weeks during therapy and during follow-up (up to 12 months). **Results:** 65 patients (median age: 63, range 31-86 years) were assigned. Median no. of prior therapies was 2. 80% had received prior taxane therapy. Patients received a median of 2 cycles of cabazitaxel. Efficacy results are shown for the per protocol (PP) population. pDCR rate was 12.7%, (95%CI: 5,3%- 24.5%). pDCR was 20.0% in 2nd line patients (95%CI: 6.8%-40.7%) and 30.0% (95%CI: 6.7%-65.2%) in all lines in patients without prior taxane use. Response Rate was 5.5% (95%CI: 1.1%-15.1%) in total PP and 20.0% in the population without prior taxane use. Median OS was 4.6 months (7.4 months without prior taxane vs 3.8 months with prior taxane). Median PFS was 1.38 months (95%CI: 1.28- 1.87) with and 2.01 months (95% CI: 0.20- 4.67) without prior taxane use. Most common grade 3/4 toxicities were neutropenia in 13% of the patients, pain (12%), leucopenia (10%), anemia (10%), fatigue (10%) and nausea (10%). **Conclusions:** Cabazitaxel is active in heavily pretreated patients with metastatic and advanced esophagogastric junction and gastric adenocarcinoma. Toxicity is moderate. Patients without prior taxane use derived more benefit from Cabazitaxel. Clinical trial information: NCT01956149.

4055 Poster Session (Board #47), Sat, 8:00 AM-11:30 AM

Circulating tumor DNA analysis for outcome prediction in localized esophageal cancer. *First Author: Tej D. Azad, Stanford Cancer Institute, Stanford, CA*

Background: Blood-based biomarkers are not used in routine clinical practice in patients with esophageal carcinomas (ECs). Circulating tumor DNA (ctDNA) is an attractive biomarker that could be applied to ECs. We performed a study to explore pre- and post-treatment ctDNA analysis using the next generation sequencing-based CAPP-Seq method as a prognostic biomarker for localized EC. **Methods:** We prospectively enrolled 29 patients with localized EC treated with chemoradiotherapy (CRT) between June 2011 and October 2015. 12 (43%) patients were treated with CRT alone and 17 (57%) were treated with CRT followed by esophagectomy. Our cohort included patients with stage IB (1; 3.4%), II (7; 24.1%), and III (21; 72.4%) disease. Eight (27.6%) harbored squamous cell carcinoma (SCC) and 21 (72.4%) adenocarcinoma (AC). All patients received pre-treatment evaluation by thoracic CT, PET/CT, and esophagoduodenoscopy. ctDNA levels were quantitated in pre-treatment and post-treatment plasma samples using CAPP-Seq. **Results:** Median follow-up time was 21 months. We detected ctDNA pre-treatment in 72.4% of cases (N = 21) with a median concentration of 2.69 haploid genome equivalents per mL (hGE/mL; range 0.34-107.3). Pre-treatment ctDNA concentrations were strongly correlated with metabolic tumor volumes (MTV; R^2= 0.74; p = 1.7e-07) and were significantly higher in SCC than AC patients (28.2 vs. 2.1 mean hGE/mL; p = 0.002). Overall survival (OS) at 2 years for pretreatment ctDNA+ vs. ctDNA- patients was 47% vs. 86% (HR = 6.0; 95% CI = 0.74-49.2; $p < 0.05$) and trended toward significance when accounting for stage, histology, and age (p = 0.09). A single post-treatment plasma sample was collected within 3 months of treatment and was available for 19 patients. Post-treatment ctDNA was detected in 3 (15.7%) patients with a median concentration of 11.5 hGE/mL (range 2.2–11.9). Post-treatment ctDNA detection was strongly predictive of poor event-free survival ($p < 0.0001$) and time to distant metastasis ($p < 0.0001$). **Conclusions:** Our data suggest that pre- and post-treatment ctDNA levels may be prognostic for patients with localized EC and could potentially guide risk-adapted adjuvant therapy approaches.

4056 Poster Session (Board #48), Sat, 8:00 AM-11:30 AM

The impact of marital status on racial disparities in esophageal cancer care. *First Author: Alan Paniagua Cruz, University of Michigan Medical School, Ann Arbor, MI*

Background: It is well known that racial disparities exist in cancer treatment and outcomes. The present study examined the impact of marital status as a surrogate for social support on esophageal cancer (EsC) care. **Methods:** We performed a secondary analysis of data collected from a state cancer registry. We included individuals with an EsC diagnosis between January 1, 2000 and December 31, 2013. A Chi-square test and Fisher's exact test was used to analyze categorical variables and two-sample t-tests to compare continuous variables. **Results:** 8754 patients (Caucasian (C) or African American (AA) only) were included, with 88.4% C and 11.6% AA. Staging at diagnosis in C and AA patients revealed that 30.6% vs 28.6% had localized disease, followed by 33.8% vs 32.0% with regional, and 35.6% vs 40.0% with metastatic, respectively (p = .0155). Rates of chemotherapy (53.6% vs 53.5%) and radiation therapy (54.1% vs 56.2%) administration were found to be similar between C and AA patients. In contrast, surgery rates were significantly different between the two groups, with 29.7% of C undergoing surgical resection in comparison to only 12.0% of AA patients ($p < .0001$). When evaluating marital status, 63.3% of C were married, compared to 33.4% of AA patients ($p < .0001$). In the AA group, 20.1% of married patients underwent surgery in contrast to only 7.6% of single AAs ($p < .0001$). Similarly, in the C group, married patients underwent surgery at a rate of 34.5%, while single patients went to surgery at a rate of 22.2% ($p < .0001$). Surgery contraindication (CI) rates were found to be similar across all groups (5.6% married Cs, 5.2% married AAs, 6.6% single Cs, and 6.5% single AAs) along with surgery refusal rates (1.56% single Cs vs 2.68% married Cs (p = .052), and 1.04% single AAs vs 2.81% married AAs (p = .210)). **Conclusions:** African American patients receive chemotherapy and radiotherapy at comparable rates to Caucasian patients, but the rates of surgery are significantly lower. Being married was associated with an almost three-fold increase in surgery rates for AA patients, and cause a significant increase in Caucasians too.

4057 Poster Session (Board #49), Sat, 8:00 AM-11:30 AM

Association of the addition of cetuximab to preoperative chemoradiotherapy (CRT) for locally advanced esophageal squamous cell carcinoma (SqCC) with rate of long term survival: Mature results of a prospective phase Ib/II trial. *First Author: Baruch Brenner, Rabin Medical Center, Petah Tikva, Israel*

Background: Current treatment results in locally advanced esophageal cancer (LAEC) are far from being satisfying. This prospective phase IB/II study evaluated the safety and efficacy of the addition of cetuximab to standard preoperative CRT in this disease. **Methods:** Patients (pts) with potentially resectable LAEC (T2-4N0-1M0, T1-4N1M0 or T1-4N0-1M1A) received an induction cycle of cisplatin 100 mg/m^2, day 1, and 5-FU 1000 mg/m^2/day as a continuous infusion (CI), days 1–5, followed 4 weeks later by 50.4 Gy radiotherapy given concurrently with 2 cycles of cisplatin 75 mg/m^2 and escalating doses of CI 5-FU, days 1–4 and 29-32. Pts received also 10 weekly infusions of cetuximab, 250 mg/m^2, with a loading dose of 400 mg/m^2, starting from the induction. The phase II part of the study started when the 5-FU dose during CRT was defined. Surgery was planned 6-8 weeks after CRT. **Results:** 64 pts were enrolled and 60 completed CRT. Median age was 65 years (range: 38-84 years) and 66% were males. The SqCC/adenocarcinoma ratio was 39%/61% (25/39). Pts had very advanced tumors: 95% T3-T4, 67% N1 and 19% M1A. The most common grade $>$ 3 toxicities were leucopenia (45% of pts) and neutropenia (41%). There were two cases (3%) of fatal toxicities (neutropenic sepsis and sudden death). Among the 55 operated pts, R0 resection was achieved in 51 (93%). There were 8 cases (14.5%) of postoperative mortality, due to infection (3 pts), esophageal leak (2), bleeding (2) and pulmonary insufficiency (1). Pathological down-staging was noted in 72% of pts and pathological complete response (pCR) in 33%. 5y-local control, progression-free survival (PFS) and overall survival (OS) rates for all pts were 94%, 40%, 39%, respectively. Pts with SqCC had a significantly higher pCR rate (52% vs 15%, p = 0.007), 5y-PFS (67% vs. 21%, p = 0.008) and 5y-OS (64% vs. 20%, p = 0.019). **Conclusions:** This study suggests that the addition of cetuximab to standard preoperative CRT is safe. R0, pCR, local control and long term PFS and OS rates in pts with SqCC tumors are encouraging. Further evaluation of this approach in this population seems warranted.

4058 Poster Session (Board #50), Sat, 8:00 AM-11:30 AM

Safety in numbers? Gastric cancer survival varies with total retrieved lymph nodes. *First Author: Omidreza Tabatabaie, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Recently published AJCC 8thTNM-staging guidelines recommend a minimum of 16 lymph nodes be assessed in gastric cancer surgery with more lymph nodes (30) being desirable. However, the independent effects of greater numbers of lymph nodes excised on the overall survival of patients with gastric adenocarcinoma are understudied. **Methods:** National Cancer Database (NCDB) was reviewed from 2010 to 2014 for patients who underwent potentially curative surgery for gastric adenocarcinoma. Patients with zero or unknown number of harvested lymph nodes were excluded, as were those with metastatic or in-situ disease, or who received neoadjuvant chemo- or radiotherapy. Cox proportional hazards modeling was used for multivariate survival analysis. **Results:** Of the 12,507 patients who met selection criteria, 4,880 (39.0%) were female. The median age was 69 years [IQR: 59-77]. Median number of lymph nodes examined for each clinical T and N-stage is provided in the table. Overall, 51.0% of patients had $<$ 16 lymph nodes examined. After adjusting for clinical T and N-stages, sex, age, tumor size, grade, facility type, receipt of adjuvant chemotherapy, resection type and race, and compared to patients with $<$ 16 nodes examined, the hazard ratios for death in patients with 16-29, 30-44 and $\geq$45 examined lymph nodes were 0.87 (95% CI = 0.82-0.93), 0.79 (95% CI = 0.71-0.88) and 0.68 (95% CI = 0.56-0.83), respectively. **Conclusions:** Total lymph node count is an important independent predictor of overall survival in resectable gastric cancer, with an increased number of excised lymph nodes being associated with progressively decreased risk of death. These findings support the latest AJCC guidelines that higher number of lymph node retrieval is desirable. The recommended oncologic standard for at least 16 nodes to be assessed pathologically is not attained in more than half of upfront gastric resections performed for cancer.

N-stage	Number (%)	Median # nodes [IQR]	T-stage	Number (%)	Median # nodes [IQR]
0	7481 (59.8%)	15 [9-22]	1	2755 (22.0%)	14 [8-22]
1	1218 (9.7%)	17 [11-25]	2	1551 (12.4%)	16 [10-23]
2	533 (4.2%)	15 [10-22]	3	1924 (15.3%)	17 [10-25]
3	485 (3.8%)	21 [15-29]	4	855 (6.8%)	16 [10-24]
Unknown	2790 (22.3%)	15 [9-23]	Unknown	5422 (43.3%)	15 [9-22]

4059 Poster Session (Board #51), Sat, 8:00 AM-11:30 AM

A phase II study (KSCC/HGCSG/CCOG/PerSeUS1501B) of trastuzumab plus S-1 and oxaliplatin for HER2-positive advanced gastric cancer. *First Author: Katsunori Shinozaki, Division of Clinical Oncology, Hiroshima Prefectural Hospital, Hiroshima, Japan*

Background: A combination of S-1 and cisplatin (SP) has been the standard regimen for advanced gastric cancer (AGC) in East Asia. The combination of S-1 and oxaliplatin (SOX100) was demonstrated to be non-inferior to SP in the randomized phase III study. The ToGA study demonstrated that trastuzumab (T-mab) combination therapies with cisplatin and fluoropyrimidines improved the overall survival of patients with HER2-positive AGC. This multicenter study is the first phase II trial to assess the efficacy and safety of T-mab in combination with S-1 and oxaliplatin (HER-SOX130) in HER2-positive AGC. **Methods:** Patients with HER2-positive AGC or recurrent gastric cancer defined to be IHC 3+ or IHC 2+/FISH positive received 80 mg/m^2 S-1 per day orally on days 1–14, 130 mg/m^2 oxaliplatin intravenously on day 1, and T-mab (8-mg/kg loading dose and 6 mg/kg thereafter) intravenously on day 1 of a 21-day cycle until one of the criteria for withdrawal of the study treatment occurred. The primary end-point was the response rate (RR). Adverse events were recorded based on the NCI-CTCAE Vers.4.0. The threshold response rate was defined as 50%, and the expected rate was set at 70%, with an 80% power and a 1-sided alpha value of 0.05. The calculated sample size was 37 patients. **Results:** For this study, 42 patients (median age, 66 years) were enrolled from June 2015 to May 2016. Three patients were excluded owing to ineligibility. Efficacy and safety analyses were conducted in the full analysis set of 39 patients. The proportion of patients with IHC 3+ was 87%. The confirmed RR assessed by the independent review committee was 82.1(32/39) % (95% confidence interval [CI]: 67.3–91.0), and the disease control rate was 87.2(34/39) % (95% CI: 73.3–94.4). The incidence rates of grade 3 or 4 adverse events were as follows: neutropenia, 12.8%; thrombocytopenia, 17.9%; anemia, 10.3%; sensory neuropathy, 5.1%; anorexia, 17.9%; diarrhea, 7.7%; and teary eyes, 2.6%. **Conclusions:** HER-SOX130 demonstrated encouraging efficacy with a favorable safety profile. The survival benefit of this regimen needs to be validated by conducting further follow-up of patients. Clinical trial information: 000017552.

4060 Poster Session (Board #52), Sat, 8:00 AM-11:30 AM

Magnitude and duration of immune checkpoint up-regulation and changes in the immune microenvironment post chemo-radiation (CRT) in esophageal cancer. *First Author: Ronan Joseph Kelly, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: PD-1 inhibitors in metastatic gastroesophageal cancer have demonstrated response rates of approximately 25%. Unfortunately, the majority of patients do not respond. Therefore, a rationale strategy of combining immunotherapeutic agents with CRT in earlier stage esophageal cancer may prevent metastatic disease in a greater proportion of patients. This study assessed the impact of CRT on the immune microenvironment and the expression patterns of multiple immune checkpoints to optimally design neoadjuvant clinical trials. **Methods:** To determine the effects of CRT on resected esophageal adenocarcinomas (EAC), we examined the immune microenvironment pre and post CRT using IHC, LCM followed by qRT-PCR, and functional analysis of tumor-infiltrating lymphocytes. Additionally, to assess the duration and dependency of radiation-induced PD-L1 sensitization, esophagojejunostomy were performed on rats to induce gastroduodenoesophageal reflux and EAC formation. First, tumor bearing animals were dosed with single fraction 13 Gy or 16 Gy radiation to determine safety, dose correlation, and PD-L1 sensitization using qRT-PCR post-radiation. Next, longitudinal PD-L1 expression levels within individual tumor bearing animals were determined using serial endoscopic biopsies at baseline, 1, 5 and 9 weeks post 16 Gy radiation. **Results:** The majority of cancers displayed enhanced interferon γ and activated CD8+ T lymphocytes at the tumor stroma interface. These tumors also demonstrated enhanced upregulation of PD-L1 and multiple other immune checkpoints including – TIM3, GITR, IDO1, LAG3, CD137, OX40 and KIR. The animal model results indicated PD-L1 upregulation is dose dependent and transiently elevated post radiation exposure. **Conclusions:** Collectively, these findings provide insights into the evolving immune landscape after CRT and have significant implications for future neoadjuvant trial designs that will combine radiotherapy with immune checkpoint inhibitors. Currently, we are conducting a neoadjuvant trial assessing Nivolumab or Nivolumab/Ipilimumab in combination with CRT in stage II/III operable esophageal cancer.

4061 Poster Session (Board #53), Sat, 8:00 AM-11:30 AM

Treatment patterns for resected gastric cancer using the National Cancer Database. *First Author: Foluso Nelson Ogunleye, Beaumont Health, Department of Hematology and Oncology, Oakland University William Beaumont School of Medicine, Royal Oak, MI*

Background: The optimal management of patients with resected gastric cancer remains a therapeutic challenge. Although the benefit of peri-operative chemotherapy or adjuvant concurrent chemoradiotherapy for these patients is clearly established, recurrence and mortality rates remain high despite aggressive treatment. The goal of this study was to characterize the treatment patterns employed for patients with resected gastric cancer using the National Cancer Database (NCDB). **Methods:** The NCDB was queried between 2004-2013 for patients with invasive resected gastric cancer and negative margins, excluding those with metastatic disease. **Results:** We identified a total of 21,156 cases. The median age was 67 (range 55-79). A majority of patients were white (74%) followed by black (14%) and other (12%). Most patients had either insurance through the government (58%) or private insurance (37%). 47% of patients had surgery alone with approximately 53% of these patients diagnosed with stage I gastric cancer. The remainder of the patients had radiation alone (1.4%), chemotherapy alone (15.2%), or combined chemotherapy and radiation (36.7%). Table 1 includes the further breakdown of treatment. **Conclusions:** A majority of patients with resected gastric cancer had treatment with either radiation, chemotherapy, or a combination of both. However, it is interesting to note that in patients receiving adjuvant or neoadjuvant treatment, only a portion of the patients received treatment options with level 1 evidence such as the MAGIC or McDonald regimens.

Breakdown of treatment for gastric cancer.

	# of patients	Percent
Surgery alone	9855	46.6
Radiation therapy alone		
Neoadjuvant	28	0.1
Adjuvant	264	1.2
Unknown	16	0.1
Chemotherapy alone		
Neoadjuvant	1183	5.6
Adjuvant	1224	5.8
Perioperative	443	2.1
Unknown	366	1.7
Combined chemotherapy and radiation		
Concurrent neoadjuvant	2607	12.3
Concurrent adjuvant	1382	6.5
Sequential neoadjuvant	513	2.4
Sequential adjuvant	2006	9.5
Sequential perioperative	180	0.9
Unknown	1089	5.1
Total	21156	100

4062 Poster Session (Board #54), Sat, 8:00 AM-11:30 AM

The Nationwide Cancer Genome Screening Project in Japan, SCRUM-Japan GI-screen: Efficient identification of cancer genome alterations in advanced esophageal cancer. *First Author: Yuichiro Nakashima, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*

Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in advanced non-colorectal gastrointestinal (GI) cancer (aNon-CRC), called as the SCRUM-Japan GI-SCREEN. The objective is to evaluate the frequency of cancer genome alterations in aNon-CRC and to identify patients who are candidate for clinical trial for corresponding targeting agents. **Methods:** This study is ongoing with the participation of 20 major cancer centers. Patients with aNon-CRC, including advanced esophageal cancer (aEC), who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect gene mutation, copy number variant (CNV) and fusions across 143 genes in a CLIA certified CAP accredited laboratory. The detected genomic variant data were classified according to genetic drivers of cancer including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase. In this presentation, we show the results of aEC cohort. **Results:** As of October 31st in 2016, a total of 180 aEC samples were analyzed. The sequence with the OCP was successfully performed in 121 (67.2%). Out of 157 patients except for the 23 patients in which precise data is not collected, the proportion of sample and histology type is followed; surgical specimen 58.0%, squamous cell carcinoma 92.4%. The frequently detected mutations in 114 samples of which results were available were *TP53* (77.2%), *NFE2L2* (23.7%), *CDKN2A* (9.6%), *PIK3CA* (7.0%), *RB1* (6.1%), and CNVs were *CCND1* (37.7%), *EGFR* (7.9%), *MYC* (7.9%), *SOX2* (6.1%), *ATP11B* (5.3%), *NKX2-1* (5.3%). *ERBB2* amplification was identified in 3 cases (2.6%) and *FGFR3-TACC3*fusion was identified in one case (0.9%). **Conclusions:** This nationwide screening system is efficient to detect rare gene alterations in aEC. This novel knowledge provides an intriguing background to investigate new target approaches and represents a progress toward more precision medicine. Clinical trial information: UMIN000016344.

4063 Poster Session (Board #55), Sat, 8:00 AM-11:30 AM

A randomized, open-label, multicenter trial of the concurrent chemoradiotherapy of capecitabine with or without oxaliplatin versus cisplatin with 5-FU for Chinese squamous esophageal cancer: An interim report from CRTCOESC. *First Author: Ruinuo Jia, Henan Key Laboratory of Cancer Epigenetics, Cancer Hospital, The First Affiliated Hospital, College of Clinical Medicine, Medical College of Henan University of Science and Technology, Luoyang, China*

Background: CRT with 5- FU and cisplatin (PF) has shown greater clinical efficacy for local advanced esophageal cancer (EC) but with high rate of acute toxicities (ATs). CRTCOESC is a randomized, open-label, multicenter trial designed to evaluate the effect and safety of capecitabine with or without oxaliplatin versus PF with CRT in Chinese EC. **Methods:** Pts with biopsy-proven squamous EC (T2-4N0-2M0) were randomized to single capecitabine (Arm1), capecitabine plus oxaliplatin (Arm2), or PF (Arm3), while daily radiation 50Gy/2Gy for all. Pts were stratified by different regimens cycles. Both grade3-5 ATs and 2-year OS were the primary endpoint, with a planned accrual of 249 pts to detect a decrease in Grade3-5 ATs from 40% to 20%. The secondary endpoint included objective response rate (ORR) and 2-year progression free survival (PFS). Interim analysis of ATs and ORR was planned for the first 120 pts. **Results:** The study accrued 128 pts from 2014.10-2016.12, 118 were eligible. 86 patients were finished 16-weeks follow-up at least and analyzed in the interim report (Arm1: Arm2: Arm3 = 24: 37: 25). There was no difference between three arms on pts pretreatment characters (age, gender, weight, performance status, clinical stage, lymphonodus status, and pathology grade). Incidence of grade3-5 ATs in Arm1/2/3 were 25%: 32.4%: 64% ($p = 0.03$); it was significantly lower in Arm1/2 than Arm3 (Arm1 vs Arm3, $p = 0.041$; Arm2 vs Arm3, $p = 0.022$); and there no meaningful different between Arm1 and Arm2 ($p = 0.738$). The pCR rate and ORR were 50%: 48.6%: 48% and 87.5%: 83.8%: 100% in Arm1/2/3 ($p = 0.99$; $p = 0.133$). 56 patients had been finished 1 year follow-up (Arm1: Arm2: Arm3 = 12: 26: 18). The 1-year OS and PFS were 75%: 91.9%: 76% and 66.7%: 62.2%: 60% in Arm1/2/3 ($p = 0.166$; $p = 0.926$). **Conclusions:** Compared with PF, CRT with single capecitabine with or without oxaliplatin shown lower incidence of ATs and similar ORR and 1-year OS. The single capecitabine seemly carried out a benefit of lower ATs than it plus oxaliplatin; there was no meaningful difference for them on ORR and 1-year OS. Ruinuo Jia and Tanyou Shan did equal work. Clinical trial information: NCT02025036.

4064 Poster Session (Board #56), Sat, 8:00 AM-11:30 AM

Results of a phase II randomized study evaluating the potential benefit of a postoperative intraperitoneal immunotherapy after resection of peritoneal metastases from gastric carcinoma metastases (IIPOP- NCT01784900). *First Author: Diane Goere, Gustave Roussy, Villejuif, France*

Background: Prognosis of patients with peritoneal extension from gastric carcinoma remains poor. The aim of this multicentre, open-label, phase 2 randomized study was to analyze the potential survival benefit of an immediate postoperative intraperitoneal immunotherapy using a bi-specific (anti-EpCAM, anti-CD3), trifonctional agent named catumaxomab. **Methods:** Patients with limited synchronous carcinomatosis from gastric carcinoma (Peritoneal cancer index (PCI) $\leq$ 12), were treated after complete resection (gastrectomy plus all peritoneal deposits), by an intraperitoneal infusion of catumaxomab during 5 days. Patients were randomized between 2 arms according to the total doses administered of catumaxomab (100μg *vs* 140μg). The first end-point was the 2-year overall survival (OS). Forty randomized patients were required (20 in each arm), considering that a 2-year OS rate $\leq$ 30% would be considered as unacceptable, and $\geq$ 55%, a promising survival rate. The study was stopped prematurely due to the manufacturing stop of the catumaxomab. **Results:** Between March 2013 and September 2014, 26 patients were included in the study; among them, 11 were randomized, with a median PCI of 9 [1-12]. Seven patients received the whole planned treatment of catumaxomab; in the remaining 4 patients, interruptions were related to postoperative complications. One patient died postoperatively of multiorgan failure and grade 3-5 complications occurred in all the patients, without difference between the 2 groups. At the end of the follow-up, 3 were alive (25, 30, 36 months). The median OS was 19 months, and the 1 and 2- year OS rates were 63.6% and 36.4% respectively. **Conclusions:** This study has to be stopped prematurely; however, encouraging results regarding overall survival were observed. Intraperitoneal immunotherapy represents an innovative and promising treatment in patients with peritoneal metastases, considering the poor response to systemic chemotherapy and the "immunocompetence" of the peritoneum. The evaluation of a potential benefit of a local immunotherapy has to be pursued. Clinical trial information: NCT01784900.

4065 Poster Session (Board #57), Sat, 8:00 AM-11:30 AM

Incidence rate and clinical-pathological features of hereditary diffuse gastric cancer patients in China. *First Author: Miaozhen Qiu, Cancer Center of Sun Yat-Sen University, Guangzhou, China*

Background: Familial clustering is seen in 10 % of gastric cancer cases and approximately 1-3 % of gastric cancer arises in the setting of hereditary diffuse gastric cancer (HDGC). Little is known about the incidence rate and clinical-pathologic features of HDGC in Chinese patients. **Methods:** We retrospectively collected gastric adenocarcinoma patients who were diagnosed in Sun Yat-sen University Cancer Center between January 2002 and December 2014. All the patients had detailed record of family history and Lauren classification. All of statistical analyses were performed using the Intercooled Stata 13.0 (Stata Corporation, College Station, TX). **Results:** 7431 patients were enrolled for analysis. The incidence rate of HDGC was 3.97% (295/7431). There were 124 (42.03%) male and 171 (57.97%) female patients. The median age was 35 (Mean ±SD: 35.23± 7.50). The most common sites were gastric body (49.47%) and fundus (35.09%) . The distribution of AJCC 7thTNM stage was 47 (16.32%) stage I, 59 (20.49%) stage II, 88 (30.55%) stage III and 94 (32.64%) stage IV. Only 92 patients received the HER2 immunohistochemistry test. 4 (4.35%) patients were HER2 IHC +++ and 8 (8.70%) patients were ++. The median survival was 80 months for the whole population and 15 months for stage IV patients. **Conclusions:** The incidence rate of HDGC was 3.97% in China. About one third of the patients were diagnosed at stage IV. Early detection of HDGC was warranted in China.

4066 Poster Session (Board #58), Sat, 8:00 AM-11:30 AM

Safety results of a phase 3 study of comparing paclitaxel plus 5-fluorouracil versus cisplatin plus 5-fluorouracil in chemoradiotherapy for locally advanced esophageal carcinoma (ESO-Shanghai 1). *First Author: Yun Chen, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Concurrent chemoradiotherapy (CCR) with cisplatin plus 5-Fu (PF) regimen is the standard modality for inoperable locally advanced esophageal squamous cell carcinoma (ESCC) patients. In this phase 3 trial, we aimed to assess the efficacy and safety of the paclitaxel plus 5-Fu (TF) regimen versus PF regimen in CCR for ESCC patients. **Methods:** ESCC patients presented with stage IIa to IVa were enrolled in a prospective multicenter phase 3 study. Patients were randomized to either PF group or TF group. Patients in PF group were treated with 2 cycles of CCR followed by 2 cycles of consolidation chemotherapy with PF (cisplatin 25 mg/m^2/d, d1-3, plus 5-Fu 1800 mg/m^2, civ 72h, q28d). Patients in TF group were treated with 5 cycles of weekly TF (5-Fu 300 mg/m^2, civ 96h plus paclitaxel 50 mg/m^2, d1) in CCR followed by 2 cycles of monthly TF (5-FU 1800 mg/m^2, civ 72h, plus paclitaxel 175 mg/m^2 d1) in consolidation chemotherapy. The radiotherapy dose in both groups was 61.2 Gy delivered in 34 fractions. Adverse events (AE) defined according to CTCAE 4.0. The primary end-point was 3-yr OS. The number and grade of participants with AE was analyzed by intention to treat. **Results:** Between April 2012 and July 2015, 436 ESCC patients in 7 centers were enrolled. TF group had a significant higher incidence of acute Grade 3/4 leukopenia (31.3% vs. 18.9%), hiccup (0.9% vs. 0.0%), dermatitis (17.5% vs. 7.5%), pneumonitis (9.8% vs. 2.3%), and esophagitis (6.0% vs. 3.2%), and lower incidence of anemia (0.5% vs. 1.9%), thrombocytopenia (0.5% vs. 13.8%), fatigue (5.6% vs. 17.3%), anorexia (0.5% vs. 14.1%), nausea (0.5% vs. 14.1%), and vomiting (0.9% vs. 17.7%) than PF group ($P < 0.05$). There were 3(1.4%) patients in TF group died of acute pneumonitis. For long-term AE, 1(0.5%) patient in each group died of pneumonitis. There was no significant difference in total numbers of incidence of ≥ Grade 3 AE between two groups. Until Jan 2017, the median survival has not reached. **Conclusions:** The safety results of this trial were acceptable. TF regimen showed a different AE profile compared with PF regimen used in CCR in ESCC patients. Clinical trial information: NCT01591135.

4067 Poster Session (Board #59), Sat, 8:00 AM-11:30 AM

Updated antitumor activity and safety of FPA144, an ADCC-enhanced, FGFR2b isoform-specific monoclonal antibody, in patients with FGFR2b+ gastric cancer. *First Author: Daniel V.T. Catenacci, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: FGFR2b-overexpressing gastric cancer is characterized by poor prognosis. FPA144, a humanized monoclonal IgG1 antibody that specifically binds to and blocks FGFR2b, has been engineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). FPA144-001 is a two-part Phase 1 study of FPA144 monotherapy in patients with advanced solid tumors, including gastric and gastroesophageal cancers (GEJ cancers). **Methods:** Part 1A was a 3+3 design to assess safety and PK and to establish a recommended dose (RD) of FPA144. Patients with gastric cancer were enrolled in Part 1B to assess PK in gastric cancer. Part 2 includes 4 cohorts of gastric cancer patients with either high, moderate, low or no FGFR2b overexpression based on a centralized immunohistochemistry (IHC) assay. Here, we describe results of gastric cancer patients that highly overexpress FGFR2b (FGFR2b+ High) enrolled in Parts 1 and 2 of the study. **Results:** As of October 28, 2016, 18 FGFR2b+ High (IHC 3+ ≥10% tumor membrane staining) patients were enrolled in the study. 12 of these patients received the RD of 15 mg/kg every 2 weeks. Enrolled patients received a median of 3 prior treatment regimens. Fatigue (22.2%, none ≥ gr 3) and infusion reaction (16.7%, 5.6% gr 3) were the most common treatment-related AEs. Treatment-related SAEs were reported in 2 patients: Grade 2 ulcerative keratitis and Grade 3 infusion reaction. There were 5 PRs, 4 confirmed and 1 unconfirmed. Disease control (PR+SD) was 55.6%, including a confirmed ORR of 22% with median DOR of 15.4 weeks. ctDNA analysis of a responding patient revealed baseline elevated FGFR2 gene copy (165 copies in the blood, mutation allele burden 66%) that decreased after monotherapy (nadir 75 copies, mutation allele burden 38.5%) corresponding with clinical response, serum tumor markers and near complete response on PET imaging. **Conclusions:** The demonstration of activity and an acceptable safety profile supports further development of FPA144 in patients with FGFR2b+ tumors. *FGFR2* gene amplification detected in ctDNA may provide a non-invasive diagnostic test for patient selection. Updated data will be presented. Clinical trial information: NCT02318329.

4068 Poster Session (Board #60), Sat, 8:00 AM-11:30 AM

Predicting survival in gastric cancer patients randomized to docetaxel with mass spectrometric quantitation of TUBB3. *First Author: Fabiola Cecchi, NantOmics, LLC, Rockville, MD*

Background: No predictive biomarker for chemotherapy has been validated for clinical use. A relationship between resistance to taxanes and expression of class III β-tubulin (TUBB3) protein has been suggested by small clinical studies, but not confirmed in randomized trials. Immunohistochemical definitions of "TUBB3 positive" vary widely between studies and depend on subjective measures of strong vs weak staining. We retrospectively evaluated the relationship between survival and TUBB3 protein quantitated by mass spectrometry in the tumor samples of 247 patients from the Intergroup Trial of Adenocarcinoma of the Stomach (ITACA-S). Patients had been randomized to a docetaxel-containing adjuvant regimen or to monotherapy with fluorouracil and leucovorin (5-FU/LV). **Methods:** Archived tumor tissues were microdissected and solubilized for proteomic analysis. TUBB3 and 44 other protein biomarkers were quantified with a mass spectrometry-based assay. A TUBB3 protein cutoff of 750 amol/ug was predetermined based on the assay's limit of detection. The Mantel-Cox log-rank test was used for survival comparisons. **Results:** Among gastric cancer (GC) patients treated with docetaxel-containing chemotherapy (n = 125), those with TUBB3 levels below the cutoff (750 amol/μg of total protein) had a longer median overall survival (mOS) than patients with TUBB3 levels above the cutoff (1563 vs 886 days, p = 0.04). TUBB3 level made no difference in survival among patients who received 5-FU/LV. Of note, among patients with high TUBB3 levels (> 750 amol), those treated with 5-FU/LV survived 3 years longer than patients in the docetaxel arm (mOS = 1991 vs 886 days, p = 0.048). **Conclusions:** Quantitative proteomic analysis of TUBB3 identified a subset of GC patients who benefitted from the addition of docetaxel to adjuvant chemotherapy. GC patients with TUBB3-expressing tumors had worse outcomes on a docetaxel-containing regimen than on 5-FU/LV. An ongoing study of triple-negative breast cancer patients treated with docetaxel suggests that proteomic TUBB3 may be predictive in other cancer indications. Personalized chemotherapy based on quantitated TUBB3 is promising and warrants broader evaluation.

4069 Poster Session (Board #61), Sat, 8:00 AM-11:30 AM

Phase II study of BKM120 in patients with advanced esophageal squamous cell carcinoma (EPOC1303). *First Author: Ken Kato, Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan*

Background: BKM120 is an oral pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, which showed promising activity in breast cancer and squamous cell carcinoma of head and neck. We prospectively investigated clinical activity, safety and biomarkers of BKM120 in advanced esophagus squamous cell carcinoma (ESCC). **Methods:** We conducted a multicenter phase II study of BKM120 monotherapy in patients with pretreated advanced ESCC. All the patients had a treatment history of fluoropyrimidine and platinum. BKM120 of 100 mg/day was orally administered in a 28-day cycle. A primary end-point was a disease control rate (DCR). Using Simon's minimax two-stage design, total of 41 patients were required for primary analysis (promising DCR of 60%, non-promising one of 40%, one-sided alpha level of 10% and power of 90%). The response rate (RR), progression-free survival (PFS), overall survival (OS), and safety were also evaluated as secondary endpoints. Tumor samples for all the patients were required for gene alternation analysis in comprehensive genomic profiling assay (FoundationOne). **Results:** A total of 42 patients (median age, 62.5 years; performance status 0/1 = 28/14) were enrolled. One ineligible patient was excluded from primary analysis. Nineteen and two patients had SD and unconfirmed PR. DCR was 51.2% (95% CI, 35.1% to 67.1%), which met the primary endpoint of the study. Median PFS and OS was 2.0 months (95% CI, 1.8 to 3.2 months) and 9.0 months (95% CI, 6.4 to 11.7 months), respectively. Common grade 3 or 4 adverse events were anorexia, rash, hyponatremia, lipase increased, and abnormal hepatic function (including increased transaminase levels), which were profiles similar to previous studies of BKM120 monotherapy. No treatment-related deaths occurred. Further analyses of the gene alternation are ongoing. **Conclusions:** BKM120 monotherapy showed promising efficacy and mild toxicity profile in patients with pretreated advanced ESCC. BKM120 is worth evaluating in a further confirmatory study. Result of subgroup analyses with respect to gene alternation status will be presented. Clinical trial information: UMIN000011217.

4070 Poster Session (Board #62), Sat, 8:00 AM-11:30 AM

Comparison of efficacy and safety of first-line palliative chemotherapy with TX and XELOX regimens in patients with metastatic gastric adenocarcinoma: A randomized phase II trial. *First Author: Xiaodong Zhu, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Docetaxel has shown antitumor activity in the treatment of MGC as a single or combination chemotherapy. This study was designed to compare the clinical outcome of docetaxel based and platinum based doublet regimen as first-line treatment in MGC patients. **Methods:** In an open, randomized, single center phase II trial, 134 pts were randomly assigned and treated with either TX (capecitabine 1g/m2/twice daily/ 1-14 days and docetaxel 75mg/m2 in 1st day) or XELOX (capecitabine 1g/m2/twice daily/ 1-14 days and oxaliplatin 130 mg/m2 in 1st day) as first-line chemotherapy. The primary endpoint is finding potential predictive factors, secondary endpoint is ORR, PFS, OS and safety. After progression, patients were switched into the other group. **Results:** Now, the potential predictive factors are testing in genomics and proteomics. In 134 randomly assigned and treated pts (TX = 69; XELOX = 65). Most pts were male (87pts).Overall survival was longer with TX versus XELOX (13.1m vs. 9.6m, p = 0.173), but no statistical differences. Progression free survival was similar with TX versus XELOX (4.57m vs. 5.27m, p = 0.297). Overall response rate was equal with TX versus XELOX (50.8% vs. 47.6%, p = 0.72). G3-4 treatment-related AE occurred in 60.6% (TX) v 55.4% (XELOX) of patients. Frequent G3-4 toxicities for TX v XELOX were: neutropenia (60.6% v 15.4%), febrile granulocyte deficiency (17.4% v 1.5%), anemia (10.1% v 10.8%), thrombocytopenia (1.4% v 15.4%), and all grade peripheral neurotoxicity (11.6% v 38.5%).After first-line treatment failure, 35 patients in the TX group switched to XELOX, and 27 patients in the XELOX group switched to TX, and there is also no significant difference in survival time from the first-line treatment between the two groups (p = 0.129). **Conclusions:** Although TX led to more neutropenia, first-line palliative chemotherapy with docetaxel based doublet regimens provides a new choice and can gain almost the same response rate and survival time as frequently-used fluorouracil and platinum based regimen. And potential predictive factors will indicate who will get more benefit from taxanes or platinums. Clinical trial information: NCT01963702.

4071 Poster Session (Board #63), Sat, 8:00 AM-11:30 AM

Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC). *First Author: Zev A. Wainberg, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: Durvalumab, an anti-PD-L1 mAb, has shown early and durable clinical activity with manageable safety in an ongoing Phase 1/2, multicenter, open-label study in pts with advanced solid tumors. Interim analyses from the HCC cohort in the dose-expansion part of this study are reported here. **Methods:** Patients with HCC (Child-Pugh class A) received durvalumab 10 mg/kg i.v. q2w for 12 months or until confirmed progressive disease, whichever occurred first. The primary objective was to evaluate the safety profile; secondary objective was to assess the antitumor activity (investigator-assessed RECIST v1.1). Clinical activity was evaluated for the total HCC population and by viral status. **Results:** As of Oct 24 2016, 40 HCC pts with median 23.9 (range 2.4–34.7) weeks follow-up received durvalumab. 93% had prior sorafenib. Treatment-related AEs occurred in 80.0% of pts, most commonly fatigue (27.5%), pruritus (25.0%) and elevated aspartate aminotransferase (AST) (22.5%). Grade 3–4 treatment-related AEs were reported in 20.0% of pts, most commonly elevated AST (7.5%) and elevated alanine aminotransferase (5.0%). 7 (17.5%) pts completed the initial 12-month treatment and 7 (17.5%) pts discontinued treatment because of an AE (none related to treatment). There were no deaths due to treatment-related AEs. Clinical activity is presented in the table. 4 pts achieved a PR; 2 were ongoing at data cut-off. **Conclusions:** Durvalumab had an acceptable safety profile and showed promising antitumor activity and OS in pts with HCC, particularly HCV+ pts. Clinical trial information: NCT01693562.

Antitumor activity	HBV+ n=9[b]	HCV+ n=8	Non-B/Non-C n=21	All N=39
ORR (CR + PR) (95% CI), %[a]	0 (0–33.6)	25.0 (3.2–65.1)	9.5 (1.2–30.4)	10.3 (2.9–24.2)
CR + PR + SD ≥24 weeks (95% CI), %	11.1 (0.3–48.2)	62.5 (24.5–91.5)	33.3 (14.6–57.0)	33.3 (19.1–50.2)
Survival	n=10	n=8	n=21	N=40
Median OS (95% CI), months	6.3 (1.4–NA)	19.3 (9.5–23.0)	13.2 (4.7–24.2)	13.2 (6.3–21.1)
OS 9-month rate (95% CI), %	38.6 (9.1–68.5)	100.0 (NA–NA)	61.9 (38.1–78.8)	62.3 (44.7–75.8)
OS 12-month rate (95% CI), %	38.6 (9.1–68.5)	83.3 (27.3–97.5)	57.1 (33.8–74.9)	56.4 (38.8–70.7)

[a]All responses were confirmed; [b]1 HBV+ pt was non-response evaluable as discontinued per pt request prior to first scheduled scan

4072 Poster Session (Board #64), Sat, 8:00 AM-11:30 AM

PrE0204: A multi-institutional, single arm, two-stage phase II trial of nab-paclitaxel and gemcitabine for first-line treatment of patients with advanced or metastatic cholangiocarcinoma—A PrECOG LLC study. *First Author: Vaibhav Sahai, University of Michigan, Ann Arbor, MI*

Background: Pts with advanced or metastatic cholangiocarcinoma (CCA) have limited response to current chemotherapy regimens and poor overall survival (OS). Nab-Paclitaxel (nabPAC) can increase the intra-cellular concentration of gemcitabine (GEM) through depletion of its metabolizing enzyme, cytidine deaminase (CDA). We investigated the nabPAC+GEM combination in a ph II single arm trial in advanced or metastatic CCA pts with exploratory biomarker evaluation, including CDA, hENT1, SPARC and circulating tumor cells (CTCs). **Methods:** Key eligibility criteria: advanced or metastatic CCA with no prior systemic chemotherapy, age $>$ 18, ECOG PS 0-1 and Child-Pugh $<$ 8. Pts received nabPAC (125 mg/m2 IV) and GEM (1000 mg/m2 IV) days 1, 8 and 15 Q4 weeks until progression. Primary endpoint: progression-free survival (PFS) rate at 6 months. Secondary endpoints: safety, time to progression (TTP), objective response (ORR) and disease control rates (DCR), median PFS and OS, as well as correlation of change in CA 19-9 to clinical efficacy. The study required $>$ 43 of 67 evaluable patients alive and progression-free at 6 months to conclude the 6-month PFS rate is at least 70% against a null hypothesis of 55% based on historical data. **Results:** 73 eligible patients (41.1% male, 91.8% Caucasian, 45.2% ECOG PS 0) were enrolled across 22 sites with a median age of 62 (range 36-87) years and received a median of 6 (range 1-18) cycles. The primary endpoint of PFS rate at 6 months was 54.7% on intention to treat analysis. Response evaluation is underway and will be reported at the meeting. The median PFS and OS were 6.5 (95% CI, 5.1-7.7) and 10.3 (95% CI, 9.1-14.6) months, respectively. The safety profile of nabPAC +GEM was similar to that reported in ph III MPACT trial. The most common treatment-related G3/4 toxicities were neutropenia (24.3%), fatigue (13.5%) and anemia (12.2%). Five patients remain on the trial. Exploratory analyses are pending. **Conclusions:** The observed PFS rate at 6 months with nabPAC+GEM in CCA is insufficient to reject the null hypothesis of 55% PFS at 6 months, and appears to be as effective as the historical control. Clinical trial information: NCT02181634.

4073 Poster Session (Board #65), Sat, 8:00 AM-11:30 AM

Phase I/II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (HCC): Phase I safety and efficacy analyses. *First Author: Robin Kate Kelley, University of California, San Francisco, San Francisco, CA*

Background: Durvalumab and tremelimumab, investigational monoclonal antibodies against PD-L1 and CTLA-4 immune checkpoints, respectively, have shown efficacy in monotherapy and offer promise in combination for patients (pts) with HCC. This is a phase I/II, open-label, randomized study of durvalumab combined with tremelimumab in unresectable HCC. **Methods:** Phase I part of this study is a safety run-in cohort treated at the recommended phase II doses of the durvalumab/tremelimumab combination (20 and 1 mg/kg IV Q4W respectively for 4 doses followed by 20 mg/kg Q4W durvalumab alone) in pts with unresectable HCC with or without concomitant HBV or HCV infection who progress on, are intolerant to, or have refused sorafenib therapy. Secondary objectives include evaluation of antitumor activity. Here we present results of a preplanned analysis from the completed phase I part of the study. **Results:** As of 10 January 2017, 40 pts have been enrolled (11 HBV+, 9 HCV+, 20 uninfected). 30% had no prior systemic therapy; 93% were Child Pugh Class A. 24 (60%) had ≥1 treatment-related AE; 20% had ≥1 grade ≥3 related AE. Most common (≥15%) treatment-related AEs: fatigue (20%), increased ALT (18%), pruritus (18%), and increased AST (15%). Most common grade ≥3 related AE was asymptomatic increased AST (10%). 24 pts have discontinued treatment: 3 due to treatment-related AEs (grade 3 pneumonitis, grade 3 colitis/diarrhea, asymptomatic grade 4 elevated AST and ALT), 16 due to progressive disease, 4 due to death unrelated to treatment (cardiac arrest, variceal bleed, progressive disease, probable HCC rupture), and 1 other (pt entered hospice care). 40 pts were evaluable for response at ≥16 weeks follow-up. **Conclusions:** No unexpected safety signals with durvalumab and tremelimumab were seen in this unresectable HCC population. Clinical activity observed predominantly in uninfected pts though interpretation limited by small subsets. Enrollment to the phase II portion of the study is ongoing. Clinical trial information: NCT02519348.

n (%)	HBV+ (N = 11)	HCV+ (N = 9)	Uninfected (N = 20)	All (N = 40)
Confirmed ORR (all PR)	0	0	6 (30)	6 (15)
CR + PR (confirmed + unconfirmed)	1 (9.1)	0	7 (35)	8 (20)
CR + PR + SD ≥16 wk (DCR16)	5 (45.5)	4 (44.4)	14 (70)	23 (57.5)

4074 Poster Session (Board #66), Sat, 8:00 AM-11:30 AM

Safety and activity of the pan-fibroblast growth factor receptor (FGFR) inhibitor erdafitinib in phase 1 study patients (Pts) with molecularly selected advanced cholangiocarcinoma (CCA). *First Author: Jean-Charles Soria, Drug Development Department (DITEP), Gustave Roussy, Villejuif, France*

Background: Erdafitinib (JNJ-42756493) is a potent, oral pan-FGFR tyrosine kinase inhibitor that demonstrated encouraging preliminary clinical activity and manageable adverse events (AEs) in its first-in-human phase 1 study in advanced solid tumors (NCT01703481). Here we report results from pts with CCA from this study. **Methods:** This 4-part study enrolled pts age ≥ 18 years (y) with advanced solid tumors. Dose escalation (part 1) followed a 3+3 design, with pts receiving ascending doses of erdafitinib continuously or intermittently (7 days on/7 days off). Subsequent parts required FGFR gene alterations in the tumor, including activating mutations and translocations or other FGFR-activating aberrations. Part 2 was a pharmacodynamics cohort. Parts 3 and 4 were dose-expansion cohorts for recommended phase 2 doses of 9 mg once daily (QD) and 10 mg intermittently, respectively. **Results:** Eleven pts with FGFR-aberrant CCA were treated at 9 mg QD (n = 1) or 10 mg intermittent (n = 10). Median age was 60 y; 7 of 11 pts were female (64%). 73% of pts had ECOG performance status 1. All had prior systemic therapy. Median treatment duration with erdafitinib was 5.3 months (mo). Systemic erdafitinib exposure, per C_{max} and AUC, in CCA pts was similar to other indications. The most common AEs were stomatitis (82%), hyperphosphatemia (64%), dry mouth (55%), dysgeusia (45%), dry skin (45%), and asthenia (45%), mostly grade 1/2 severity. No drug-related grade ≥3 AEs were reported in > 1 pt except grade 3 stomatitis (n = 2; 18%). The objective response rate, all confirmed partial responses (PRs) per RECIST 1.1, was 27.3% (3/11; 95% CI 6, 61); an additional 27.3% (3/11) had stable disease as their best response. Overall disease control rate was 55%. All 3 PRs were at the 10 mg intermittent dosage, and the median duration of response was 12.9 mo. With a median follow-up of 5.1 mo, median progression-free survival was 5.1 mo (95% CI 1.6, 16.4). As of the cutoff date, 2 pts continue on study treatment. **Conclusions:** Erdafitinib showed encouraging clinical activity and minimal toxicity in pts with advanced CCA and FGFR alterations. These results warrant further study. Clinical trial information: NCT01703481.

4075 Poster Session (Board #67), Sat, 8:00 AM-11:30 AM

A phase I study of DKN-01 (D), an anti-DKK1 monoclonal antibody, in combination with gemcitabine (G) and cisplatin (C) in patients (pts) for first-line therapy with advanced biliary tract cancer (BTC). *First Author: Jennifer Rachel Eads, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: DKK1 is a secreted modulator of Wnt signaling often expressed in tumors, including BTC. DKK1 expression in BTC is associated with advanced stage and shorter survival. Depletion of DKK1 has efficacy in BTC xenograft models, inhibits cell invasion, and decreases MMP9 and VEGF-C expression, known promoters of metastasis and angiogenesis. D is a humanized monoclonal antibody against DKK1. This study evaluated the safety and efficacy of D in combination with GC in pts with advanced BTC. **Methods:** In Part A, pts received D at either 150 or 300 mg (and 300 mg D in Part B expansion) with 1000 mg/m2 G and 25 mg/m2 C on days 1 and 8 of each 21-day cycle. Response assessed every 2 cycles using RECISTv1.1. **Results:** 27 pts were enrolled; 4 dosed at 150 mg and 23 dosed at 300 mg. Median age: 65; Female: 74%; White: 85%. Gallbladder cancer 37%, intrahepatic cholangiocarcinoma 59%. 3 pts had prior G: 2 pts with adjuvant G; 1 pt with 2 prior regimens. Median number of cycles with D: 8 (range 1, 17). Median duration on study 6.8 mos; 8 pts still on therapy. No dose limiting toxicities or D-related serious adverse events have been observed. 24 pts (89%) had grade 3/4 treatment emergent adverse events (TEAEs); events in ≥ 3 pts include: neutropenia (n = 19), leukopenia (n = 9), thrombocytopenia (n = 9), hyperbilirubinemia (n = 6), anemia (n = 5), AST/ALT elevation (n = 4), and ALP elevation, bacteremia, hypertension, and hyponatremia (n = 3 each). The MTD of D + GC was 300 mg. At the MTD; 7 pts had a confirmed partial response (PR), 14 pts had stable disease > 6 weeks, and 1 pt had progressive disease. Both overall and MTD median PFS were 9.4 mos (95% CI 4.6, NE); median overall survival and duration of response were not reached. **Conclusions:** The addition of D (300 mg) to GC demonstrated a preliminary PFS of 9.4 mos and disease control rate of 96% with a 32% PR rate in pts with BTC. D + GC is well tolerated with no new emerging safety trends. Clinical trial information: NCT02375880.

4076 Poster Session (Board #68), Sat, 8:00 AM-11:30 AM

Precision medicine for gallbladder cancer using somatic copy number amplifications (SCNA) and DNA repair pathway gene alterations. *First Author: Milind M. Javle, Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Gallbladder carcinoma (GBC) is commonly diagnosed at an advanced, unresectable disease stage and has a poor prognosis. Comprehensive genomic profiling (CGP) has a developing role in guiding systemic, precision anti-cancer therapy. **Methods:** We performed hybrid capture-based CGP on FFPE samples for 491 consecutive advanced GBCs. Mean coverage depth was >550X for up to 315 cancer-related genes plus 37 introns from 28 genes frequently rearranged in cancer. All 4 classes of genomic alterations (GA) were detected. Tumor mutational burden (TMB) was determined on up to 1.1 Mb of sequenced DNA. **Results:** Median age was 64 (range 25-88) and 69% (337/491) of patients were female. 96% (470), 2.9% (14), and 1.4% (7) of GBC patients had the diagnosis of adenocarcinoma, adenosquamous, or carcinoma not specified (NOS), respectively. Commonly altered genes were *TP53* (62%), *CDNK2A* (31%), *ARID1A* (18%), and *SMAD4* (15%), and most of the genetic aberrations (GA) were short variants. Potentially targetable SCNAs (including *ERBB* genes, *MET*, *FGFR*s, and the *CCND1-FGF3/4/19* 11q13 amplicon) were identified in 21% of cases (Table). Oncogenic *BRAF*, *ALK*, or *FGFR2/3* rearrangements were found in 7 cases (1.4%). Moreover, 7.8% of cases had *BRCA2* or *ATM* GA, and 0.8% had *INI1* loss suggesting benefit from PARP or EZH2 inhibitors, respectively. TMB was low; the 25th, 50th, and 75th percentiles were 2.5, 3.8 and 6.3 mutations/Mb, respectively. Less than 1% of cases had microsatellite instability. Radiological response to TKIs and immunotherapy was noted. **Conclusions:** In addition to the significant opportunity for anti-HER targeted therapies, other subsets of GBC cases harbored kinase GA (particularly SCNA), the 11q13 amplicon, or *BRCA2*/*ATM*/*INI1* mutations that are linked to therapeutic benefit. How the frequency of both driver SCNA and DNA repair alterations in GBC can be linked with inflammation awaits additional investigation.

Gene	SCNA cases (%)	Median copy number
EGFR	5 (1)	14
ERBB2	51 (10)	16
ERBB3	19 (4)	8
ERBB4	1 (0.2)	6
MET	8 (2)	19
FGFR1	1 (0.2)	12
FGFR2	2 (0.4)	184
FGFR3	13 (3)	11
FGFR4	0 (0)	NA
11q13	18 (4)	12
TOTAL	103* (21)	

*15 cases had ≥1 SCNA.

4077 Poster Session (Board #69), Sat, 8:00 AM-11:30 AM

BBI608-503-103HCC: A phase Ib/II clinical study of napabucasin (BBI608) in combination with sorafenib or amcasertib (BBI503) in combination with sorafenib (Sor) in adult patients with hepatocellular carcinoma (HCC). *First Author: Bassel F. El-Rayes, Winship Cancer Institute, Atlanta, GA*

Background: Napabucasin, a first-in-class cancer stemness inhibitor in clinical development, suppresses cancer stemness by targeting STAT3-driven gene transcription. Amcasertib targets multiple serine threonine stemness kinases and inhibits Nanog and other cancer stemness pathways. Preclinically, potent and broad-spectrum anti-cancer activity was observed *in vitro* and *in vivo*, alone and in combination with sorafenib. **Methods:** A phase Ib/II open-label, multi-center study in adult patients with advanced HCC who have not received prior systemic chemotherapy was performed to determine the safety, tolerability, and recommended Phase II dose (RP2D) , according to the criteria for DLT and for dose-escalation of Napabucasin (Arm 1), administered at 160 mg BID (dose level I) and at 240 mg BID (dose level II) in combination with sorafenib and of Amcasertib (Arm 2), administered at 100 mg QD (dose level I) and at 200 mg QD (dose level II) in combination with sorafenib. **Results:** 20 pts were enrolled, 10 in Arm 1 and 10 in Arm 2. 12 patients were evaluable for DLT determination; 2 pts d/c prior to starting protocol treatment; 11 pts received evaluation by RECIST, 6 pts in Arm 1 and 5 pts in Arm 2. The safety profile was consistent with that of each agent as monotherapy and most common AEs were attributed to *(Sor)* and included rash, PPE, grade 1/2 diarrhea, nausea, abdominal cramps, and vomiting. No signs of drug-drug interactions were observed in pharmacokinetics. Among all patients who received RECIST evaluation, Disease Control Rate (DCR=CR+PR+SD) for Arm 1 was 100% (6/6pts) and 100% (5/5pts) for Arm 2. DCR in ITT Arm 1 population was 67% and 50% in Arm 2. Median OS is not yet reached. **Conclusions:** In this phase Ib study, RP2D were determined for napabucasin and amcasertib to be safely combined with sorafenib at full dose, showing encouraging anti-tumor activity in patients with HCC who have not received prior systemic chemotherapy. A randomized phase II is schedule to start. Clinical trial information: NCD02279719.

Population	Subgroup	mPFS (wks)
ITT	BBI608 + *(Sor)* n=10	24.9
	BBI503 + *(Sor)* n=10	22
Eval	BBI608 + *(Sor)* n=6	32.6
	BBI503 + *(Sor)* n=5	39.7

4078 Poster Session (Board #70), Sat, 8:00 AM-11:30 AM

Efficacy of regorafenib (REG) in patients with hepatocellular carcinoma (HCC) in the phase III RESORCE trial according to alpha-fetoprotein (AFP) and c-Met levels as predictors of poor prognosis. *First Author: Michael Teufel, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ*

Background: REG is a multikinase inhibitor which improved overall survival (OS; HR 0.63, 95% CI 0.50, 0.79; P<0.0001) and time to progression (TTP; HR 0.44, 95% CI 0.36, 0.55; P<0.0001) compared with placebo in patients with HCC who progressed during prior sorafenib treatment in the RESORCE trial. This exploratory analysis evaluated the impact of baseline AFP and c-Met on REG treatment benefit (OS and TTP) in the RESORCE trial. **Methods:** Circulating AFP and c-Met protein (shed ectodomain) levels were quantified by a Luminex assay (Myriad RBM) in plasma samples collected at baseline from patients enrolled in the RESORCE trial. Valid biomarker data were available from 497 (AFP) and 499 (c-Met) out of 573 patients. Patients were subgrouped according to the median protein concentration (high vs low), and the treatment effect HR and its 95% CI were evaluated using a Cox proportional hazards model. The predictive effect was modeledas a protein–treatment interaction effect and subjected to Akaike information criterion (AIC)-based selection to assess its association with OS and TTP. **Results:** Baseline characteristics of patients were balanced across protein subgroups. While increased levels of both AFP (HR 1.09, 95% CI 1.07, 1.12; P<0.001) and c-Met (HR 1.32, CI 95% 1.06, 1.63; P=0.011) were associated with a worse prognosis for OS, increased AFP levels were also associated with poor prognosis for TTP (HR 1.05, 95% CI 1.03, 1.07; P<0.001). REG treatment benefit for both OS and TTP was independent of AFP and c-Met protein expression (Table). The protein–treatment interaction effect was not statistically significant. **Conclusions:** The treatment benefit of REG in patients with HCC was independent of AFP and c-MET protein expression at baseline. So far, no single protein has been associated with REG clinical benefit. Clinical trial information: NCT01774344.

Protein, expression	OS HR (95% CI)	OS P-value	TTP HR (95% CI)	TTP P-value
AFP, low	0.62 (0.44, 0.87)	0.006	0.39 (0.28, 0.52)	<0.001
AFP, high	0.58 (0.42, 0.79)	<0.001	0.46 (0.34, 0.62)	<0.001
c-Met, low	0.55 (0.39, 0.76)	<0.001	0.37 (0.27, 0.50)	<0.001
c-Met, high	0.65 (0.47, 0.90)	<0.01	0.48 (0.36, 0.65)	<0.001

4079 Poster Session (Board #71), Sat, 8:00 AM-11:30 AM

Predictive model for microvascular invasion of hepatocellular carcinoma among candidates for either hepatectomy or liver transplantation. *First Author: Hidetoshi Nitta, Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Villejuif, France*

Background: Microvascular invasion (MVI) is the strongest prognostic factor following surgery of hepatocellular carcinoma (HCC). However, it is usually not available on the preoperative setting. A predictive model of MVI in patients scheduled for hepatic resection (HR) or liver transplantation (LT) would thus help guiding treatment strategy. The aim of this study was to develop a predictive model for MVI of HCC before either HR or LT. **Methods:** HCC patients who consecutively performed HR or LT from January 1994 to June 2016 at a single institution were subdivided into a training and validation cohort. Risk factors for MVI in the training cohort were used to develop a predictive model for MVI, to be validated in the validation cohort. The outcomes of the HR and LT patients with high or low MVI probability based on the model, were compared using propensity score matching (PSM). Cut-off values for continuous factors were determined based on ROC curve analysis. **Results:** A total of 910 patients (425 HR, 485 LT) were included in the training (n = 637) and validation (n = 273) cohorts. In the training cohort, multivariate analysis demonstrated that alpha-fetoprotein ≥100ng/ml ($p < 0.0001$), largest tumor size ≥40mm ($p = 0.0002$), non-boundary HCC type on contrast-enhanced CT ($p = 0.001$), neutrophils-to-lymphocytes ratio ≥3.2 ($p = 0.002$), aspartate aminotransferase ≥62U/l ($p = 0.02$) were independently associated with MVI. Combinations of these 5 factors varied the MVI probability from 15.5% to 91.1%. This predictive model achieved a good c-index of 0.76 in the validation cohort. In PSM (109 HR, 109 LT), there was no difference in survival between HR and LT patients among the high MVI probability (≥50%) patients, (5y-OS; 46.3% vs 42.2%, $p = 0.77$, 5y-RFS; 54.0% vs 28.8%, $p = 0.21$). Among the low probability (< 50%), survival was significantly decreased following HR compared with LT (5y-OS; 54.1% vs 78.8%, $p = 0.007$, 5y-RFS; 17.3% vs 86.1%, $p < 0.0001$). **Conclusions:** This model developed from preoperative data allows reliable prediction of MVI, and may thus help with preoperative decisions about the suitability of HR or LT in patients with HCC.

4080 Poster Session (Board #72), Sat, 8:00 AM-11:30 AM

Stereotactic body radiation therapy to generate comparable survival to surgery in treating hepatocellular carcinoma (HCC): Results of 756 patients. *First Author: Feng Ming Kong, Indiana University Department of Radiation Oncology, Indianapolis, IN*

Background: Stereotactic Body Radiation Therapy (SBRT) has emerged as a viable treatment option in patients with hepatocellular carcinoma (HCC). This study aimed to compare survival outcomes after SBRT with other front line local treatments for HCC. **Methods:** This is a retrospective analysis of patients identified through our cancer registry from 2000 to 2016. Patients treated with any local therapy alone were eligible: SBRT, surgery, conventional external beam radiation (CEBRT), and other local therapies including brachytherapy. Patients treated with combined therapies such as SBRT plus liver transplant were excluded. The primary endpoint was overall survival which was estimated from the time of diagnosis. Differences between the groups were compared using log-rank test. The data are presented as median (95%CI). **Results:** A total of 756 patients with a median follow-up of 45 months (mo) met the selection criteria: 116, 380, 43, and 217 patients received SBRT, surgery, CEBRT, and other local treatment, respectively. Median age was 61, 60, 61 and 60 years, respectively. The median overall survival/3 year overall survival rate were 49 (32-66) mo /53% (44-65%) for patients treated with SBRT, which were not significantly different from 75 (57-94) mo /63% (58-69%) of surgery (p = 0.27), non-significantly better than 22 (13-31) mo /41% (27-60%) of CEBRT (p = 0.13), significantly better than 15 (13-20) mo /26% (20-34%) of other local treatments ($p = 3\times10^{-7}$). After adjusting for significant prognostic factors including age, race, status of tobacco abuse, history of alcohol use, tumor size, histology grade and stage, the survival outcomes of SBRT remained to be insignificantly different from surgery (HR = 0.8, p = 0.2), have a trend of significant difference from CEBRT (HR = 1.4, p = 0.1) and remarkably superior to that of other local treatments (HR = 1.8, $p = 2\times10^{-4}$). **Conclusions:** This study suggests that SBRT is an excellent front line option for HCC, potentially comparable to surgical resection and associated with longer survival than other front line local treatments. Randomized studies are needed to validate these findings.

4081 Poster Session (Board #73), Sat, 8:00 AM-11:30 AM

A phase 2 trial of regorafenib as a single agent in patients with chemotherapy refractory advanced and metastatic biliary adenocarcinoma/cholangiocarcinoma. *First Author: Weijing Sun, University of Pittsburgh, Pittsburgh, PA*

Background: Biliary adenocarcinoma/cholangiocarcinoma is a rare but aggressive neoplasm. Most patients present with unresectable or metastatic disease with 5-year survival rate ~5%. No second-line regimen has demonstrated clinical benefit in this disease. Regorafenib is an oral multi-kinase inhibitor with potent antitumor activity. This single arm phase II study evaluates the efficacy and safety of regorafenib as a single agent in advanced or metastatic biliary carcinoma/cholangiocarcinoma pts who failed systemic chemotherapy. **Methods:** Patients with ECOG PS 0-1and adequate liver, kidney and bone marrow function were given regorafenib orally once daily, 21 days on and 7 days off in a 28-day cycle. The initial dose of 160 mg was given to the first 3 patients. After toxicity assessment, the dose was reduced to 120 mg for the subsequent pts. The primary endpoint is PFS with the null hypotheses of 2.0 months, and median PFS $\geq$3.5 months as evidence of the study drug activity ($\alpha = 0.10$, 80% power). Secondary objectives include OS, RR, and DCR. **Results:** Thirty-seven patients received at least one dose of regorafenib, of whom 28 were evaluable for efficacy. All had previous gemcitabine/cisplatin treatment. The mean age was 62.5 (34.5-82.8) with 17 (46%) females. PR was achieved in 3 (10.7%), SD in 18 (64.3%, with DCR of 75%), and PD in 7 (25%). For all 37 patients, median PFS was 3.55 months (95% CI = 2.1- 5.72) and mOS was 5.55 months (95% CI = 4.04 -NA) with survival rate of 42 % at 12 months, and 38% at 18 months. Medan PFS and OS of 30 patients who had $\geq$1 cycle were 3.91 months (95% CI = 3.55-9.79) and 13.4 months (95% CI = 5.06 - NA), respectively. The overall toxicity profile was as expected, with G3/4 AE's of 40.5%. The most common toxicities were HTN, hypophosphatemia, hand-foot skin reaction, and increased serum bilirubin. Dose modification was required in 11 (30.6%) patients. Tumor samples were collected in 80% of patients, with planned correlative studies underway. **Conclusions:** This study showed promising efficacy of regorafenib in chemotherapy refractory advanced/metastatic cholangiocarcinoma. Further studies to confirm the clinic efficacy are recommended. Clinical trial information: NCT02053376.

4082 Poster Session (Board #74), Sat, 8:00 AM-11:30 AM

Pharmacokinetic/pharmacodynamic (PK/PD) profile of AG-120 in patients with IDH1-mutant cholangiocarcinoma from a phase 1 study of advanced solid tumors. *First Author: Bin Fan, Agios Pharmaceuticals, Inc., Cambridge, MA*

Background: Somatic mutations in isocitrate dehydrogenase 1 (IDH1) produce the oncometabolite D-2-hydroxyglutarate (2-HG). AG-120 is a first-in-class selective inhibitor of mutant IDH1 (mIDH1) under evaluation in an ongoing phase 1 study in patients with mIDH1 advanced solid tumors, including cholangiocarcinoma (CC) (NCT02073994). Objectives for this abstract were to 1) characterize the PK profile of AG-120 and the relationship between AG-120 exposure and 2-HG suppression, and 2) evaluate the influence of intrinsic patient factors on AG-120 clearance, in patients with mIDH1 CC. **Methods:** AG-120 was administered orally once daily (QD) or twice daily (BID) in continuous 28-day cycles. As of Dec 5, 2016, 60 of 73 patients enrolled with mIDH1 CC had PK/PD samples available for analysis at 100 mg BID, 300 mg QD, 400 mg QD, 500 mg QD, 800 mg QD, and 1200 mg QD in dose escalation (n = 24) and 500 mg QD (n = 36) in dose expansion. Blood (n = 60) and fresh tumor biopsy samples (n = 14) were collected to assess AG-120 and 2-HG using qualified liquid chromatography-tandem mass spectrometry methods. **Results:** Following both single and multiple doses, AG-120 plasma exposure increased less than dose proportionally from 100 to 1200 mg. Mean terminal half-life was 38.4–85.8 h, supporting a QD dosing regimen. Following multiple doses, steady state was reached within 15 days, with approximately 2-fold accumulation in plasma AG-120 exposure. No patient-specific factors were identified as clinically significant covariates affecting AG-120 plasma clearance. After multiple doses, plasma 2-HG levels were reduced (up to 98.4% inhibition, achieving levels similar to those in healthy volunteers) and tumor biopsy 2-HG levels were also substantially reduced (by up to 99.9%) at all dose levels tested. The 500 mg QD dose resulted in the largest magnitude of 2-HG inhibition vs. other dose levels. **Conclusions:** AG-120 demonstrated a long half-life in patients with mIDH1 CC and robustly inhibited 2-HG in plasma and tumor samples. These PK/PD data, along with emerging safety and clinical activity data, support the selection of 500 mg QD for future clinical investigation. Clinical trial information: NCT02073994.

4083 Poster Session (Board #75), Sat, 8:00 AM-11:30 AM

A phase II study of sorafenib and yttrium-90 glass microspheres for advanced hepatocellular carcinoma, BCLC stage C. *First Author: Ahmed Omar Kaseb, GI Medical Oncology Department, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Combined use of sorafenib and local therapy for treating unresectable hepatocellular carcinoma (HCC) is not well established. Notably, most common cause of death in HCC is liver failure, therefore we tested the promise of controlling the local tumors even in the setting of advanced/metastatic disease to improve survival. Our study aimed to assess the efficacy and safety of combined use of sorafenib and yttrium-90 resin microspheres (Y90 RMS) in unresectable HCC defined as Barcelona Clinic Liver Cancer class C. **Methods:** Between October 2013 and August 2016 we enrolled 40 advanced stage HCC patients, 38 patients were treated with sorafenib followed (after 4 weeks) with Y90 RMS at MD Anderson Cancer Center. Survival analysis was done to evaluate median overall survival (OS) and progression-free survival (PFS). We used modified Response Evaluation Criteria in Solid Tumors (RECIST) to assess response to treatment and the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 to evaluate the grading of treatment related toxicity. **Results:** The majority of our patients were males (74%), white (47%), 66% of patients had underlying liver cirrhosis, 26% had vascular invasion, and 26% had extrahepatic disease. The estimated median OS and 95% confidence interval (CI) in months was 18.46 (12.29 – NA) and the estimated PFS was 12.29 months (5.72 – 18.79). Stable disease (SD) was observed in 44.74% of patients, while 28.95% achieved partial response (PR). Grade III-IV adverse events included fatigue (n = 3), hyperbilirubinemia (n = 2), thrombocytopenia (n = 1), proteinuria (n = 1), hyponatremia (n = 1), elevated liver enzymes (n = 4), hypertension (n = 4), diarrhea (n = 1), nausea (n = 1) and vomiting (n = 2). **Conclusions:** This is the first prospective study to evaluate sorafenib followed by Y90 in HCC. Our study included patients with metastatic HCC and showed that combined use of sorafenib and Y90 was tolerable and was associated with longer OS and PFS compared to previous studies which evaluated sorafenib alone. However, future randomized phase III studies are warranted to assess sorafenib+/-Y90 in metastatc disease setting. Clinical trial information: NCT01900002.

4084 Poster Session (Board #76), Sat, 8:00 AM-11:30 AM

Effect of sorafenib (S) starting dose and dose intensity on survival in patients with hepatocellular carcinoma (HCC): Results from a Canadian multicenter HCC database. *First Author: Mohammed Abdullah Alghamdi, Tom Baker Cancer Centre, Calgary, AB, Canada*

Background: The SHARP trial showed that S improves survival in advanced HCC. Full dose (FD) S at 400mg bid can be difficult to tolerate, so some clinicians begin with a reduced dose (RD) & escalate as tolerated to maximum dose. The purpose of this study was to determine whether starting dose or dose intensity of S affects survival. **Methods:** All patients treated with S for HCC from 01/2008 to 06/2016 in British Columbia, Alberta, Ontario (Princess Margaret Cancer Centre & Sunnybrook Odette Cancer Centre), were included. Patient demographics, clinical, tumor characteristics, S starting dose & mean dose intensity were collected & analyzed. Patients were dichotomized into starting FD or RD of S. Mean dose intensity was categorized into $>$ 75%, 50-75% & $<$ 50%. Survival outcomes were assessed with Kaplan-Meier curves & compared with the log-rank test. A Cox-proportional hazard model was constructed with starting dose, dose intensity & relevant clinical & pathologic factors to assess their impact on survival. **Results:** We included 681 patients. Median age 64 years, 80% men, 37% East Asian, & most frequent causes of liver disease were hepatitis B (33%) & C (29%). ECOG performance status prior to starting S was 0 in 30% & 1 in 60%. Most patients were Childs-Pugh A (86%) at start of S. Overall median survival was 9.1 months (m). S was started at FD in 42% of patients & 31% had a dose intensity $>$ 75%. The median survival for starting FD & RD was 9.4 m & 8.9 m, respectively (p = 0.15). The median survival for a dose intensity $>$ 75% was 9.5 m, 50-75% was 12.9 m & $<$ 50% was 7.1 m (p = 0.005). In multivariate models that adjusted for demographic, stage, performance status, AFP, prior treatment, toxicity & liver function, starting dose (HR 1.1, 95%CI 0.86-1.3, p = 0.51) & dose intensity (50-75% HR 0.93, 95% CI 0.73-1.2; $<$ 50% HR 0.89, 95% CI 0.69-1.1, p = 0.65) were not predictors of survival. **Conclusions:** Based on our multi-center database, starting HCC patients on a RD of S may be a reasonable since it does not appear to compromise survival. Patients receiving a dose intensity of S at 50-75% appear to have a superior median survival, though this is not significant after controlling for baseline characteristics.

4085 Poster Session (Board #77), Sat, 8:00 AM-11:30 AM

A prospective analysis of germline alterations (GA) in biliary tract cancer (BTC). *First Author: Maeve Aine Lowery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The incidence of hereditary cancer predisposition syndromes in patients (pts) with BTC is unknown. Cholangiocarcinoma has been reported in pts with germline mutations in BAP1, BRCA1/2, and mismatch repair genes. These associations are poorly characterized to date and the majority of pts do not undergo clinical germline analysis (CGA). **Methods:** Pts with BTC were offered consent to CGA between 01/2016 and 01/2017 under an IRB approved protocol (NCT01775072). Using the MSK-IMPACT platform, 76 genes associated with hereditary cancer predisposition were analyzed for germline variants and matched tumor samples were analysed for somatic alterations in > 340 genes. Demographic and clinical data were collected. **Results:** 78 patients were accrued: Intrahepatic = 52, extrahepatic = 13, gallbladder = 13. Median age at diagnosis was 57 years (range 21-80), 45 (58%) had a positive family history of cancer in at least one 1st degree or two 2nd degree relatives. 7 patients had a personal history of cancer. A pathogenic or likely pathogenic GA was identified in 16 pts (20%). (See table). **Conclusions:** Prospective analysis of GAs in pts with BTC, unselected by family history or age, revealed potentially actionable findings in 20% of pts. CGA in pts with BTC may benefit patients and their families in view of screening and therapeutic implications.

Gene	Alteration	Penetrance	Site	Sex	age	Ethnicity	Family hx cancer	Personal hx cancer
APC	p.I1307K	Low	GB	M	53	AJ	Y	N
APC	p.I1307K	Low	EHC	F	57	AJ	Y	N
APC	I1307K	Low	IHC	F	71	AJ	Y	N
ATM	p.L1224*	Moderate	IHC	F	36	WHITE	Y	N
BRCA2	p.L1072*	High	IHC	M	49	INDIAN	n	N
BRCA2	p.D1868EFS*4	High	GB	M	50	INDIAN	Y	N
BRCA2	p.N1377-T1378INS	High	IHC	F	55	WHITE	y	Breast
BRCA2	p.S1982RFS*22	High	GB	F	61	AJ	Y	Ovary
FH	p.K477DUP	Recessive	IHC	M	60	WHITE	UK	N
MITF	p.E419K	Moderate	IHC	F	52	WHITE	y	N
MUTYH	p.G393D	Low	IHC	M	39	WHITE	Y	N
MUTYH	p.E466DEL	Low	IHC	M	42	WHITE	Y	N
MUTYH	Y90*	Low	EHC	M	66	WHITE	Y	N
NBN	p.L128*	Moderate	GB	F	48	INDIAN	N	N
PALB2	p.Y1183*	High	IHC	F	43	WHITE	UK	N
TSC2	p.Q1286*	UK	IHC	M	47	WHITE	Y	N

4086 Poster Session (Board #78), Sat, 8:00 AM-11:30 AM

Tumor mutational burden (TMB) and co-existing actionable mutations in biliary tract cancers (BTC). *First Author: Apurva Jain, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Mutations in DNA repair pathway were identified in 13% of Biliary Tract Cancers (BTC) [*Cancer*2016;122:3838–3847]. High TMB tumors including melanoma, lung cancer and those with microsatellite instability (MSI-H) are associated with susceptibility to immune blockade using checkpoint inhibitors. TMB data in BTC is limited and its association with actionable somatic mutation (mut) profiles in BTC is unknown. **Methods:** Comprehensive genomic profiling (CGP) of 309 FFPE tissue blocks of BTC pts with a hybrid capture of all coding exons of 236 cancer-related genes and 47 introns of 19 genes rearranged in cancer was done using FoundationOne. Base substitutions, indels, gene fusion/rearrangements, TMB, and MSI status were assessed. TMB was calculated by counting mutations across a 1.25Mb region and classified into high (TMBH; ≥20 mut/Mb), intermediate (TMBI; 6 - 19mut/Mb) and low (TMBL; < 6mut/Mb). MSI high (MSIH) and Stable (MSS) status was assigned by a computational algorithm examining 114 intronic homopolymer loci. Patients with TMB ≥6 mut/Mb (N = 60) were included in the clinical correlative portion of this study. **Results:** Sixty patients with TMB ≥6 mut were identified out of 309 pts of which 9 (15%) were TMBH and 51 (85%) were TMBI. These included 3 (5%) MSIH and 18 (30 %) MSS. The median age was 59 years (range: 29-86), 35 (58%) were females, majority were intrahepatic cholangiocarcinoma (n = 31; 52%) and 28 (47%) presented with advanced disease at diagnosis. Twenty three (38%) pts had received radiation therapy, 28 (47%) surgery and 3 (5%) received immunotherapy. Most frequent co-existing mut seen was *TP53* (N = 35; 58%). *APC* mut was seen in 7 (12%) pts. DNA repair pathway muts (*MSH6, BRCA1, BRCA2, ATM, MLH1*, or *MSH2* genes) were identified in 78% of TMBH versus 16% in TMBI cases ($p < 0.0001$). Frequency of *PIK3CA* mut differed significantly between TMBH and TMBI (44% vs 10%, $p < 0.0001$). Pts with TMBI had a significantly better median OS (110 weeks) as compared to TMBH (43 weeks) (p = 0.003). **Conclusions:** DNA repair pathway and *PIK3CA* mut maybe associated with TMBH in BTC. A better understanding of TMB and associated actionable mutations in BTC may be of value for the management of BTC patients with targeted agents and immunotherapy.

4087 Poster Session (Board #79), Sat, 8:00 AM-11:30 AM

Phase Ib trial of tepotinib in Asian patients with advanced hepatocellular carcinoma (HCC): Final data including long-term outcomes. *First Author: Shukui Qin, Nanjing Bayi Hospital, Nanjing, China*

Background: The incidence of hepatocellular carcinoma (HCC), a leading cause of cancer death, is increasing with the increasing incidence of chronic liver disease. Sorafenib, the only approved systemic therapy for advanced HCC, provides modest improvement in overall survival. Preclinical studies suggest c-Met is a valid target in HCC, but non-selective TKIs with c-Met inhibitory activity have not shown efficacy in trials, possibly due to lack of c-Met inhibition. Tepotinib (MSC2156119J) is a highly selective c-Met inhibitor that has favorable safety and promising activity, particularly against c-Met+ solid tumors. We report the final results of a phase Ib trial of tepotinib in patients (pts) with advanced HCC. **Methods:** Pts were Asian adults with confirmed HCC of BCLC Stage C, Child-Pugh Class A liver function without encephalopathy, and ECOG PS 0–2. Pts received tepotinib 300, 500 (the RP2D) or 1,000 mg/day on a 21-day cycle. c-Met expression status was retrospectively determined by IHC. **Results:** 27 pts were enrolled (median age 57 [38-69]; male 23; ECOG PS 0/1 11/16); 7 received tepotinib 300 mg/day, 14 500 mg/day, and 6 1,000 mg/day (3 with dose reduction). No DLTs were observed. 22 pts experienced treatment-related treatment-emergent adverse events (TRTEAEs), most commonly diarrhea (n = 10), nausea (8), elevated AST (7), and elevated ALT (6). 9 pts had grade ≥3 TRTEAEs, including elevated AST (3) and elevated ALT (3). Best overall response (BOR) was partial response (PR) in 2 pts, one of whom received tepotinib 500 mg (response duration 16.1 months) and one 1,000 mg (4.4 months); both had c-Met+ tumors. A further 8 pts had a BOR of stable disease (SD), 1 pt non-complete response (CR)/non-progressive disease (PD), and 14 pts had PD (2 pts not evaluable). Five pts had progression free survival > 8 months. PK were as expected from previous studies. **Conclusions:** Tepotinib at doses of up to 1,000 mg/day was well tolerated by Asian pts with advanced HCC and a maximum tolerated dose was not reached. Antitumor activity was observed, particularly in pts with c-Met+ tumors. The ongoing phase II part of this study is comparing the efficacy and safety of first-line tepotinib and sorafenib in pts with c-Met+ HCC. Clinical trial information: NCT01988493.

4088 Poster Session (Board #80), Sat, 8:00 AM-11:30 AM

Lanreotide depot (LAN) for symptomatic control of carcinoid syndrome (CS) in neuroendocrine tumor (NET) patients previously responsive to octreotide (OCT): Subanalysis of patient-reported symptoms from the phase III elect study. *First Author: George A. Fisher, Stanford University, Stanford, CA*

Background: In ELECT, LAN significantly reduced the need for short-acting OCT rescue therapy for symptomatic control of CS in NET patients (pts) vs placebo (PBO) (primary result). Here we present flushing and diarrhea symptom data and biochemical response for pts with or without prior OCT use from ELECT. **Methods:** Adults with histopathologically-confirmed NET and history of stable CS (diarrhea and/or flushing) who were OCT-naive or responsive to OCT long-acting release (LAR) (≤30 mg q4W) or short-acting OCT (≤600 μg daily) were randomized to LAN 120 mg (SC q4W) or PBO for 16 wks. Pts administered SC OCT if needed and recorded daily frequency and severity of symptoms using Interactive Voice/Web Response System for 1 month pre-randomization and throughout the study. 24-hr urinary 5-hydroxindoleacetic acid (5HIAA) and plasma chromogranin A (CgA) were assessed at baseline and wk 12. **Results:** Of 115 pts randomized, 51 were OCT-naive and 64 received prior OCT. The least squares (LS) mean percentages of days with moderate/severe diarrhea and/or flushing were lower in both naive and prior OCT LAN pts vs naive and prior OCT PBO pts; LS mean difference (LAN-PBO) was significant in the naive group (Table). By week 12, 5HIAA and CgA levels dropped by ≥30% to normal in 35.3% and 15.8% of naive LAN pts and 28.6% and 4.5% of prior OCT LAN pts; 5HIAA and CgA reductions were seen in 15.4% and 21.4% of naive PBO pts and 5HIAA in 7.1% of prior OCT PBO pts. **Conclusions:** Pts showed improvement in CS symptoms of flushing and diarrhea and reduction in 5HIAA levels with LAN treatment, indicating efficacy of LAN regardless of prior OCT use. Transition from OCT to LAN was well tolerated among prior OCT pts in ELECT. Clinical trial information: NCT00774930.

Percentage of days with moderate/severe diarrhea and/or flushing (ANCOVA, ITT population).

	OCT-Naive			Prior OCT		
	LAN n = 26	PBO n = 25	LAN-PBO	LAN n = 33	PBO n = 31	LAN-PBO
LS Mean (95% CI)	4.4 (0.00, 16.42)	19.0 (7.09, 30.86)	-14.5 (-26.03, -3.09)	33.0 (24.75, 41.32)	43.9 (35.33, 52.43)	-10.9 (-22.81, 1.11)
P-value			0.014			0.075

4089 Poster Session (Board #81), Sat, 8:00 AM-11:30 AM

Final progression-free survival (PFS) analyses for lanreotide autogel/depot 120 mg in metastatic enteropancreatic neuroendocrine tumors (NETs): The CLARINET extension study. *First Author: Edward M. Wolin, Montefiore Einstein Cancer Center, Bronx, NY*

Background: In the CLARINET core study, lanreotide Autogel (LAN) 120 mg deep sc monthly significantly improved PFS vs PBO in metastatic grade-1/2 enteropancreatic NETs. An interim analysis of patients with stable disease (SD) in the core study continuing LAN in the open-label extension (OLE, of which safety was primary objective) showed continued antitumor effects. Here, we report final LAN PFS analyses for subgroups according to tumor origin and prior therapy. **Methods:** In the core study, patients with metastatic well/moderately differentiated non-functioning (N-F) enteropancreatic NETs, Ki-67 <10%, no prior somatostatin-analog treatment and no other prior medical therapies in the previous 6 months were randomized to LAN 120 mg (n=101) or PBO (n=103) for 96 weeks or until death/progressive disease (PD; RECIST 1.0). Patients with SD receiving LAN and any patient receiving PBO could enter a single-arm (LAN) OLE (NCT00842348). Main efficacy endpoint: PFS (time from core-study randomization to death/PD) for core-study intent-to-treat population from Kaplan–Meier survival analysis. Here, PFS was analyzed in subgroups of LAN–LAN patients. **Results:** OLE final population comprised 89 patients (LAN–LAN 42 [41 with SD]; PBO–LAN 47 [15 with SD]); 38% had pancreatic and 38% midgut NETs. During the OLE, 40% continuing LAN vs 47% switched to LAN had treatment-related adverse events. No new safety concerns were identified. Overall LAN median PFS from the LAN–LAN group was 38.5 months, and varied with tumor origin and prior therapy (Table). **Conclusions:** CLARINET OLE suggests sustained antitumor effects with LAN 120 mg in enteropancreatic NETs irrespective of tumor origin, and suggests benefits with LAN as early treatment. Clinical trial information: NCT00842348.

LAN PFS for patients with SD: overall and in pre-specified subgroups.

	Median PFS [95% CI](no. patients), months*
Overall	38.5 [30.9; 59.4] (101)
Tumor origin	
Midgut	61.5 [30.9; NC] (33)
Pancreas	29.7 [12.0; 38.5] (42)
Hindgut	55.0 [2.9; NC] (11)
Other/unknown	59.4 [32.8; 74.8] (15)
Previous therapy for N-F NET	
Yes	29.7 [6.0; 31.3] (16)
No	50.8 [32.4; 74.8] (85)

*Approximated (4 weeks/month). NC, not calculable

4090 Poster Session (Board #82), Sat, 8:00 AM-11:30 AM

Predictors of outcome in patients treated with peptide radio-labelled receptor target therapy (PRRT). *First Author: Dalvinder Mandair, Royal Free Hospital Neuroendocrine Tumour Unit, London, United Kingdom*

Background: The efficacy of peptide-radiolabelled receptor targeted therapy (PRRT) in patients with well differentiated neuroendocrine tumours has been demonstrated in Phase II and Phase III studies. The recently completed phase IV NETTER-01 demonstrated disease stabilisation or partial response in approximately 80% of patients. However, more studies are needed to identify predictors of PRRT response. We sought to investigate the clinicopathological characteristics in patients that had radiological progression or death within 12 months of completion of treatment with PRRT. **Methods:** We performed a retrospective analysis of all patients who had PRRT from 2011-2016. Patient with at least one year of follow-up data from the last treatment dose were included. Patients with evidence of radiological progression within one year of finishing treatment (Group 1) were compared to a similar group with disease stabilisation/response (Group 2)that were matched for age, grade, primary and distribution of metastases. The indication for PRRT was defined as either small volume progression (< 20%) or progression by RECIST. **Results:** 307 patients underwent PRRT with Lu-177 or Y-90 DOTATATE during this period. 66 patients in Group 1 were compared to 64 patients in Group 2. There was a significant difference in median overall survival, Group 1 = 21 months compared to Group 2 = 35 months, ($p < 0.002$). A significantly higher proportion of patients in group 1 had more than 50% liver volume ($p < 0.0001$). Mean CgA was significantly higher in Group 1, 1250 pg/ml vs 608 pg/ml in Group 2 ($p < 0.03$). 18 patients in Group 2 had small volume progression prior to treatment commencement compared to 6 in Group 1 ($p < 0.003$). **Conclusions:** Radiological progression within 12 months of completion of PRRT is associated with a worse outcome in terms of OS. Patients with greater liver involvement and highest CgA levels are more likely to progress within 12 months of treatment completion. Earlier treatment with PRRT in patients with radiological progression not meeting RECIST criteria may need to be conisdered. There may be a greater survival benefit if PRRT is given prior to the development of large volume disease.

4091 Poster Session (Board #83), Sat, 8:00 AM-11:30 AM

Blood measurements of neuroendocrine tumor (NET) transcripts and gene cluster analysis to predict efficacy of peptide radioreceptor therapy. *First Author: Lisa Bodei, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Peptide receptor radionuclide therapy (PRRT) capitalizes on somatostatin receptor (SSR) overexpression on NETs to deliver targeted isotope therapy. Objective prediction of efficacy remains to be established. Functional imaging of SSR expression (SRE) is used as a predictor of efficacy. Biomarkers e.g. circulating CgA, are ineffective. Circulating NET transcript analysis (NETest) integrated with tumor grade provides a *Predictive Quotient Index* (PQI) of PRRT. We validated the utility of this PRRT complementary diagnostic in a prospective, blinded study. **Methods:** ^{177}Lu-PRRT (29.1±2.2 GBq). NETs (n= 35); with progressive disease (66%). Baseline evaluations: Clinical status, Grade (Ki67), SRE, CgA (NeoLisa, ULN > 108ng/ml), and NETest (qRT-PCR - multianalyte algorithmic analyses, ULN > 14%). PQI: "omic" NETest gene expression (regulating metabolism and growth factor signaling) mathematically combined with Ki67 index. PQI has two prediction outputs: "responder" (R) vs "non-responder" (NR). Disease control was by RECIST criteria (R vs NR). All samples were blinded. Statistics: Cox proportional multiple regression, Kaplan-Meier survival, & McNemar-test. **Results:** At restaging, the overall response (disease control rate) was 77%; median PFS not reached (follow-up 4-13 months). Histology: GI: 5; GII: 21; GIII 1; and lung: TC: 2; AC: 5. SRE was Grade 3 (80%). Baseline CgA was 1556±1454ng/ml (89% elevated) and NETest was 60±21% (100% elevated) respectively. Predictive accuracies of SRE, clinical status, CgA levels (> 2ULN) and NETest ranged from 25-54% (not-significant). PQI was the only predictive marker by multivariate analysis (p= 0.002). The PQI diagnostic was 92% concordant with outcome and significantly more accurate than all other markers (McNemar: p< 0.002). Cox-proportional modeling confirmed PQI utility (OR: 9.1, p< 0.004). K-MS analysis identified significantly different mPFS between R (not reached) and NR (9.3 months; HR: 8.3, p< 0.0005). **Conclusions:** A pre-PRRT analysis of circulating NET genes, the predictive quotient index comprising "omic" analysis and grading, is validated to predict the efficacy of PRRT therapy in GEP and lung NETs.

4092 Poster Session (Board #84), Sat, 8:00 AM-11:30 AM

Pre-existing symptoms, resource utilization, and healthcare costs prior to diagnosis of neuroendocrine tumors: A SEER-Medicare database study. *First Author: Chan Shen, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The incidence and prevalence of neuroendocrine tumors (NETs) are continually increasing. While it is known that NET symptoms often predate diagnosis, the prevalence of these symptoms and the impacts on resource utilization and costs are largely unknown. **Methods:** We identified 12,052 elderly patients diagnosed with NET between 1/2003 and 12/2011 by ICD-0-3 codes from the Surveillance, Epidemiology and End Results (SEER)-Medicare database with continuous Medicare Parts A and B enrollment during the one year before NET diagnosis. We used propensity score matching to identify a group of comparable elderly patients from a non-cancer Medicare cohort. We captured patients' potentially relevant conditions (defined as > 1 indicative claim), resource utilization and costs from patients' medical claims during the year before diagnosis. We examined a) resource utilization in terms of number of outpatient visits, percentage of patients having any emergency room (ER) visits and hospitalizations, and b) health care costs including inpatient, outpatient and total costs. We used chi-square test for categorical variables and Mann-Whitney U test for continuous variables. **Results:** NET patients were more likely to have diagnoses of diarrhea (8% vs. 2%), abdominal pain (37% vs. 8%), irritable bowel syndrome (1.5% vs. 0.6%), hypertension (72% vs. 55%), heart failure (16% vs. 8%), and peripheral edema (7% vs. 4%) compared to the non-cancer control group. They also had much higher resource utilization including number of outpatient visits (mean: 27.25 vs. 18.45); and percentage with ER visits (64% vs. 36%), and hospitalizations (66% vs. 34%). Similarly, NET patients incurred significantly higher total (mean: $32924 vs. $10048), outpatient (mean: $8869 vs. 4580), and inpatient costs (mean: $24055 vs. $10048). All $p < 0.001$. **Conclusions:** To the best of our knowledge, this is the first population-based study to examine potentially relevant pre-existing symptoms, resource utilization and healthcare costs before NET diagnosis. NET patients were more likely to have certain conditions and incurred higher resource utilizations and costs in the year preceding diagnosis of NET.

4093 Poster Session (Board #85), Sat, 8:00 AM-11:30 AM

68Ga-DOTATATE PET/CT to predict response to peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumours (NETs). *First Author: Rohini Sharma, Imperial College London, London, United Kingdom*

Background: PRRT represents a step change in NET management, significantly improving survival. However, objective response to PRRT, approximately 20%, is poor. There are no predictive biomarkers of response. Uptake on ^{68}Ga-DOTATATE PET/CT imaging is used to assess patient suitability for PRRT, highlighting the presence of somatostatin receptors (SSTR) to which PRRT selectively binds. We hypothesise that the density of SSTRs, as defined by a minimum SUV uptake, predicts for response to PRRT. **Methods:** 54 patients underwent PRRT. Modified PERCIST assessment was performed: up to 2 target lesions per organ were identified and volume of interest drawn. Maximum 5 targets were counted. Average SUV (SUVave) was calculated by dividing sum of SUVmax of target lesions by number of lesions. Response was determined by RECIST 1.1. Ki67 and SSTR2 expression were assessed on tumour samples and compared with SUVave. **Results:** Response to PRRT: partial response (PR) 26%, stable disease (SD) 40% progressive disease (PD) 12%. Response to PRRT predicted progression free survival (PFS) with patients experiencing PR having a PFS 2.5x that of those with SD, and almost 20x as long as PD. Using ROC curve analysis, SUVave of 21.6 predicted for tumour response with high sensitivity (0.74) and specificity (1.0), p = 0.15, 95% CI 0.71-3.96. No association between baseline SUVave and SSTR2 or Ki-67 was observed. SUVave $>$ 21.6 was an independent predictor of clinical outcome. **Conclusions:** Objective response to PRRT defines a subset of patients with markedly improved PFS. SUVave 21.6 defines a threshold below which patients have a poor response to PRRT. This threshold should be taken forward into prospective study.

4094 Poster Session (Board #86), Sat, 8:00 AM-11:30 AM

Theranostic trial of well differentiated neuroendocrine tumors (NETs) with somatostatin antagonists ^{68}Ga-OPS202 and ^{177}Lu-OPS201. *First Author: Diane Lauren Reidy, Weill Cornell Medical College, New York, NY*

Background: Radiolabeled somatostatin receptor 2 (sstr2) antagonists have shown higher tumor uptake and tumor-to-organ ratios than agonists in preclinical models. We performed a phase I study to evaluate the safety and radiation dosimetry of the sstr2 antagonists ^{68}Ga-OPS202 and ^{177}Lu-OPS201 (^{68}Ga/^{177}Lu-DOTA-JR11) in patients (pts) with metastatic well differentiated NETs (NCT02609737). Efficacy data after ^{177}Lu-OPS201were recorded. **Methods:** Pts with RECIST disease progression underwent a ^{68}Ga-OPS202 PET/CT to confirm in-vivo binding of the sstr2 antagonists and if positive, underwent treatment with 3 doses of ^{177}Lu-OPS201. The first dose of 50 mCi ^{177}Lu-OPS201was used to calculate tumor and normal organ radiation doses. Dosimetry was then calculated to administer ^{177}Lu-OPS201in divided doses for the 2nd and 3rdfractions, 8-10 weeks apart. **Results:** 19 pts enrolled (primary tumors: 1 lung, 7 small bowel, 8 pancreatic NETs, 1 gastric NET, 1 rectal NET, 1 kidney). Average age was 55 y (22-73 y), 52% female; mean number of prior treatments was 3. All pts received 1 therapeutic dose of ^{177}Lu-OPS201, 7 pts received 2 doses. All tumors were visualized by ^{68}Ga-OPS202 PET/CT. With the exception of the kidneys and bladder, no organ demonstrated uptake of ^{68}Ga-OPS202 above background. Tumor radiation doses ranged from 0.15 Gy/mCi to 0.48 Gy/mCi. Subacute hematologic toxicity after cycle 1 was mild-moderate (G3 2/19 leukopenia that reversed before cycle 2). 4/7 (57%) pts that received the second dose of ^{177}Lu-OPS201had G4 hematological toxicities, which occurred 4-6 weeks after administration. G 3/4 toxicities in the four pts have resolved to G2 or lower; none of these pts demonstrated fever, infection, bleeding, or renal toxicity. Substantial efficacy was observed: 1 patient achieved a CR (1/19, 5%), 32% PR (6/19), 47% SD (9/19) and 16% POD (3/19). Median PFS has not yet been reached. **Conclusions:** In this trial of heavily treated NETs, preliminary data are promising for the use of ^{68}Ga-OPS202/^{177}Lu-OPS201 as a theranostic combination for imaging and therapy. Additional studies are planned to determine an optimal therapeutic dose and schedule. Clinical trial information: NCT02609737.

4095 Poster Session (Board #87), Sat, 8:00 AM-11:30 AM

Effect of lanreotide depot (LAN) on 5-hydroxyindoleacetic acid (5HIAA) and chromogranin A (CgA) in gastroenteropancreatic neuroendocrine (GEP NET) tumors: Correlation with tumor response and progression-free survival (PFS) from the phase III CLARINET study. *First Author: Alexandria T. Phan, University of New Mexico Comprehensive Cancer Center, Albuquerque, NM*

Background: 5HIAA or CgA are biomarkers in some GEP NETs. We present posthoc analyses using prospectively collected urinary 5HIAA and serum CgA data from CLARINET. **Methods:** Adults with moderately or well differentiated, nonfunctioning (no symptoms of carcinoid syndrome), locally advanced or metastatic GEP NETs were randomized to LAN 120mg or placebo (PBO) every 4 weeks (wks) for 96 wks. Tumor response evaluated centrally (RECIST 1.0) and PFS were assessed by treatment. Biochemical response was defined as baseline $>$ upper limit of normal (ULN, 41.6μmol/d 5HIAA; 98.1μg/L CgA) and $\geq$50% decrease from baseline to $\leq$ULN value on study. CgA analyses excluded gastrinoma patients (pts). **Results:** 48% (82/171) (45LAN; 37PBO) and 66% (129/195) (65LAN, 64PBO) of pts had $>$ ULN baseline 5HIAA and CgA. In those pts with no radiologic progression, significantly greater reductions in 5HIAA (Table) and CgA were observed in LAN vs PBO pts at all assessments (all $P<$ 0.05). PFS was significantly prolonged in LAN 5HIAA responders vs nonresponders (median not reached vs 22.1 months, P= 0.0076) but was not significantly different in PBO 5HIAA responders vs nonresponders. There were no significant differences in PFS by CgA response (responders vs nonresponders) in either LAN or PBO pts. **Conclusions:** These data suggest that serotonin is secreted by nonfunctioning tumors, but does not reach the threshold required for clinical carcinoid symptoms. Monitoring 5HIAA and CgA may be useful during LAN treatment of nonfunctional GEP NETs. Clinical trial information: NCT00353496.

Median (IQR) 5HIAA levels and changes from baseline.

	No Tumor Progression (RECIST)	
	LAN	PBO
Baseline, n	35	17
Median (IQR)	86.3 (58.8, 217.4)	95.7 (64.0, 330.7)
Wk 12, n	29	13
Median change (IQR)	-55.2 (-83.7, -23.4)	25.5 (-29.7, 120.7)
Wk 48, n	30	9
Median change (IQR)	-46.3 (-124.3, -32.2)	37.0 (25.4, 80.6)
Wk 96, n	26	7
Median change (IQR)	-39.8 (-102.5, -22.9)	86.8 (-23.4, 174.2)
Last value, n	34	16
Median change (IQR)	-39.0 (-102.5, -22.9)	66.3 (-9.6, 200.7)

IQR: interquartile range.

4096 Poster Session (Board #88), Sat, 8:00 AM-11:30 AM

Use of antiresorptive therapy (ART) and skeletal-related events (SREs) in patients with bone metastases of neuroendocrine neoplasms (NEN). *First Author: Leonidas Apostolidis, Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany*

Background: Antiresorptive therapy (ART) with bisphosphonates or denosumab is effective in preventing skeletal-related events (SREs) in patients with bone metastases (BM). In neuroendocrine neoplasms (NEN), BM are a negative prognostic factor, however tend to be asymptomatic and SREs are considered a rare event. The role of ART in preventing SREs in NEN has not been investigated so far. **Methods:** Retrospective analysis of all patients with bone metastases in the NEN database of the National Center for Tumor Diseases who presented at our center between 12/2012 and 01/2017. Overall survival (OS) from diagnosis of BM as well as time to SRE (TTSRE) were calculated. In patients experiencing an SRE within 1 month after diagnosis (i.e. before efficacy of ART could be assessed), TTSRE was defined as the time to a subsequent SRE. **Results:** In a total of 513 patients in the database, 108 patients with BM could be identified. Median OS was not reached in a median follow-up of 15.2 months. ART was applied to 42.6 % of patients. OS with or without ART did not differ significantly (p = 0.2538). 28.7 % of patients experienced at least 1 SRE, 20.4 % after more than 1 month. Median TTSRE was 63.8 months with ART and 127.0 months without ART (p = 0.1751). TTSRE was shortened in grade 3 vs. grade 1+2 NEN (172 months vs. not reached, HR 4.058, p = 0.0032), as well as in lytic vs. non-lytic metastases (24.5 vs. not reached, HR 7.319, p $<$ 0.0001), however not significantly different in oligometastatic vs. disseminated bone disease (not reached vs. 63,8 months, HR 1.415, p = 0.4287). Application of ART did not significantly change TTSRE in either of these subgroups. Significant toxicity attributable to ART was observed in 15.2 % of ART patients. **Conclusions:** SREs in NEN patients with BM were not uncommon, especially in patients with grade 3 NEN and osteolytic metastases. Application of ART did not significantly alter median OS or TTSRE, no subgroup with a benefit of ART could be identified. The use of ART in NEN should be questioned and evaluated prospectively.

4097 Poster Session (Board #89), Sat, 8:00 AM-11:30 AM

A phase 2 study of galunisertib (TGF-B R1 inhibitor) and sorafenib in patients with advanced hepatocellular carcinoma (HCC). *First Author: Robin Kate Kelley, University of California, San Francisco, San Francisco, CA*

Background: TGFβ signaling is associated with HCC progression. Inhibition of TGFβ R1 potentiates activity of sorafenib in in-vitro and in-vivo models. Here we report the clinical activity of galunisertib (G) plus sorafenib (S) in pts with incurable HCC and no prior systemic therapy. **Methods:** Eligibility criteria included incurable HCC with measurable disease per RECIST 1.1, no prior systemic therapy, Child Pugh A, ECOG PS ≤1.G was administered as 80 mg PO BID (lead-in Cohort 1) or 150 mg PO BID (lead-in Cohort 2 and expansion cohort), as intermittent dosing of 14 days on/off (28 days = 1 cycle). S was administered continuously as a 400 mg PO BID. Primary objective was to characterize time-to-progression (TTP) and biomarker changes in pts. Secondary objectives included evaluation of OS, PK, and toxicity (CTCAE v 4.0). **Results:** 47 pts were enrolled (Cohort 1 = 3, Cohort 2 and expansion cohort = 44). In the 150 mg BID cohort: Male = 88.6%; median age = 64 years; PS = 0/1, 81.8%/18.2%; etiology: hepatitis C = 34.1%, hepatitis B = 18.2%, alcohol = 20.5%, multiple = 13.6%; AFP≥200 μg/L = 50%; portal vein invasion = 34.1%. Incidence of AEs was similar between G dose levels. Overall in the 150mg BID cohort, treatment related AEs (> 15%) were hand and foot syndrome (61.4%), diarrhea (40.9%), pruritus (22.7%), anemia and weight loss (20.5%), fatigue (29.5%), alopecia (18.2%), myalgia (22.7%), decrease in platelet count and nausea (15.9%). Two pts on 150 mg BID discontinued treatment due to study drug related AEs (anemia and weight loss). PK of G at 150 mg BID (n = 12) when co-administered with S, was similar to that observed in the G monotherapy study. G was rapidly absorbed and had an elimination half-life of approximately 8h. Median TTP (RECIST) was 4.1 (2.8, 5.5) months. OS, with a high censor rate of 55% was not mature at the time of this data cutoff. Median OS was 17.9 (14.8, NE) months. **Conclusions:** The combination of G plus S demonstrated acceptable safety and a meaningful OS of 17.9 months in an advanced HCC population. TTP was similar to S monotherapy in contemporary clinical trials though interpretation is limited by single arm design. Clinical trial information: NCT01246986.

4098 Poster Session (Board #90), Sat, 8:00 AM-11:30 AM

Long-term outcomes with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from appendiceal cancer: An 18-year experience. *First Author: Carlos A. Munoz-Zuluaga, Mercy Medical Center, Baltimore, MD*

Background: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) have become standard of care for patients with peritoneal carcinomatosis (PC) from appendiceal cancer (AC). We reviewed our experience and outcomes. **Methods:** A retrospective review of 614 CRS/HIPEC procedures from 1998-2016 was performed. Patient characteristics, surgical variables, and postoperative outcomes of first CRS/HIPEC were analyzed. **Results:** Two hundred ninety patients with PC from AC underwent 334 CRS/HIPEC's. Median age at diagnosis and surgery was 52 (22-79) and 53 (23-81) years, respectively; 65% (187) were female. Prior surgical score was 0, 1, 2, and 3 in 20%, 38%, 37%, and 5%, respectively. Prior systemic chemotherapy was reported in 30% of patients. Median time from diagnosis to CRS/HIPEC was 4 months (0-182). Pre-operative tumor markers (CEA, CA-125, CA-19-9) were positive in 48% with one, two, and three positive markers in 21%, 15%, and 13% patients, respectively. Median Peritoneal Cancer Index was 29. Mitomycin-C was the HIPEC agent of choice. Mean operative time was 10 hours (R: 4-19) and median length of stay was 10 days (R: 4-93). Histology included 59% (171) peritoneal mucinous carcinomatosis (PMCA), 41% (119) disseminated peritoneal adenomucinosis (DPAM). Lymph nodes were positive in 47% PMCA. Complete cytoreduction rate was 87% (84% PMCA, 92% DPAM [p = 0.048]). Grade III-V complications occurred in 21%, with one 30-day mortality (0.3%). Overall, median progression-free survival (PFS) was 84 months with 5-year PFS of 56%. Median PFS was 43 months in PMCA and not reached in DPAM. Five year PFS was 40% PMCA and 82% DPAM (p < 0.001). Median overall survival (MOS) was 139 months with 61% 5-year OS. MOS was 53 months in PMCA and not reached in DPAM. Five year OS was 47% PMCA and 85% DPAM (p < 0.001). At 42-month median follow-up, 68% were alive (92 PMCA/103 DPAM) with 84% disease free (72 PMCA/92 DPAM), 28% died of disease (73 PMCA/7 DPAM). **Conclusions:** CRS/HIPEC is an effective treatment for patients with PC from AC providing meaningful long term survival in low and high grade tumors and should be considered the standard of care.

4099 Poster Session (Board #91), Sat, 8:00 AM-11:30 AM

TAS-118 (S-1 plus leucovorin) versus S-1 in gemcitabine-refractory advanced pancreatic cancer: A randomized, open-label, phase III trial (GRAPE trial). *First Author: Makoto Ueno, Division of Hepatobiliary and Pancreatic Medical Oncology, Kanagawa Cancer Center, Yokohama, Japan*

Background: Addition of oral leucovorin (LV) to S-1 significantly improved progression-free survival (PFS) in a previous randomized phase II trial in Japanese patients (pts) with gemcitabine (GEM)-refractory advanced pancreatic cancer (PC). TAS-118 is an oral drug containing S-1 and LV. This phase III trial conducted in Japan and Korea compared overall survival (OS) between GEM-refractory advanced PC pts treated with TAS-118 and S-1. **Methods:** GEM-refractory PC pts were randomized in a 1:1 ratio to receive TAS-118 (S-1; 40-60 mg and LV; 25 mg bid for 1w, q2w) or S-1 (S-1; 40-60 mg bid for 4w, q6w). The primary endpoint was OS. The secondary endpoints included PFS, overall response rate, disease control rate, duration of response, and safety. **Results:** Five hundred and eighty-six pts were eligible for efficacy assessment (TAS-118: n=296 and S-1: n=290). Baseline characteristics were well balanced between the treatment arms. TAS-118 did not result in a statistically significant improvement in OS compared with that achieved with S-1 (median OS, 7.6 months vs. 7.9 months; hazard ratio [HR], 0.98; 95% CI, 0.82 to 1.16; P=0.756). However, it significantly improved PFS compared to that achieved with S-1 (median PFS, 3.9 months vs. 2.8 months; HR, 0.80; 95% CI, 0.67 to 0.95; P=0.009). Pre-planned subgroup analysis of OS showed significant interactions between the treatment effects and pancreatic resection (P=0.025), and between the treatment effects and country (P=0.004). Grade 3/4 drug-related adverse events (≥5% incidences) in TAS-118 and S-1 arms included diarrhea (7.0% vs. 7.3%), anorexia (6.7% vs. 5.0%), stomatitis (6.7% vs. 0.7%), and anemia (3.3% vs. 5.0%). **Conclusions:** The primary endpoint was not met. Further, the interactions between the treatment effects and pancreatic resection, and between the treatment effects and country, might affect the results. Clinical trial information: 132172.

Subgroup		Number of pts (TAS-118 vs. S-1)	Median OS (months) TAS-118	S-1	HR (95% CI)	P value for interaction
Pancreatic resection	Yes	85 vs. 81	8.7	9.4	1.51 (1.07-2.14)	0.025
	No	211 vs. 209	7.3	7.4	0.85 (0.70-1.04)	
Country	Japan	235 vs. 231	8.0	7.9	0.85 (0.70-1.04)	0.004
	Korea	61 vs. 59	6.0	7.4	1.57 (1.07-2.30)	

4100 Poster Session (Board #92), Sat, 8:00 AM-11:30 AM

A randomized phase II trial comparing different schedules of nab-paclitaxel (nabP) combined with gemcitabine (GEM) as first line treatment for metastatic pancreatic adenocarcinoma (mPDAC). *First Author: Philippa Corrie, Cambridge Cancer Trials Centre, Cambridge, United Kingdom*

Background: NabP+GEM chemotherapy improves survival compared with GEM monotherapy as treatment for mPDAC. A PDAC mouse model suggested that *nab*P potentiates GEM activity by reducing cytidine deaminase levels and scheduling may be critical to optimise clinical benefit. **Methods:** Patients (pts) were randomised to receive standard concomitant (CON) nabP+GEM or sequential (SEQ) administration, with nabP given 24 hours before GEM. After 6 cycles, pts benefiting from treatment could continue the same regimen until disease progression. The primary endpoint was progression-free survival (PFS) by RECIST v1.1; secondary endpoints included safety, objective response rate (ORR), overall survival (OS) and quality of life (QoL). Serial blood and baseline tumour samples were collected for exploratory biomarkers. **Results:** Between March 2014 and 2016, 146 pts (71 SEQ, 75 CON) were recruited. Median age (range) was 66 (45-82) years; Karnofsky performance status was 70 (in 12% pts), 80 (27%), 90 (38%) or 100 (24%); 47% had pancreatic head primaries; 84% had liver metastases. Median no. cycles received was 4 SEQ, 3 CON; 51 pts (35%) received ≥6 cycles of treatment (42% SEQ, 28% CON). A 24+2hr interval was achieved in > 90% SEQ admin. Grade ≥3 adverse events experienced by ≥10% pts (SEQ, CON) were neutropaenia (54%, 30%; p = 0.003), febrile neutropaenia (12%, 12%), fatigue (22%, 15%), vomiting (7%, 11%) and anaemia (10%, 5%). G-CSF was administered at local investigator's discretion to 35 pts (23 SEQ, 12 CON; p = 0.015). To date, 112 pts have died. 6 month (m) PFS by SEQ and CON arms were 47% and 33%; median PFS were 5.8 and 4.0m; hazard ratio (HR) = 0.66, 95% CI = 0.46-0.95; 12m OS by SEQ and CON arms were 29% and 26%; median OS were 10.1 and 7.9m; HR = 0.88, 95% CI = 0.61-1.29. ORR was 50% SEQ and 33% CON (p = 0.065). Mean baseline QoL Global health status score was 60.6 SEQ and 63.4 CON. The mean change in QoL score from baseline at 24 weeks was -2.1 SEQ and -12.1 CON. **Conclusions:** Sequential delivery of nabP combined with GEM trended towards improving all clinically relevant efficacy end points: PFS, OS, and ORR. Translational correlates will be reported in due course. Clinical trial information: ISRCTN71070888.

4101 Poster Session (Board #93), Sat, 8:00 AM-11:30 AM

Potential role of circulating tumor DNA (ctDNA) in the early diagnosis and post-operative management of localised pancreatic cancer. *First Author: Belinda Lee, The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia*

Background: Pancreatic cancer remains a devastating disease, with the diagnosis typically being made late. ctDNA has shown promise as a screening test for various tumor types. The detection of ctDNA post curative intent surgery has been associated with a high risk of recurrence in multiple solid tumors. We explored the potential of ctDNA to improve pancreatic cancer outcomes. **Methods:** Data from separate US and Australian series were combined. Plasma samples were collected prior to surgery in both studies and post-operative samples were collected in Australia from cases undergoing curative intent surgery. Clinicians were blinded to ctDNA results and adjuvant therapy was at clinician discretion. Tissue samples from both series were analyzed at Johns Hopkins University. Next generation sequencing was used to search for somatic KRAS mutations in the primary tumors and in cell-free DNA in the plasma. Clinico-pathologic, treatment and outcome data were collected. **Results:** 119 pts had a ctDNA sample at diagnosis (median age 67 years, 56.3% male). Sixty six pts (55.5 %) had detectable ctDNA, including 3/7 (42.9%) with stage I disease, 54/99 (54.5%) with stage II disease, 4/8 (50%) with stage III disease and 5/5 (100%) with metastases. Specific codon 12 KRAS (G12D, G12V or G12R) mutations were identified in the tumor tissue of 12/16 (75%) patients who had a ctDNA sample collected post-surgery. At a median follow-up of 15.2 months, 7/12 (58.3%) pts had recurred, including 3/8 (37.5%) with no detectable ctDNA and 4/4 (100%) with detectable ctDNA post-surgery (HR 4.9, p = 0.04). Detectable ctDNA post-surgery was significantly associated with poor overall survival (HR 6.93, p = 0.006), with a median of 8 months for pts with detectable ctDNA. **Conclusions:** ctDNA shows promise as a pancreatic cancer screening test, being detectable in a high proportion of pts with early stage disease. The detection of ctDNA post operatively predicts a very high risk of recurrence. The clinical utility of ctDNA to guide adjuvant therapy decision making, and its potential as a real-time marker of treatment effect, are being explored in further studies. Clinical trial information: ACTRN12612000763842.

4102 Poster Session (Board #94), Sat, 8:00 AM-11:30 AM

Prospective assessment for pathogenic germline alterations (PGA) in pancreas cancer (PAC). *First Author: Emmet Jordan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cancer predisposition syndromes are identified in a subset of PAC. Identifying PGA has implications for therapy as well as for cancer predisposition in blood relatives. Germline testing (GT) in the US is currently performed in a small subset of PAC patients according to NCCN/other guidelines. At MSKCC, we have implemented an 'opt in' strategy to perform germline testing in all patients evaluated in PAC clinics at MSKCC. **Methods:** PAC pts consented prospectively for GT had samples analyzed for pathogenic or likely pathogenic variants using the MSK-IMPACT germline platform (NCT01775072). All pts first had somatic profiling of tumor samples for $>$ 340 genes by MSK-IMPACT. Clinicopathological features, time to progression on platinum (TTPP) and overall survival (OS) were collated. **Results:** N = 305 PAC pts consented for GT between 9/2015-11/2016.164/305 (54%) were male, 70/305 (23%) were Ashkenazi Jewish. 242 pts (79%) had a family hx of cancer. 67/305 (22%) had a GA identified, 45/67 (67%) were stage III/IV at dx. Median age at PAC dx for all GA carriers was 60 years (y) (range 29-81) compared to 66 y (18-69) without GA. Median age at dx was 54 y (32-68) for BRCA1 and 61 y (37-77) for BRCA2 GA. 3/9 and 3/20 pts with BRCA1/2 GA had a PAC dx $<$ 50 y. 2/63 pts (3%) with no family hx had a GA (CDKN2A, PMS2). N = 5/22 pts (23%) with a 1st degree relative (DR) with PAC had a GA. N = 13/45 pts (29%) had a GA with either a 1st or 2nd DR with PAC. 19/84 pts (23%) with $\geq$2 1stDR with cancer had a GA detected. For median OS and TTP on platinum therapy, see Table. Pts with BRCA1/2, ATM and those with coexisting GA tended to have a better median OS as well as longer TTP on platinum therapy (Table). **Conclusions:** GA's are significantly under identified in PAC using current practices with a high, frequency (22%) observed in this relatively unselected cohort. BRCA mutations are the most frequent GA noted. There are significant implications of these observations for therapy and for blood relatives.

	N =	TTPP (mths)	OS Stage IV (mths)
No GA detected	**238**	7	13 (1-43)
GA detected	**67**		
BRCA2	16	12	16
BRCA1	9	10	16
CHEK2	7	6	10
APC	7	6	8.5
ATM	6	11	18
CDKN2A	6	5	9
BLM	2	5	5
BRCA2 + CHEK2	2	1 PR to GTX	51
APC + CHEK2	1	18	35
BRCA2 + PMS2	1	NP	26
BRCA2 + APC	1	13	24
BARD1	1		
FAM175A + MUTYH	1		
FH	1		
MITF	1		
MUTYH	1		
NF1	1		
PALB2	1		
PMS2	1		
RAD50	1		

4103 Poster Session (Board #95), Sat, 8:00 AM-11:30 AM

Chemotherapy with or without definitive radiation therapy in locally advanced pancreatic cancer. *First Author: Jim Zhong, Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, GA*

Background: The recently reported LAP07 randomized trial calls into question the role of radiation therapy (RT) in the modern treatment of locally advanced pancreatic cancer (LAPC). However, advances in chemotherapy and RT limit application of the LAP07 results to current clinical practice. Here we utilize the National Cancer Database (NCDB) to evaluate the effects of RT in patients receiving chemotherapy for LAPC. **Methods:** Using the NCDB, patients with AJCC clinical stage T2-T4, N0-1, M0 adenocarcinoma of the pancreas from 2004-2014 were analyzed. Only those that received chemotherapy and did not undergo surgery were included. Patients were stratified into chemotherapy only (CT) and chemoradiation (CRT) cohorts. Patients undergoing definitive RT, defined as at least 20 fractions (fxs) or $\geq$ 5 Gy per fraction (i.e. SBRT) were included in the CRT cohort. Propensity-score matching (PSM) and landmark analysis were used to address selection bias and lead-time bias, respectively. The primary endpoint was overall survival (OS). **Results:** 13,004 patients met inclusion criteria, of which 7,034 (54%) received CT and 5,970 (46%) received CRT. After PSM, 5,215 patients remained in each cohort. Median follow-up was 22.6 months. The CRT group had younger median age (65 vs. 67) and less treatment at academic centers (44 vs. 51%); performance status was similar between groups. The median fractionated RT dose was 50.4 Gy in 28 fxs and SBRT dose was 24 Gy in 3 fxs. The CRT cohort demonstrated better OS compared with CT alone, with median and 1-yr OS of 12 vs. 10 months, and 50% and 41%, respectively ($p < 0.001$). On multivariable analysis, CRT was associated with superior OS with a hazard ratio (HR) of 0.79 (95% confidence interval (CI): 0.76-0.83, $p < 0.001$) compared with CT alone. The SBRT subgroup demonstrated the best survival (HR 0.71 [95% CI: 0.64-0.80], $p < 0.001$). OS was superior for CRT after PSM and for all patient subsets. **Conclusions:** In unresected LAPC, the addition of definitive radiotherapy to chemotherapy is associated with superior OS when compared with chemotherapy alone. Survival was greatest when SBRT was used. Definitive radiotherapy should remain a standard option for LAPC but optimal selection criteria remain unclear.

4104 Poster Session (Board #96), Sat, 8:00 AM-11:30 AM

Biomarker prediction of efficacy to vandetanib plus gemcitabine in a phase II double blind multicenter randomized placebo-controlled trial in locally advanced or metastatic pancreatic carcinoma. *First Author: John P. Neoptolemos, University of Liverpool, Liverpool, United Kingdom*

Background: We investigated the potential of biomarkers to predict efficacy of vandetanib and gemcitabine in patients with locally advanced (N = 41) or metastatic (N = 101) pancreatic cancer in a phase II double-blind multicentre randomised placebo-controlled trial. **Methods:** All patients were 18y or above, (ECOG = 0-2), with at least 3 mths life expectancy had gemcitabine (1000mg/m^2 30min iv wkly for 7 wks, followed by a 1wk break, then cycles of wkly treatment for 3wks with a 1-wk break) and randomly assigned to 300mg/d vandetanib or placebo once daily until disease progression. The primary outcome was overall survival (OS) by intention to treat. A panel of potential biomarkers was tested to predict best survival with vandetanib and gemcitabine. **Results:** 142 patients were randomised, median FU = 24·9 mths with 131 deaths. The median (95% CI) OS in the 70 gemcitabine-placebo patients was 8·95 (6·55-11·7) mths and 8·83 (7·11-11·6) mths in the 72 gemcitabine-vandetanib patients (HR = 1·21, 95% CI = 0·85, 1·73; log rank X^2_{1df} = 1·1; P = 0·303). A CTCAE V.4.02 rash grade 2 or above occurred in 4 (6 %) of 70 placebo patients versus 14 (19%) of 72 vandetanib patients. The median OS for the 14 vandetanib patients and with rash was 11·92 (10·89 – NA) mths, 7·76 (4·34 – 11·5) mths for the 58 vandetanib patients and without rash and 8·95 (6·55 – 11·7) mths for the gemcitabine-placebo patients (log rank X^2_{2df} = 7·23; P = 0·03). We identified two biomarkers that could select patients for response to vandetanib (JN101, JN102). The biomarker combination was present in 26 patients with median OS of 12.1 (10.9, 16.0) mths versus 8.15 (6.67, 11.7) mths for 23 patients with the same biomarker profile in the placebo group (HR = 0.53 [0.29, 0.97], p = 0.0396). A logistic regression model showed that patients with JN102 were more likely to develop a rash (OR =0.81 [0.713, 0.925] p = 0.002). **Conclusions:** A two biomarker combination and a rash grade 2 or above may predict response to vandetanib and gemcitabine. This requires prospective evaluation. Clinical trial information: 96397434.

4105 Poster Session (Board #97), Sat, 8:00 AM-11:30 AM

A novel scoring system to predict survival in patients with advanced pancreatic adenocarcinoma: The Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Score (MPS). *First Author: Andrew Chung Yang, Brown University Hematology and Oncology-Rhode Island Hospital, Providence, RI*

Background: A major limitation of several common prognostic tools, e.g. the Eastern Cooperative Oncology Group (ECOG), Karnofsky, and Palliative Performance Scales, is a reliance on subjective clinical assessment. An objective tool, the Glasgow Prognostic Score (GPS) derived from C-reactive Protein (CRP) and albumin levels, has been validated in patients with operable and inoperable malignancies but has the disadvantage that CRP is not routinely measured in the United States. We examined if the Neutrophil-Lymphocyte Ratios (NLR) (Ahn, H.K., et al., *Neutrophil-Lymphocyte Ratio Predicts Survival in Terminal Cancer Patients.* J Palliat Med, 2016) could be substituted for CRP in the GPS to predict survival in patients with advanced pancreatic adenocarcinoma. **Methods:** A retrospective review chart identified patients at MSKCC with pathology-confirmed stage IV pancreatic adenocarcinoma diagnosed between 2011 to 2014. Pre-treatment absolute neutrophil count, absolute lymphocyte count, and albumin were extracted. The NLR for each patient was calculated and assigned NLR ≤ 4 a value of 0; NLRs > 4 a value of 1, serum albumin > 4 g/dl assigned a value of 0; and serum albumin < 4 g/dl assigned a value of 1. Combining NLR and albumin scores results in a composite MPS score of 0-2, similar to GPS. We evaluated the association of the MPS with overall survival. **Results:** N = 833 patients were identified with median survivals in the table below. A log-rank test showed statistically significant differences in survival between MPS groups ($p < 0.00005$). The MPS on univariate analysis had a HR of 1.36 (95% CI 1.23 – 1.50, $p < 0.0005$) associated with overall survival. **Conclusions:** The MPS, a composite of NLR and albumin, is an objective prognostic tool that divided this sample of patients into three clinically and statistically significant subgroups. Further interrogation will control for performance status, disease characteristics and therapy.

Cohort	Median OS (months)	Interquartile Range	Percent Alive (N)
MPS 0 (n = 213)	14.7	8.5-26.3	22.1 (47)
MPS 1 (n = 332)	10.3	4.5-21.9	17.2 (57)
MPS 2 (n = 288)	6.2	2.3-14.8	13.2 (38)
Overall (n = 833)	10.2	4.4-21.5	17.0 (142)

4106 Poster Session (Board #98), Sat, 8:00 AM-11:30 AM

A phase Ib/II study of cancer stemness inhibitor napabucasin (BBI-608) in combination with gemcitabine (gem) and nab-paclitaxel (nabPTX) in metastatic pancreatic adenocarcinoma (mPDAC) patients (pts). *First Author: Tanios S. Bekaii-Saab, Mayo Clinic Cancer Center, Phoenix, AZ*

Background: Cancer stem cells are fundamentally important for resistance to therapy, recurrence and metastasis. Napabucasin is a first-in-class cancer stemness inhibitor in development identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells (Li et al, PNAS 112(6):1839, 2015). Preclinical studies suggest that napabucasin sensitizes heterogeneous cancer cells to chemotherapy and targeted agents. **Methods:** A phase Ib/II multi-center study in mPDAC pts was performed to confirm the RP2D, PK profile and evidence of anticancer activity of napabucasin in combination with nabPTX and Gem. Pts received napabucasin 240 mg BID with weekly nabPTX 125 mg/m^2 and gem 1000 mg/m^{2}for 3 out of every 4 weeks until disease progression (PD) or other discontinuation criterion. **Results:** Of 71 intent to treat (ITT) pts enrolled, 49 (69%) were treatment-naïve and 22 (31%) received neoadjuvant treatment. There were no significant PK interactions, dose-limiting or unexpected toxicities. Most common adverse events (AEs) included grade 1 diarrhea/cramping, nausea and fatigue with grade 3 AEs noted in 12 pts: fatigue (8), electrolyte imbalance (2), diarrhea (1), dehydration (1), nausea (1) and weight loss (1). Among pts who received RECIST evaluation (60), disease control (DCR; CR+PR+SD) was observed in 55 (92%), with 1 CR (2%) and 26 PR (43%) (31 - 78% regression). Of 11 pts with non-evaluable disease, treatment stopped due to compliance (4), consent withdrawal (3), clinical PD (1), toxicity (1), insurance (1) and death (1). Among 71 ITT pts, DCR was observed in 55 (77%), with 1 CR (1.4%) and 26 PR (37%). Maturing median progression free survival and overall survival (OS) in ITT pts is >7.1 and >10.4 m, respectively. **Conclusions:** This study showed that napabucasin can be combined with nabPTX and gem, with encouraging signs of efficacy in mPDAC now being confirmed in a phase 3 study. Clinical trial information: NCT02231723.

	DCR %		ORR %		
Subset	**Evaluable**	**ITT**	**Evaluable**	**ITT**	**OS-1 %**
All	92 (55/60)	77 (55/71)	45 (27/60)	38 (27/71)	N/A
Enrolled > 1 yr ago	93 (28/30)	76 (28/37)	53 (16/30)	43 (16/37)	48
Enrolled >1 yr & Rx'ed >8 wks (27)	93 (25)		59 (16)		56

4107 Poster Session (Board #99), Sat, 8:00 AM-11:30 AM

Phase II trial of neoadjuvant S-1 and concurrent radiotherapy for borderline resectable pancreatic cancer: Interim results of JASPAC05. *First Author: Shinichiro Takahashi, Department of Hepato-Biliary Pancreatic Surgery, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Borderline resectable pancreatic cancer (BRPC) has a high probability of a positive surgical margin and poor prognosis because the tumor interacts with surrounding arteries or veins. Chemoradiotherapy (CRT) with S-1 has shown favorable activity in locally advanced pancreatic cancer. This study was designed to assess S-1 and concurrent radiotherapy in a neoadjuvant setting to determine whether it increases R0 resection rate for BRPC. **Methods:** This was a multicenter, single-arm phase II study. Patients with BRPC received S-1 (40 mg/m^2 BID) and concurrent radiotherapy (50.4 Gy in 28 fractions) before surgery if they fulfilled any of the following: (1) bilateral impingement of superior mesenteric vein or portal vein; (2) tumor contact with superior mesenteric artery $\leq$180°; or (3) tumor contact with common hepatic artery or celiac axis $\leq$180°. Primary endpoint was R0 resection rate in BRPC confirmed by central review. At least 40 patients were required, with one-sided $\alpha = 0.05$ and $\beta = 0.05$, with an expected and a threshold values for primary endpoint of 30% and 10%. **Results:** Fifty-two patients were eligible between December 2012 and May 2016. CRT was completed in 50 patients (96%) and was safe, with mostly grade 1 or 2 adverse events. Protocol treatment was withdrawn before surgery in 12 patients because of progressive disease diagnosed by computed tomography, and in one because of treatment refusal. Ten patients received exploratory laparotomy, or palliative/noncurative resection. In the rest of 29, R0 resection was conducted in 27, and R1 and RX in 1 patient each. This gave an R0 resection rate of 52% in all 52 eligible patients. In the 41 cases of BRPC confirmed by central review, R0 was confirmed in 26 (63%). Destruction of > 50% of tumor cells was confirmed pathologically in 10 (32%). Postoperative grade III/IV adverse events according to Clavien–Dindo classification were observed in 6 (15%). **Conclusions:** S-1 and concurrent radiotherapy were well tolerated and found to be effective in BRPC. A randomized controlled trial comparing neoadjuvant CRT and chemotherapy, including gemcitabine+nab-paclitaxel, for BRPC is under planning. Clinical trial information: NCT02459652.

4108 Poster Session (Board #100), Sat, 8:00 AM-11:30 AM

Efficacy of gemcitabine with erlotinib in rash-positive patients selected according to eligibility for FOLFIRINOX. *First Author: Michael Haas, Department of Internal Medicine III and Comprehensive Cancer Center, Klinikum Grosshadern, Ludwig-Maximilians University of Munich, Munich, Germany*

Background: The efficacy and safety of gemcitabine + erlotinib has not yet been defined prospectively in patients (pts) with metastatic pancreatic cancer (mPC) selected according to the inclusion criteria defined by Conroy et al. for FOLFIRINOX (e. g. ECOG 0-1, age < 75, bilirubin < 1.5xULN). **Methods:** In this German phase II trial, 150 pts with histologically confirmed mPC were recruited between July 2012 and July 2015 in 20 centers. If pts showed skin rash of any grade within 4 weeks after start of treatment with gemcitabine (1000 mg/m^2 weekly) and erlotinib (100 mg daily), this regimen was continued; rash-negative pts were switched to FOLFIRINOX. The primary study endpoint was the 1-year survival rate in rash-positive pts (hypothesis: $\geq$40%). **Results:** Ninety pts who were under treatment with gemcitabine + erlotinib for 4 weeks developed skin rash of any grade: the 1-year survival rate in those pts positive for skin rash was 40.0% (95%CI 29.8-50.9); median overall survival (OS) counted from day of first treatment was 10.1 months (mo) (95%CI 9.0-12.5), progression-free survival (PFS) 3.9 mo (95%CI 3.5-4.9), objective response rate (ORR) and disease control rate (DCR) were 21% and 64%, respectively. Median treatment duration with gemcitabine+erlotinib was 3.7 mo (Range 0.7-17.5). In rash-negative pts who were switched to FOLFIRINOX after 4 weeks of gemcitabine + erlotinib (n = 28) the 1-year survival rate was 46.4% (95%CI 27.5-66.1), median OS 10.6 mo (95%CI 6.6-13.6), median PFS 5.2 mo (95%CI 2.3-7.9) and the corresponding ORR and DCR rates were 29 and 54%, respectively. The rate of salvage therapy was 53% after gemcitabine+erlotinib, mostly consisting of 5-FU-based schemas (42 % 5-FU/folinic acid + irinotecan or oxaliplatin, 38% FOLFIRINOX) and 43% after FOLFIRINOX (all pts received gemcitabine, 67% in combination with nab-paclitaxel). In the Intention To Treat (ITT) population (n = 145) OS was 9.7 mon (95%CI 7.8-10.9). **Conclusions:** In rash-positive pts deemed fit for FOLFIRINOX first-line treatment with gemcitabine + erlotinib appears effective achieving a one-year-survival rate of 40%. Early switch to FOLFIRINOX was an effective strategy in rash-negative patients. Clinical trial information: NCT01729481.

4109 Poster Session (Board #101), Sat, 8:00 AM-11:30 AM

Nomogram for predicting overall survival (OS) in patients (pts) treated with *nab*-paclitaxel (*nab*-P) plus gemcitabine (Gem) or Gem alone for metastatic pancreatic cancer (MPC). *First Author: David Goldstein, Prince of Wales Hospital, University of New South Wales, Cancer Survivors Centre, Sydney, Australia*

Background: Prognostic nomograms have been developed in various cancers, including ovarian, breast, and gastrointestinal; however, there is limited information on nomograms in MPC. The large, phase 3 MPACT study of *nab*-P + Gem vs Gem alone for the treatment of MPC provides a robust database for the development of a nomogram to predict OS using baseline patient variables. **Methods:** A multivariable Cox model was created from MPACT data using factors that were significantly predictive of OS in univariable analysis or considered clinically important (stepwise selection to remain in model). From the Cox model, a nomogram was derived that assigned points equal to the weighted sum of relative significance of each variable. The nomogram was internally validated using bootstrapping, a concordance index (c-index), and calibration plots. **Results:** Data from all 861 pts were used. Seven of the 34 considered variables were retained in the multivariable analysis (Table; all factors significant at the $P < 0.01$ level, except for analgesic use [$P = 0.07$]). The resulting nomogram was able to distinguish low (n = 216), medium (n = 430), and high (n = 215) risk groups (c-index: 0.69; CI: 0.67-0.71) with median OS values of 12.9, 8.2, and 3.7 months, respectively. Calibration curves showed that the nomogram's predicted probabilities were mostly consistent with observed probabilities for 6-, 9-, and 12-month OS. **Conclusions:** Treatment arm, Karnofsky performance status (KPS), neutrophil-to-lymphocyte ratio (NLR), albumin level, sum of longest tumor diameters (SLD), and presence of liver metastasis were the key predictors of OS. This nomogram, which will be presented in visual format in the final presentation, may help physicians and pts make informed treatment decisions. Clinical trial information: NCT00844649.

Multivariable cox model for OS.

Variable[a]	HR	CI
Treatment arm	1.56	1.34-1.82
NLR	1.05	1.04-1.07
Albumin	0.94	0.92-0.95
KPS (per 10-unit increase)	0.97	0.96-0.98
SLD	1.02	1.01-1.03
Presence of liver metastasis	1.62	1.29-2.03
Analgesic use	1.16	0.99-1.36

[a] Results similar in a sensitivity analysis that excluded CA19-9 non-secretors

4110 Poster Session (Board #102), Sat, 8:00 AM-11:30 AM

Single agent HuMab-5B1 (MVT-5873), a monoclonal antibody targeting sLe[a], in patients with pancreatic cancer and other CA19-9 positive malignancies. *First Author: Eileen Mary O'Reilly, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: MVT-5873, a fully human IgG1 monoclonal antibody (mAb), targets sialyl Lewis A (sLe[a]), an epitope on CA19-9. CA19-9 is expressed in pancreatic (PDAC) and other GI cancers, plays a role in tumor adhesion and metastasis, and is a marker of an aggressive tumor phenotype. MVT-5873 is active as a single agent and with chemotherapy in murine xenografts. **Methods:** MVT-5873 was given IV every other week (Group 1) or weekly (Group 2). Eligible patients had progressive, locally-advanced or metastatic PDAC or other CA19-9+ malignancy and ECOG PS $\leq$1. Dose escalation followed a 3+3 design with a 10 patient expansion at MTD. Endpoints include safety, MTD, pharmacokinetics (PK) and efficacy. Exploratory endpoints include changes in serum CA19-9 levels. **Results:** As of 2-Feb 2017, data are available from N = 25 in Groups 1 (N = 9) and 2 (N = 16) at doses ranging from 1 to 3 mg/kg. Dose limiting toxicities of transient grade 3 elevations in AST, ALT, and total bilirubin were encountered at 3 mg/kg in both groups. Liver function laboratory abnormalities typically emerged and resolved within a week of dosing without significant clinical sequelae. Of toxicities deemed possibly related, most were low grade and included GI toxicity (abdominal pain/cramps/diarrhea/nausea) and infusion reactions. Infusion reactions were mitigated by using pre-medications and decreasing the infusion rate. Initial PK data demonstrate initial (20 hours) and terminal (211 hours) half-lives, comparable to other mAbs. Stable disease of $>$ 4 months was observed in 24% of patients. CA19-9 levels were measured pre- and post-dose with each treatment. Immediate reductions showed dose-dependent reductions of up to 97% from baseline at 3 mg/kg. Downward trends of CA19-9 with successive doses were seen, with 48% and 22% of patients exhibiting $\geq$50% and $\geq$90% reductions in CA19-9 levels, respectively. **Conclusions:** Single agent MVT-5873 appears safe and tolerable at biologically active doses. DLTs included reversible serologic liver toxicity. The safety profile, efficacy, and reductions in serum CA19-9 levels over time support further development of MVT-5873 in this indication both as a single agent and in combination. Clinical trial information: NCT02672917.

4111 Poster Session (Board #103), Sat, 8:00 AM-11:30 AM

Efficacy, safety, and immune activation with pegylated human IL-10 (AM0010) plus FOLFOX in metastatic pancreatic adenocarcinoma (PDAC). *First Author: J. Randolph Hecht, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: Oxaliplatin or nal-irinotecan plus 5-FU are used as 2nd-line PDAC therapy (mOS 5-6 months (m)). PDAC also has been largely refractory to immune therapies which may depend on the expansion of activated, intratumoral, tumor specific cytotoxic CD8+ T cells that are low in most PDACs. AM0010 stimulates survival, expansion and cytotoxicity of intratumoral CD8+ T cells. Immune activation, durable stable disease and a 1yr survival of 22.5% was seen in salvage PDAC patients (pts) receiving AM0010 alone. Platins or 5-FU may activate immune responses to cancer and AM0010 has shown synergistic anti-tumor results with FOLFOX in preclinical models. In this phase 1b clinical study, the safety and efficacy of AM0010 +FOLFOX was studied in PDAC pts. **Methods:** PDAC pts progressing on a median of 1 prior therapy (range 1-3) were treated with AM0010 (5ug/kg SQ, qd) + FOLFOX (n = 21), an additional 4 pts with prior oxaliplatin and 5-FU were included in the safety population (n = 25). Tumor responses were assessed using irRC. Serum cytokines, activation of blood derived T cells and peripheral T cell clonality were analyzed. Pretreatment archival tissue samples were evaluated by IHC for tumor infiltration by CD8+ T cells. **Results:** On AM0010 + FOLFOX, G3/4 TrAEs included thrombocytopenia (52%), anemia (36%) and neutropenia (36%). A modified AM0010 dose schedule (5 days on 2 days off) avoided G3/4 thrombocytopenia. As of 01/31/2017, 2 patients remained on treatment for $>$ 1 year. 19 pts had objective tumor response assessment; 2 had irCR, 1 irPR, 11 irSD. ORR is 15.8%, DCR is 73.7%. With median follow-up of 11.0 m (range 5.8-16.3), mPFS was 3.5 m and mOS 10.0 m. Pts with more intra-tumoral CD8+ T cells had longer OS. AM0010 + FOLFOX increased serum Th1 cytokines and reduced mediators of chronic inflammation and TGFb. AM0010 induced de-novo oligoclonal expansion of T cell clones in patients with prolonged survival. **Conclusions:** AM0010 plus FOLFOX is well tolerated in patients with PDAC. The observed immune activation including clonal T cell expansion and prolonged objective tumor responses are encouraging in this advanced PDAC population. This regimen is currently being studied in a phase 3 trial. Clinical trial information: NCT02009449.

4113 Poster Session (Board #105), Sat, 8:00 AM-11:30 AM

FOLFIRINOX (F-NOX) followed by individualized radiation for borderline-resectable pancreatic cancer (BRPC): Toxicity, R0 resection, and interim survival data from a prospective phase II study. *First Author: Janet E. Murphy, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: F-NOX is increasingly utilized in BRPC as neoadjuvant therapy. However, prospective data remains limited; the largest series is a 22 patient (pt) cooperative group trial (Alliance A021101), in which 14 pts had R0 resection. In this study, we evaluate neoadjuvant F-NOX followed by individualized chemoradiation (CRT) for BRPC. **Methods:** Pts ECOG PS 0-1 with biopsy-proven BRPC defined by NCCN criteria were enrolled in a single institution, NCI-sponsored phase II study (NCT01591733). Pts received F-NOX for 8 cycles. If after chemotherapy the tumor was radiographically resectable, pts received short course CRT in 5 (protons 25 GyE) or 10 fractions (photons 30 Gy) with capecitabine 825 mg/m2 bid. If the tumor was still abutting vasculature, pts received CRT to 50.4 Gy with a vascular boost to 58.8 Gy. Primary endpoint was R0 resection rate. **Results:** 50 pts were enrolled from 8/2012 to 8/2016. Two pts were ineligible (lung metastasis, negative biopsy); 48 pts were evaluable. Median age was 62y (46-74). Median tumor size was 37 mm (21-56). Thirty-six pts (75%) had pancreatic head tumors. Median follow up was 18.2 months among 31 patients still alive. Of the evaluable pts, 40 (83%) completed therapy. Reasons for not completing therapy include pt withdrawal (3), physician decision (3), unacceptable toxicity (1) and progression (1). Grade 3 or greater toxicity occurred in 48% of pts, but no individual grade 3 toxicity exceeded 15%. Twenty-seven pts (56%) had short course CRT, while 13 pts (27%) had long course CRT. Twenty-nine pts were resected; R0 resection was achieved in 28/29 (96.5%). R0 resection rate among all evaluable pts was 58.3%. Median PFS among all evaluable pts was was 14.7 months; mOS was 37.7 months, with 1y OS 79.5% and 2y OS 59.3%. Among resected patients, mOS has not been reached. 1y PFS was 78.1% and 2y PFS 55.4%; 1y OS was 92.6% and 2y OS was 80.6%. **Conclusions:** Preoperative F-NOX followed by individualized chemoradiation in BRPC results in high R0 resection rates as well as prolonged mPFS and mOS in this large prospective cohort. Clinical trial information: NCT01591733.

4114 Poster Session (Board #106), Sat, 8:00 AM-11:30 AM

Adjuvant chemotherapy and outcome in patients (pts) with nodal (N-) and resection margin negative (R0) pancreatic adenocarcinoma (PC): A systematic review and meta-analysis. *First Author: Nicola Flaum, Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Adjuvant chemotherapy following PC resection improves overall survival (OS). It is uncertain whether benefit is influenced by nodal and resection status or other factors. **Methods:** A systematic review of electronic databases identified published phase 2/3 studies investigating use of adjuvant chemotherapy in pts with resected PC. Efficacy (disease-free survival [DFS], OS, 5 yr OS) was explored using meta-analysis. Subgroup analysis explored effects based on nodal/resection status. Meta-regression also explored influence of age, gender, performance status [PS] and proportion of pts with head of pancreas (HOP) tumors on benefit of adjuvant chemotherapy. **Results:** Ten studies comprising 3644 pts were included. Two prospective phase 2 studies; 8 phase 3 trials. Median age was 63 yrs (range 24-84), 46% male. In 2268 pts with PS reported; 42% were PS 0, 51% PS 1. Tumor location was reported in 719 pts; 82% had HOP tumors. Of 3524 pts with available data; 33% N- and 67% R0. Overall, in studies of experimental vs control, adjuvant therapy significantly improved DFS (HR 0.67, CI 0.48-0.93, P = 0.02), OS (HR 0.77, 95% CI 0.68-0.87, P $<$ 0.001) and odds of death risk at 5 yrs (OR 0.53, 95% CI 0.41-0.70, P $<$ 0.001). In studies comparing chemotherapy to surgery only, adjuvant therapy also significantly improved DFS (HR 0.57, 95% CI 0.49-0.76, P $<$ 0.001) and OS (HR 0.74, 95% CI 0.64-0.87, P $<$ 0.001). There was a numerical but non-significant greater effect of adjuvant therapy in N- vs N+ pts (HR 0.58 vs 0.71, P for difference = 0.29). There was no difference in effect between pts with R0 or R1 disease (HR 0.70 vs 0.69, P for difference = 0.95). There was greater OS benefit from adjuvant therapy in pts with PS 0 (P = 0.04) and significantly less benefit on 5 yr OS in pts with HOP tumors (P = 0.04). **Conclusions:** The relative benefit of adjuvant chemotherapy seems similar in N-/N+ and in R0/R1 pts. This will translate into greater absolute benefit in the N+ and R1 pts due to their greater absolute risk of recurrence/death. Adjuvant chemotherapy is recommended for all pts with resected PC, where clinically appropriate, and greater benefit was seen in pts with PS 0 and body/tail tumors.

4115 Poster Session (Board #107), Sat, 8:00 AM-11:30 AM

Defining DDR defectiveness in pancreatic cancer. *First Author: Stephan Dreyer, Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom*

Background: Recent whole genome sequencing analysis of Pancreatic Cancer (PC) revealed that up to 24% of PC may harbor defects in DNA damage response (DDR). There is increasing evidence that DDR defective tumors preferentially respond to DNA damaging agents, representing novel therapeutic strategy for PC using a synthetic lethality approach. The aim of this study is to define and refine DDR defective phenotypes in PC using next-generation preclinical model systems. **Methods:** From a panel of 40 patient-derived cell lines (PDCL) and 64 patient-derived xenografts (PDX), generated and extensively characterized as part of the International Cancer Genome Initiative (ICGC), we identified DDR defective models using recently described putative biomarkers of DDR defectiveness. Cytotoxic viability assays were performed using a panel of DNA damaging agents and inhibitors of key molecules in DDR pathway, including Cisplatin, PARP inhibitors, ATR inhibitor (AZD6738); and ATM inhibitor (AZD0156). Appropriate subcutaneous PDX models were also generated to test the hypothesis using various therapeutic regimens. **Results:** DDR defective PDCLs were selected based on a combination of an unstable genome, and/or a high *BRCA* mutational signature, and/or deleterious mutations in *BRCA1/2*, *PALB2* or *ARID1A*. DDR defective PDCLs were significantly more sensitive to Cisplatin, PARP and ATR inhibitors. The ATR inhibitor AZD6738, and ATM inhibitor AZD0156 sensitized PDCLs with no putative biomarkers of DDR defectiveness to Cisplatin, demonstrating a 'fabricated' synthetic lethality. A *BRCA1* mutant PDX model responded exceptionally to Cisplatin and the PARP inhibitor Olaparib monotherapy. **Conclusions:** This study provides proof of concept data that DDR deficiency represents an attractive segment to target in PC using a variety of DNA damaging agents and novel agents targeting key molecules of the DDR pathway in PC. In addition, the DDR defective segment may be significantly larger than just germline *BRCA1/2* mutants, which is current clinical trial recruitment criteria. Robust molecular assays with clinical utility to define DDR defectiveness is urgently needed.

4116 Poster Session (Board #108), Sat, 8:00 AM-11:30 AM

Characterization of germline genomic alterations in familial pancreas cancer. *First Author: Jennifer Brooke Goldstein, The University of Texas MD Anderson Cancer Center, Medical Oncology Fellowship, Houston, TX*

Background: Family history of BRCA-related tumors may correlate with response to chemotherapy and overall survival in patients with pancreatic cancer (PC). We retrospectively compared family history of such cancers with clinical outcomes and underlying molecular aberrations. **Methods:** A retrospective chart review was conducted of 350 metastatic PC patients treated with first line FOLFIRINOX and Gem/Abraxane at MDACC from 1/2010 -1/2016. Family history was defined as 1st through 3rdgeneration relatives with breast, ovarian, or pancreas cancer. Germline DNA was collected and sequenced using a familial cancer panel using an Illumina 2500. Average coverage was 200X. Platypus calls were analyzed for germline mutations. We assessed mutations in BRCA1, BRCA2, PALB2, MMR genes, ATM, and PolE. **Results:** Average age was 61. 60% of patients were male. We sequenced blood and tissue samples where available. We found at lease one mutation in 47 of 129 patients tested. There were 56 mutations identified among the 47 patients. Of patients with 0-1,2, or 3 or more affected family members we found mutations in 44%, 47%, and 29%, respectively. Patients with 3+ family members affected tended to have mutations in BRCA1 or PolE. Among the subset of patients with possible deleterious mutations, there were trends towards improved survival in pts with BRCA or PALB aberrations (307d vs 271d, p = ns) but worse outcomes in those with MMR gene defects (181d vs 387d, p = .126). Table 1 indicates outcomes based on number of family members with cancer and their associated mutations. **Conclusions:** Approximately one third of all patients tested had at least one germline mutation in previously described familial pancreas cancer genes. Screening for inherited cancer susceptibility genes may have prognostic value.

Overall survival by number of affected family members and associated germline mutations.

# Affected Family Members	OS All Patients	95% CI	OS Sequenced Pts	95% CI	Mutations Found
3+	518	251 - 785	518 d	377 - 659	BRCA1 (14%); POLE (14%)
2	296	189 - 403	312 d	233 - 400	BRCA2 (10%), MMR (16%), POLE (10%), ATM (10%)
0-1	283	249- 317	267 d	213 - 320	BRCA1 (3%), BRCA2 (8%), PALB2 (6%), POLE (6%), MMR(12%), ATM (9%)

4117 Poster Session (Board #109), Sat, 8:00 AM-11:30 AM

Neoadjuvant FOLFIRINOX for patients with borderline resectable or locally advanced pancreatic cancer: Results of a decision analysis. *First Author: Jin Choi, Institute for Technology Assessment, Massachusetts General Hospital, Boston, MA*

Background: With the advent of more effective therapies for metastatic pancreatic ductal adenocarcinoma (PDAC), efforts to incorporate these agents, such as FOLFIRINOX, into the neoadjuvant setting are increasing. However, the efficacy and cost-effectiveness of using neoadjuvant FOLFIRINOX for patients with borderline resectable or locally advanced PDAC are unknown. We performed a decision analysis to assess the value of neoadjuvant FOLFIRINOX versus upfront surgery and adjuvant therapy. **Methods:** We developed a mathematical simulation model to evaluate the efficacy and cost-effectiveness of neoadjuvant FOLFIRINOX compared to upfront surgery and adjuvant therapy. We used published and institutional data as inputs to inform model development. Model outcomes included overall and disease-free survival, net benefits expressed as discounted quality-adjusted life-years (QALYs), costs in US dollars, and cost-effectiveness expressed as an incremental cost-effectiveness ratio. We used deterministic and probabilistic sensitivity analyses to explore the uncertainty of model assumptions. **Results:** Model estimated median overall survival (29 vs 23 months) and disease-free survival (14 vs 13 months) were better for neoadjuvant strategy compared with upfront surgery. Neoadjuvant strategy resulted in an additional 0.68 life-years gained, or 0.57 QALYs, at a cost of $59,000/QALY gained. Sensitivity analysis found that cancer recurrence rates affected model results the most. Our findings were otherwise robust with respect to changes in other model parameters, including chemotherapy toxicity, surgical complications and cancer mortality. Probabilistic sensitivity analyses showed that neoadjuvant strategy was cost-effective 80% of the time with a willingness-to-pay threshold of $100,000/QALY. **Conclusions:** Our model results demonstrate that neoadjuvant strategy is preferable to upfront surgery for patients with borderline resectable or locally advanced PDAC from both an efficacy and cost-effectiveness standpoint. Additional clinical data are needed to further define the long-term effectiveness of neoadjuvant FOLFIRINOX to confirm our results.

4118 Poster Session (Board #110), Sat, 8:00 AM-11:30 AM

Phase II study of autophagy inhibition with hydroxychloroquine (HCQ) and preoperative (preop) short course chemoradiation (SCRT) followed by early surgery for resectable ductal adenocarcinoma of the head of pancreas (PDAC). *First Author: Theodore S. Hong, NSABP/NRG Oncology, and Massachusetts General Hospital, Boston, MA*

Background: PDAC is highly dependent on autophagy, a metabolic process that renders cancer cells resistant to cytotoxic therapies. HCQ is an inhibitor of autophagy, and has preclinical activity in PDAC. We evaluate the efficacy of concurrent and adjuvant HCQ with preop SCRT and adjuvant chemotherapy in early, resectable PDAC. **Methods:** Pts with radiographically resectable, biopsy-proven PDAC of the head were enrolled from 12/2011-9/2016 on this IRB-approved, NCI-sponsored clinical trial (NCT01494155). Eligibility included no involvement of SMA or celiac artery on CT; adequate renal, hepatic and hematopoetic function; and ECOG PS 0/1. SCRT was 5 Gy x 5 with protons or 3 Gy x 10 with photons concurrent with Cape 825 mg/m2 BID wk 1 and 2 M-F. HCQ was started at 400 mg po BID 1 wk prior to radiation through SCRT until the day of surgery. Surgery was performed 1-3 wks after completion of SCRT. Pts were recommended to receive 6 mo of gemcitabine-based chemotherapy after surgery. Pts resumed HCQ after discharge from surgery and continued until progression. Follow-up was performed every 3 months with CT scanning every 6 mo. Sample size of 50 to evaluate an increase of 2-year PFS from 30% to 45%. **Results:** 50 pts were enrolled on study and all are evaluable for this analysis. Median age- 69 (range 54-86); pre-treatment CA19-9 median 69.5 U/mL ($<$ 1-10235), female- 24 pts (48%). Gr 3 toxicity was noted in 2 (4%) pts (nausea-1, hyperglycemia-1). All 50 pts completed SCRT. 46 pts underwent resection. Reasons for no resections: metastatic disease-2, toxicity-1, intercurrent illness- 1. 38 pts had R0 resection, 8 had R1 resection. 29 of 46 pts had positive nodes. 1 pt achieved pathologic complete response (CR), 2 pts had near CR . 11 pts remain on HCQ. Median follow up in 26 surviving pts is 18.3 months. mPFS is 11.7 mo, mOS 23.3 mo. OS-2 yr- 43.1%, PFS-2-yr 32.0%. **Conclusions:** HCQ with preop SCRT and adjuvant gemcitabine-based chemotherapy is well tolerated but did not meaningfully impact DFS. Further pathologic/correlative studies, particularly in outstanding pathologic responders and long term survivors are ongoing. Clinical trial information: NCT01494155.

4119 Poster Session (Board #111), Sat, 8:00 AM-11:30 AM

A phase I/II trial of TG01/GM-CSF and gemcitabine as adjuvant therapy for treating patients with resected RAS-mutant adenocarcinoma of the pancreas. *First Author: Daniel H. Palmer, Department of Molecular and Clinical Cancer Medicine, University of Liverpool and Clatterbridge Cancer Centre, Liverpool, United Kingdom*

Background: TG01 (a mixture of 7 RAS peptides) is an injectable antigen-specific cancer immunotherapy targeted to treat patients (Pts) with KRAS mutations, found in more than 85% of pancreatic adenocarcinomas. There is scope for improvement in adjuvant treatment of resected pancreatic cancer; with 1- and 2-year published overall survival (OS) rates ranging from 56-80% and 30-54% respectively. TG01 induces RAS mutant-specific T-cell responses which are enhanced by co-administration of GM-CSF. This study evaluates safety, immunological response and OS of TG01-immunotherapy with adjuvant gemcitabine chemotherapy. **Methods:** Pts were eligible after an R0 or R1 pancreatic adenocarcinoma resection. As soon as possible after surgery, TG01 (0.7 mg intradermal injection (id)) together with GM-CSF (0.03 mg id) was given on days 1, 3, 5, 8, 15, 22 and 2-weekly thereafter until the end of gemcitabine (starting within 12 weeks of surgery and given for 6 cycles). Thereafter TG01/GM-CFS were given 4-weekly up to 1 yr and 12-weekly up to 2 yrs. Immune response was assessed using antigen-specific (TG01) Delayed-Type Hypersensitivity (DTH) and T-cell proliferation. OS was assessed from surgery; ~8 weeks before first TG01 injection. **Results:** To date**,** 19 pts (68% R1) from 3 sites (Norway and UK**)** and have been followed for 2 yrs**.**Eight SARs in 5 pts have occurred; 4 related to gemcitabine (anemia, pulmonary infection and 2 fever); 3 related to TG01/GM-CSF (2 anaphylaxes and 1 hypersensitivity); and 1 possibly related to all products (dyspnea). The allergic reactions only occurred after several cycles of gemcitabine and resolved within 1-2 hrs. There was no treatment related deaths.16/19 (84%) pts had a positive DTH by week 11. Proliferation of mutant RAS specific T-cells is being analyzed. OS rate at 1 and 2 yrs were 89.5% (95% CI 75.7, 100.0) and 68.4 (95% CI 47.5, 89.3), respectively. Median OS was 33.1 months (95% CI 16.8, 40.1). **Conclusions:** TG01/GM-CSF generated early immune responses in 84% of patients with R0/R1 resected pancreatic cancer. The regimen was generally well tolerated although some late, manageable allergic reactions were seen. OS was encouraging in view of published reports. Clinical trial information: NCT02261714.

4120 Poster Session (Board #112), Sat, 8:00 AM-11:30 AM

Neutrophil count and efficacy of chemoradiation in patients with locally advanced unresectable pancreatic carcinoma: An ancillary study of in the LAP 07 trial. *First Author: Antoine Schernberg, Hôpital Tenon, Paris, France*

Background: Predictive biomarkers of Overall Survival (OS) and Progression Free Survival (PFS) in locally advanced pancreatic cancer (LAPC) pts are mandatory. Baseline leukocyte, neutrophil and monocyte counts in addition to lymphocyte ratio (NLR) may predict OS in LAPC pts. Efficacy of chemoradiation (CRT) depending on neutrophil count was retrospectively analyzed in the largest Phase III cohort of LAPC. **Methods:** The international multicenter randomized LAP07 phase III trial (NCT00634725) has recruited 442 LAPC pts. We have studied the predictive and prognostic value of systemic inflammation, as defined: *(i)* baseline neutrophilia (neutrophil count $>$ 7 G/L at first randomization) or *(ii)*increased absolute neutrophil count (IANC) after induction chemotherapy vs baseline. Univariate and multivariate Cox analysis evaluated the benefit of CRT for OS, PFS and Local Control (LC) in pts without systemic inflammation. **Results:** Patients with baseline neutrophilia (11%) had a worse OS (median 8.9 vs 13.3 months, p = 0.01). At 2nd randomization, 9% and 29% pts had baseline neutrophilia or IANC, respectively. Both neutrophilia (median OS 10.6 vs 16.1 months, p = 0.03) and IANC (median OS 14.6 vs 17.4 months, p = 0.02) predicted poor OS. Systemic inflammation predicted local resistance to CRT (p = 0.02, interaction = 0.015). After excluding pts with systemic inflammation, 1-year local control was 80% in CRT vs 54% in chemotherapy arms ($p < 0.001$). Pts without systemic inflammation in CRT arm had improved PFS vs chemotherapy arm (median 10.3 vs 8.3 months, p = 0.04). In multivariate analysis in this population, CRT increased PFS (HR = 0.66, 95%CI: 0.45 - 0.97, p = 0.03), after adjusting on age, tumor size, pain at enrollment, albumin, and CA 19.9 according to PROLAP nomogram parameters. **Conclusions:** In LAPC pts with tumor controlled after induction chemotherapy, systemic inflammation may help to better predict those who will benefit from CRT. This result may impact clinical management and the design of future clinical trials for LAPC. An external validation with a cohort from the ARCAD pancreas meta-analysis is under consideration. Clinical trial information: NCT00634725.

4122 Poster Session (Board #114), Sat, 8:00 AM-11:30 AM

Selective benefit of adjuvant chemoradiation in resectable pancreatic cancer. *First Author: Jesse P Wright, Division of Surgical Oncology, Department of Surgery, Vanderbilt University Medical Center, Nasvhille, TN*

Background: Although level 1 data supports the use of adjuvant chemotherapy (ACT) in resected pancreatic adenocarcinoma (PDAC), the role of adjuvant chemoradiation (ACRT) remains controversial. The objective of this study is to investigate the impact of adding ACRT to ACT on overall survival (OS), based on lymph node (LN) and margin status. **Methods:** Resected AJCC Stage I and II PDAC patients from 2004-2013 identified within the National Cancer Database were classified into groups based on treatment: surgery alone (SX), ACT alone, ACT+ACRT, and ACRT only. Kaplan-Meier analyses were performed to determine median OS. Multivariable (MV) Cox regression models with interactions of treatment with LN and margin status were constructed to examine the independent effects of ACT and ACT+ACRT in these subgroups. **Results:** Of 31,348 patients, 30% were treated with SX, 30% with ACT, 38% with ACT+ACRT, and 2% with ACRT alone. Median OS (mos.) for ACT (22.5, 95% CI 21.9-23.1) and ACT+ACRT (23.7, 23.3-24.2) were significantly longer than SX (14, 13.4-14.5) or ACRT (11.2, 9.8-12.9). MV analysis confirmed a significant OS benefit of both ACT and ACT+ACRT controlling for patient and tumor related factors. ACRT+ACT was associated with improved OS compared to ACT in patients with positive margins and/or LN. Those with negative margins and LN did not benefit from the additional use of ACRT (Table). **Conclusions:** This large hospital-based study demonstrates that ACT and ACRT are associated with improved OS when compared to SX. The addition of ACRT to ACT, however, was only beneficial in high-risk patients with positive margins and/or LN. ACT+ACRT in patients with both margin and LN negative disease may not be warranted. Future clinical trials should stratify patients based on LN and margin status in order to determine which patients are most likely to benefit from the use of ACRT.

MV cox proportional hazard model: HR and 95% CI.

	ACT	SX	ACRT	ACT+ACRT
LN -, MARGIN -	Ref	1.44 (1.33 – 1.55)	1.45 (1.10 – 1.91)	1.00 (0.93 – 1.08)
LN -, MARGIN +	Ref	1.64 (1.45 – 1.86)	1.69 (7.23 – 2.32)	0.88 (0.79 – 0.98)*
LN +, MARGIN -	Ref	1.53 (1.44 – 1.63)	1.68 (1.40 – 2.03)	0.89 (0.85 – 0.94)*
LN +, MARGIN +	Ref	1.75 (1.59 – 1.93)	1.96 (1.52 – 2.55)	0.79 (0.73 – 0.85)*

(*Significant survival benefit)

4123 Poster Session (Board #115), Sat, 8:00 AM-11:30 AM

Effect of inflammatory and nutritional (IN) status on induction chemotherapy (CT) followed by chemoradiotherapy (CRT) for locally advanced pancreatic cancer (LAPC): An exploratory subgroup analysis of JCOG1106. *First Author: Nobumasa Mizuno, Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan*

Background: JCOG1106 is a randomized selection phase 2 trial to evaluate the efficacy and safety of CRT (S-1 concurrent RT) with (Arm B) or without (Arm A) induction CT of gemcitabine (GEM) for LAPC. In the final analysis, we selected Arm A as a promising regimen due to a poorer 2-year overall survival (OS) of Arm B, in spite of a favorable 1-year OS with crossing of the survival curves around 1-year (Ioka, ESMO2016). Therefore, this study aimed to explore subgroups benefit more from either treatment. IN statuses defined by such as serum C-reactive protein (CRP) and serum albumin (Alb) are recognized as prognostic and predictive factors in patients (pts) with various cancers receiving CT or CRT. We hypothesized that IN status may modify the effect of induction CT. **Methods:** Subjects were all eligible pts who were enrolled in JCOG1106 (n = 51/49 in Arm A/B). Glasgow Prognostic Score (GPS) was classified by baseline CRP and Alb. Pts with a CRP $\leq$ 10 mg/L and Alb $\geq$ 35 g/L were allocated to GPS 0, with a CRP $>$ 10 mg/L or Alb $<$ 35 g/L to GPS 1, and with a CRP $>$ 10 mg/L and Alb $<$ 35 g/L to GPS 2. This exploratory subgroup analysis was performed by Cox regression analysis to investigate the impact of IN status at baseline on OS. Less than 0.1 of P-value for interaction was regarded as significant. **Results:** GPS, CRP and Alb showed significant treatment interactions in terms of OS. HRs of Arm B to Arm A were 1.35 (0.82–2.23) and 0.59 (0.24–1.50) in the GPS 0 (n = 44/34 in Arm A/B) and GPS 1/2 group (n = 7/15) (*P*-interaction = 0.06). HRs were 2.57 (1.36–4.86) and 0.70 (0.37–1.32) in the low CRP group ($\leq$ 1.35 mg/L, n = 25/25) and high CRP ($>$ 1.35 mg/L, n = 26/24) (*P*= 0.01). HRs were 1.62 (0.77–3.40), 2.70 (1.17–6.23) and 0.52 (0.24–1.13) in the 1st ($\leq$ 0.7 mg/L, n = 16/16), 2nd ($>$ 0.7, $\leq$ 3.0 mg/L, n = 20/16), and 3rd tertiary CRP group ($>$ 3.0 mg/L, n = 15/17) (*P*= 0.01). HRs were 2.29 (1.11–4.69) and 0.89 (0.51–1.54) in the high Alb group ($>$ 40 g/L, n = 23/17) and low Alb ($\leq$ 40 g/L, n = 28/32) (*P*= 0.04). Arm B showed better survival in subgroups of GPS 1/2, higher CRP or lower Alb compared to Arm A. **Conclusions:** Pts with poor IN status may have treatment benefit of induction CT followed by CRT for LAPC. Clinical trial information: UMIN000006811.

4124 Poster Session (Board #116), Sat, 8:00 AM-11:30 AM

Molecular profiling of advanced pancreatic cancer (PC) patients from a phase I/II study using circulating tumor DNA. *First Author: Daniel V.T. Catenacci, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: PC has a poor prognosis with a 5-year survival of 9%. Targeted therapies have yet to demonstrate improved outcomes in this disease. Circulating tumour DNA (ctDNA) may be used as a non-invasive method for the detection and quantification of genomic abnormalities. We performed a retrospective-prospective study to assess molecular alterations in the ctDNA of advanced PC patients. **Methods:** Plasma samples were banked from patients enrolled in the previously reported Phase Ib/II trial of gemcitabine with placebo or vismodegib (NCT01064622; Catenacci et al JCO 2015). Eligible patients had unresectable PC and no prior therapy for metastatic disease. Patient samples ($<$ 3ml) collected pre-treatment and at regular intervals and stored for ~6-8 years were analyzed using InVision (enhanced tagged-amplicon sequencing) for "hotspot" regions of 34 genes, including *KRAS* (exons 2 and 3), and select full gene coverage. **Results:** Of 113 patients enrolled in the trial, a cohort of 72 patients were included in this study. Baseline plasma ctDNA profiling detected any genomic event in 88% of patients (SNV/indels found at range of 0.07%-23% allele fraction (AF) with 20% detected at $<$ 0.5% AF). Patients had between 1-5 mutations (median, 2): *KRAS* mutations were detected in 80% of patients tested, of which 86% had concurrent *KRAS/TP53* mutation(s) and 16% with concurrent *KRAS/TP53/CDK2NA*. Of note, 2 cases presented with *IDH1* point mutations (R132C, R132H). An *ERBB2* amplification and a *FGFR2* amplification were detected in 2 individuals. An update on the analyses will include serial ctDNA testing during treatment and correlation with outcomes. **Conclusions:** ctDNA analysis of this cohort of banked PC plasma samples described the landscape of genomic aberrations at baseline and over time, including rare but potentially important actionable events including *ERBB2* and *FGFR2* amplifications and *IDH1* mutation. We demonstrate a sensitive method for re-analysing trial outcomes, despite limiting plasma volume and time lapse since samples were collected.

4125 Poster Session (Board #117), Sat, 8:00 AM-11:30 AM

Preliminary safety data from a randomized multicenter phase Ib/II study of neoadjuvant chemoradiation therapy (CRT) alone or in combination with pembrolizumab in patients with resectable or borderline resectable pancreatic cancer. *First Author: Matthew H. G. Katz, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pancreatic cancer (PC) is a challenging target for immunotherapy.Tumor-infiltrating lymphocytes (TILs) do not reach the PC cells in significant numbers due to the presence of stroma and a suppressive microenvironment. Neoadjuvant chemoradiation (CRT) can increase the presence of TILs in the PC microenvironment. We hypothesized that combination of CRT and pembrolizumab can lead to further increase in TILs and their activation. **Methods:** Patients with resectable or borderline resectable PC have been randomized 2:1 to the investigational treatment (Arm A) to receive pembrolizumab 200mg IV every 3 weeks on days 1, 22, and 43 during concurrent CRT with capecitabine (825 mg/m2 orally twice daily, Monday-Friday, on days of radiation only) and radiation (50.4 Gy in 28 fractions over 28 days) or Arm B to receive only concurrent CRT with capecitabine. Restaging CT scan or MRI is performed at 4-6 weeks after completion of neoadjuvant treatment, and patients with resectable disease will undergo surgical resection. Here we report the preliminary safety data based on 22 enrolled patients. **Results:** As of February 3-2017,22 patients have been enrolled (14 Arm A and 8 Arm B). 50% of the patients had resectable disease (7 arm A; 4 arm B) and the other 50% had borderline resectable disease (7 Arm A; 4 arm B). Post-neoadjuvant therapy, 6 patients had unresectable disease (3 on each arm), and 14 patients underwent surgery (10 arm A and 4 arm B). There were 7 grade 3 treatment-related toxicities in Arm A (5 patients): 2 grade 3 diarrhea attributed to CRT; 4 grade 3 lymphopenias attributed to pembrolizumab, CRT or the combination; and one patient had elevated alkaline phosphatase probably related to the combination that met the definition of DLT and resolved after holding the treatment and receiving steroids. There was only one grade 3 toxicity on Arm B: lymphopenia attributed to CRT. No grade 4 toxicities have been reported on either arm. There were no major surgical complications reported within 30 days post-surgery. **Conclusions:** The combination of CRT and pembrolizuamb is safe based on the presented data. Clinical trial information: NCT02305186.

4126 Poster Session (Board #118), Sat, 8:00 AM-11:30 AM

Initiation and shift of antidiabetic therapy and pancreatic cancer. *First Author: Philippe Autier, University of Strathclyde Institute for Global Public Health at iPRI, Ecully, France*

Background: Concerns have been raised on the risk of pancreatic cancer associated with specific anti-diabetic therapies. We have examined the risk of pancreatic cancer among patients with diabetes prescribed with an oral anti-diabetic drug (OAD) or an incretin drug (DPP4i and GLP-1 RA) or insulin. **Methods:** The public health insurance databases of Belgium and of Lombardy Region, Italy include nearly 100% of the population living in these countries. We created within these databases two cohorts that included adult patients who were first prescribed an incretin drug or another noninsulin antidiabetic drug (NIAD) during 01/07/2008-31/12/2013 in Belgium and during 01/01/2008-31/12/2012 in Lombardy Region. The risk of pancreatic cancer after prescription of an anti-diabetic drug was evaluated using multivariate adjusted Cox models including time-dependent variables. Adjusted hazard ratios (aHRs) from Belgium and Italy were pooled using fixed effects meta-analyses. **Results:** Results in both cohorts were similar. Among those patients prescribed an OAD, 45% of pancreatic cancers occurred within the 6 months following first prescription, 20% in months 7 to 12 after first prescription and proportions decreased progressively during follow-up. The aHR of pancreatic cancer among subjects prescribed an incretin compared to an OAD was 2.14 [95% CI, 1.71 to 2.67]. The aHR decreased from 3.35 [CI, 2.32 to 4.84] in the first 3 months after first incretin prescription, 2.12 [CI, 1.22 to 3.66] in months 3 to 5.9, 1.95 [CI, 1.20 to 3.16] in months 6 to 11.9, to 1.69 [CI, 1.12 to 2.55] after 12 months. The risk of pancreatic cancer among subjects who were subsequently prescribed insulin was 6.89 [CI, 6.05 to 7.85]. The time from OAD prescription to a shift to incretins or to insulin was significantly lower in patients who were subsequently diagnosed with a pancreatic cancer. **Conclusions:** The increased risk of pancreatic cancer associated with anti-diabetic therapies could be the consequence of an occult pancreatic cancer that provokes diabetes (reverse causation bias). The search for an occult pancreatic cancer in subjects with newly diagnosed diabetes or patients shifting to more potent anti-diabetic therapy may lead to earlier detection of this cancer.

4127 Poster Session (Board #119), Sat, 8:00 AM-11:30 AM

Subgroup analysis by prior lines of metastatic therapy (mtx) in NAPOLI-1: A global, randomized phase 3 study of liposomal irinotecan (nal-IRI) ± 5-fluorouracil and leucovorin (5-FU/LV), vs. 5-FU/LV in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) who have progressed following gemcitabine-based therapy. *First Author: Teresa Mercade Macarulla, Vall d'Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain*

Background: In the NAPOLI-1 study, nal-IRI+5-FU/LV significantly increased median OS vs. 5-FU/LV control (6.1 vs. 4.2 mo; unstratified HR = 0.67 [0.49–0.92]; p = .012). This is a subgroup analysis by prior lines of mtx. **Methods:** Study methodology has been published (Wang-Gillam; Lancet 2016). This exploratory subgroup analysis compares outcomes in pts with 0–1 vs. ≥2 prior mtx lines, based on primary survival analysis data (cut-off February 2014) of the ITT population. **Results:** OS, PFS and CA19-9 response rates in pts with 0–1 (65.8% of pts) or ≥2 (34.2%) prior mtx lines are shown (see Table). Median OS for nal-IRI+5-FU/LV improved vs. 5-FU/LV by 2.1 mo to 6.2 mo (HR = 0.66; p = .03) in pts with 0–1 prior mtx lines and by 1.1 mo to 5.4 mo (HR = 0.68; p = .18) in pts with ≥2 prior mtx lines. The safety profile was similar between subgroups with nal-IRI+5-FU/LV (≥grade 3 drug-related AEs: 43 [55%] with 0–1 and 20 [51%] with ≥2 prior mtx lines). **Conclusions:** This post-hoc subgroup analysis shows significant increases for nal-IRI+5-FU/LV over 5-FU/LV in OS, PFS and CA19-9 response in pts with 0–1 prior mtx lines. Median OS benefit was less prominent in later lines, but conclusions are restricted by limited pt numbers. Clinical trial information: NCT01494506.

	0–1 prior mtx lines		
	nal-IRI+5-FU/LV (n = 77 [65.8%])	5-FU/LV (n = 82 [68.9%])	Unstratified HR (95%CI); p-value
Median OS, mo (95%CI)	6.24 (4.70–8.97)	4.17 (3.35–5.82)	0.66 (0.45–0.96); p = .03
Median PFS, mo (95%CI)	2.89 (2.40–4.34)	1.46 (1.38–1.87)	0.51 (0.35–0.73); p < .001
CA19-9 response rates, n/N (%)	21/68 (30.9)	6/56 (10.7)	p < .01
	≥2 prior mtx lines		
	nal-IRI+5-FU/LV (n = 40 [34.2%])	5-FU/LV (n = 37 [31.1%])	
Median OS, mo (95%CI)	5.42 (4.44–9.30)	4.34 (2.63–6.37)	0.68 (0.38–1.20); p = .18
Median PFS, mo (95%CI)	4.01 (1.41–4.53)	1.56 (1.35–2.66)	0.65 (0.37–1.14); p = .13
CA19-9 response rates, n/N (%)	7/29 (24.1)	1/25 (4.0)	p = .06

4128 Poster Session (Board #120), Sat, 8:00 AM-11:30 AM

Genomic profiling of circulating tumor DNA (ctDNA) from patients (pts) with pancreatic ductal adenocarcinoma (PDA). *First Author: Nathan Bahary, University of Pittsburgh Medical Center Cancer Center Pavilion, Pittsburgh, PA*

Background: PDA is a lethal and increasingly common malignancy and tissue samples for genomic characterization may be limited. As PDA has a high and consistent frequency of *KRAS*, *p53* and *CDKN2A* mutations it serves as a robust indication to test the utility of ctDNA in accurately characterizing genomic alterations (GA). A prior study suggested significant differences between ctDNA and tissue base profiling but assays were not conducted on the same platform (PMID27833075). We undertook this study to see whether ctDNA could recapitulate the known genomic hallmarks of tumor based profiling. **Methods:** Hybrid-capture based genomic profiling of 62 genes (FoundationACT) was performed on ctDNA from 78 pts with advanced PDA with samples received in the course of clinical care. The fraction of ctDNA in the blood was estimated using the maximum somatic allele frequency (MSAF) for each sample. Frequencies of alterations in these common drivers were then compared to those seen in tumors of pts who underwent comprehensive genomic profiling (CGP) tissue testing performed on the same core platform, FoundationOne, and The Cancer Genome Atlas (TCGA). **Results:** Pt characteristics: Median age 65 (range, 47-88); Female (33) /Male (45). FoundationACT results show that 53/78 (68%) cases had MSAF >0 (56%-78%%, 95% CI). ≥1 GA was reported in 81% of the cases with evidence of ctDNA in the blood. The most common GA detected by FoundationACT (based on cases with evidence of ctDNA in blood) vs FoundationOne were in *KRAS* (59% vs 89%, p< 0.0001), *TP53* (69% vs.74%, p=0.19), and *CDKN2A* (14% vs.45%). Other detected clinically relevant GA detected by FoundationACT included: *BRCA1, ERBB2, NF1, PIK3CA*. **Conclusions:** This study demonstrates significant differences between the established driver oncogenic alterations for PDA, as assessed by ct DNA and tissue based genomic profiling which are unlikely to be explained by differences in assay, but rather novel cancer biology. At present use of ctDNA genomic profiling in PDA should not routinely replace tissue based genomic characterization.

GENE	F-ACT- Clinical cases (n=78) %	FACT-MSAF > 0 (n=53)%	F1(FoundationCORE) (n>2000) %	TCGA (n=146) %
TP53	47	69	74	70
KRAS	40	59	89	91
CDKN2A	10	14	45	46

4129 Poster Session (Board #121), Sat, 8:00 AM-11:30 AM

Characteristics and outcomes of resected pancreatic cystadenocarcinoma: 1,205 cases from the National Cancer Data Base. *First Author: Jiping Wang, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA*

Background: Cystadenocarcinoma (CAC) of the pancreas is a rare pancreatic and therefore there is limited data on the characteristics, treatment and prognosis of this disease. **Methods:** Patients who underwent resection for CAC (n = 1,205) between 2003 and 2012 were identified from National Cancer Data Base. The clinicopathological characteristics and treatment outcomes were compared to patients with resected ductal adenocarcinoma (DAC) (n = 15,696). Cox-proportional hazard model was used to adjust for potential prognostic factors. A nomogram was constructed and validated to predict the outcomes of patients with CAC by using multiple variable Cox-proportional model and receiver operating characteristics curve methods. **Results:** Compared with resected DAC, patients with resected CAC are diagnosed at a younger age (58.7 vs. 61.2, p < 0.0001); female predominant (63.7% vs. 48.8%, p < 0.0001); more often Black (15.0% vs. 9.3%, p < 0.0001);had larger tumor (0-2, 2-4 and > 4cm:17.5%, 24.3%, 53.5% vs. 16.8%, 48.3% , 32.1%, respectively, p < 0.0001); have less total number of examined lymph nodes (10.6 vs. 14.5, p < 0.0001) and fewer positive lymph nodes(0.6 vs. 2.3, respectively). CAC patients were less likely to receive chemotherapy (28.8% vs. 62.5%, p < 0.0001) and radiation therapy (16.4% vs. 36.9%, p < 0.0001). CAC patients had significantly better overall survival than those with DAC (5 year survival: 55.6% vs. 17.3%, p < 0.0001). The survival advantage was primarily seen in patients with early stage disease (5 year survival: 70.9% vs. 36.9% in stage I patients, p < 0.0001, and 32.7% vs. 14.5% in stage II patients, p < 0.0001 respectively) and persisted after adjusting the known prognostic factors including age, AJCC staging, Charlson-Deyo score, type of surgery, chemotherapy, tumor size, and lymph node ratio (adjusted hazard ratio: 0.43, 95% confidence interval: 0.39-0.48, p < 0.0001). **Conclusions:** Patients with CAC had significantly better survival than those with pancreatic DAC even after controlling for known prognostic factors. The proposed nomogram could accurately predict patients' outcome and may be used as a tool for clinical decision making.

4130 Poster Session (Board #122), Sat, 8:00 AM-11:30 AM

***BRCA1/2* reversion mutations in pancreatobiliary cancer identified from patient biopsies.** *First Author: Laurie M. Gay, Foudation Medicine, Inc., Cambridge, MA*

Background: Germline genomic alterations (GA) in *BRCA1* or *BRCA2* (*BRCA*) are associated with increased risk of pancreatic cancer. Tumors with *BRCA* GA may be more sensitive to platinum (Pt) therapies or PARP inhibitors (PARPi). However, secondary reversion mutations (revGA) that may restore *BRCA* function and underlie reduced sensitivity to Pt compounds or PARPi can arise. **Methods:** DNA extracted from FFPE tumor tissue obtained during routine clinical care for 7077 patients with predominantly relapsed, refractory or metastatic pancreatobiliary carcinoma was analyzed using comprehensive genomic profiling (CGP) for all classes of GA: base substitutions, indels, rearrangements, and copy number changes. RevGA were any GA that could restore the reading frame if in cis with a nonsense or frameshift (fs) GA. Tumor tissue only was used to predict germline (g*BRCA*) or somatic status by an algorithm with a call rate of 85% and > 95% accuracy. **Results:** 417/7077 (5.9% ± 0.5%) tumors had ≥1 deleterious *BRCA* GA; 205 (2.9% ± 0.4%) had a predicted g*BRCA* GA. Significantly fewer women had deleterious *BRCA* GA (182/417; 43.6%)(p = 0.02); g*BRCA* GA frequency did not differ significantly (96/205; 46.8%)(p = NS). Overall, 49.1% of patients were women. 12 samples harbored potential revGA: pancreatic ductal adenocarcinoma (ACa) (7) or acinar cell carcinoma (Ca) (2), gallbladder ACa (2), and pancreatobiliary Ca NOS (1). 10/12 samples with revGA were metastases. Potential revGA were of 3 types: overlapping indel (7), compensatory fs (4), and missense (2). One case harbored 2 indels, both with potential to excise a fs GA. Apparent g*BRCA* were present in 7 cases, only somatic *BRCA* GA in 3 cases, and g*BRCA*/somatic status was ambiguous in 2 cases. For 2 patients, testing of multiple samples reveals the acquisition of revGA over time. KRAS mutation frequencies were similar for all samples (57.1%), *BRCA*-mutated samples (58.8%) and revGA-positive samples (58.3%). Clinical histories for patients with revGA will be presented. **Conclusions:** CGP of 7077 pancreatobiliary carcinomas reveals 5.9% had ≥1 deleterious *BRCA* GA, nearly 50% of which were g*BRCA*. Although rare, revGA can be acquired over time and potentially compensatory missense, fs and indel mutations were observed.

TPS4131 Poster Session (Board #123a), Sat, 8:00 AM-11:30 AM

CheckMate 577: A randomized, double-blind, phase 3 study of adjuvant nivolumab (nivo) or placebo in pts with resected esophageal (E) or gastroesophageal junction (GEJ) cancer. *First Author: Ronan Joseph Kelly, Johns Hopkins School of Medicine, Baltimore, MD*

Background: Expression of the PD-1 ligands PD-L1 and PD-L2 has been reported in ≈ 40% of pts with E/GEJ cancer and is associated with a poor prognosis. In a phase 3 trial, the PD-1 inhibitor nivo demonstrated an OS benefit vs placebo (HR, 0.63; $P < 0.0001$), resulting in a 37% reduction in the risk of death and double the OS rate at 12 mo (27% vs 11%) in pts with advanced gastric (G)/GEJ cancer refractory to ≥ 2 lines of chemotherapy (Kang YK, et al. *J Clin Oncol.* 2017;35 (suppl 4S) [abstract 2]). In this study, nivo was well tolerated, with a safety profile comparable with that of the placebo arm. These results indicate that nivo could be a new standard of care (SOC) for pts with heavily pretreated advanced G/GEJ cancer and provide a strong rationale to explore nivo in earlier lines of treatment for G/E/GEJ cancer. Currently, no effective adjuvant SOC is available after chemoradiotherapy (CRT) followed by resection for pts with E/GEJ cancer. This multinational, double-blind, phase 3 trial will evaluate nivo as an adjuvant therapy for pts with resected E/GEJ cancer (CheckMate 577; NCT02743494). **Methods:** In this study, an estimated 760 pts aged ≥ 18 years with stage II/III E/GEJ cancer are randomized to receive nivo or placebo. Prior to randomization, pts must have completed preoperative CRT followed by surgery and been diagnosed with residual pathologic disease after being surgically rendered free of disease with negative margins following complete resection. Pts with stage 4 resectable disease, cervical esophageal cancer, or those who have not received concurrent CRT prior to surgery are not eligible for study enrollment. Primary endpoints are OS and disease-free survival. Other key endpoints include the OS rate at 1, 2, and 3 years and safety. Clinical trial information: NCT02743494.

TPS4132 Poster Session (Board #123b), Sat, 8:00 AM-11:30 AM

CheckMate 649: A randomized, multicenter, open-label, phase 3 study of nivolumab (nivo) + ipilimumab (ipi) or nivo + chemotherapy (CTX) vs CTX alone in pts with previously untreated advanced (adv) gastric (G) or gastroesophageal junction (GEJ) cancer. *First Author: Markus H. Moehler, University Medical Center Mainz, Mainz, Germany*

Background: Pts with adv G/GEJ cancer have an OS of ≈ 1 y, indicating an unmet medical need for new first-line treatments (Tx). Expression of the PD-1 ligands PD-L1/PD-L2 is observed in up to 40% of pts with G/GEJ cancer and is associated with poor prognosis. In a phase 3 study of the PD-1 inhibitor nivo vs placebo in pts with adv CTX-refractory (CTX-R; ≥ 2 lines) G/GEJ cancer, nivo reduced the risk of death by 37% (HR, 0.63; $P < 0.0001$) and increased the OS rate at 12 mo (27% vs 11%; Kang YK, et al. *J Clin Oncol.* 2017;35 (suppl 4S) [abstract 2]). In a phase 1/2 study in pts with CTX-R G/GEJ/esophageal cancer (79% ≥ 2 prior Tx lines), nivo 1 mg/kg + ipi 3 mg/kg had a manageable safety profile and resulted in 26% ORR (44% ORR in pts with PD-L1$^+$ tumors), a median OS of 6.9 mo, and a 34% OS rate at 12 mo (Janjigian Y, et al. ASCO, 2016 [abstract 4010]). In the phase 1 CheckMate 012 trial, nivo + CTX had clinical activity and manageable safety in pts with NSCLC (Rizvi NA, et al. *J Clin Oncol.* 2016;34:2969-2979). These positive results support investigation of nivo, nivo + ipi, and nivo + CTX in earlier lines of Tx for G/GEJ cancer. The open-label, phase 3 CheckMate 649 trial will evaluate nivo + ipi and nivo + CTX vs CTX alone as first-line Tx for pts with adv G/GEJ cancer (NCT02872116). **Methods:** 1266 pts aged ≥ 18 y with untreated, inoperable adv/metastatic G/GEJ cancer (histologically confirmed adenocarcinoma) regardless of PD-L1 status will be randomized to receive either nivo + ipi, nivo + CTX (capecitabine/oxaliplatin [XELOX] or fluorouracil/leucovorin/oxaliplatin [FOLFOX]), or investigator choice of XELOX or FOLFOX. Tumor tissue for determination of PD-L1 status (Dako assay) must be provided from ≤ 6 mo before study Tx. No prior systemic Tx, including HER2 inhibitors, are allowed. Pts with known HER2$^+$ status, suspected autoimmune disease, grade > 1 peripheral neuropathy, or active infection are excluded. Primary endpoint is OS in pts with PD-L1$^+$ (≥ 1%) tumors. Other endpoints include OS in all pts; PFS and time to symptom deterioration in all pts and in pts with PD-L1$^+$ tumors; and safety. Clinical trial information: NCT02872116.

TPS4133 Poster Session (Board #124a), Sat, 8:00 AM-11:30 AM

Perioperative trastuzumab and pertuzumab in combination with FLOT versus FLOT alone for HER2 positive resectable esophagogastric adenocarcinoma: Petrarca—A phase II trial of the German AIO. *First Author: Ralf Hofheinz, University Medical Center Mannheim, Mannheim, Germany*

Background: Neoadjuvant or perioperative chemotherapy has become a standard of care for locally advanced, resectable gastric cancer and adenocarcinoma of the GEJ. However, patient's outcome is still unsatisfactory and 5-year survival, even in prospective trials, has been below 40%. Targeting HER2 with Trastuzumab and Pertuzumab prolonged survival in patients with HER2-positive advanced breast cancer as did Trastuzumab in patients with HER2-positive advanced gastric cancer. This provides a rationale for the evaluation of anti-HER2 treatment for resectable patients. **Methods:** This is a prospective, multicenter, randomized, investigator initiated phase II trial. Patients with HER2-positive locally advanced adenocarcinoma of the stomach and GEJ (i.e. ≥cT2 any N or any T N-positive) with exclusion of distant metastases are enrolled. HER2 status is centrally assessed. Patients are randomized 1:1 to 4 pre-operative 2-week cycles (8 weeks) of FLOT (Docetaxel 50 mg/m²; Oxaliplatin 85 mg/m²; Leucovorin 200 mg/m²; 5-FU 2600 mg/m²) followed by surgery and 4 additional cycles of FLOT (arm A); or the same therapy in combination with Trastuzumab 8/6 mg/kg and Pertuzumab 840 mg every 3 weeks pre- and postop, followed by a total of 9 additional cycles of Trastuzumab/Pertuzumab monotherapy (arm B). Primary endpoint of the phase II part (n = 100) of the trial is to show numerical improvement of the rate of pathological complete remission to approx. 25% with antibodies compared to approx. 16% with FLOT alone as assessed by a centralized pathology. Main secondary endpoints are safety and tolerability. Once results from phase II become available, study transition into phase III will be evaluated based on de facto results and current medical standards. Recruitment has already started; by February 2017 a total of 19 patients have been randomized. EudraCT: 2014-002695-86 Clinical trial information: NCT02581462.

TPS4134 Poster Session (Board #124b), Sat, 8:00 AM-11:30 AM

Phase III trial to evaluate the efficacy of neoadjuvant chemotherapy with S-1 plus oxaliplatin followed by D2 gastrectomy with adjuvant S-1 in locally advanced gastric cancer: Japan Clinical Oncology Group study JCOG1509 (NAGISA trial). *First Author: Masanori Tokunaga, Division of Gastric Surgery, Shizuoka Cancer Center, Nagaizumi, Japan*

Background: In Japan, while post-operative adjuvant chemotherapy with S-1 or capecitabine plus oxaliplatin is standard care for pStage II/III gastric cancer after curative resection with D2 lymph node dissection, the clinical outcomes of pStage III patients are not satisfactory. In Europe, neoadjuvant chemotherapy (NAC) followed by gastrectomy is standard. The Japan Clinical Oncology Group (JCOG) has conducted several phase II trials of NAC, and deemed NAC as one of the most promising treatment strategies for gastric cancer with lymph node metastasis (Stage III). However, no established criteria exists for diagnosis of lymph node metastasis. JCOG1302A which was a cross-sectional study evaluating the accuracy of preoperative staging by imaging, showed that cT3-4N1-3M0 (positive lymph node was defined as that with a long axis diameter ≥ 10 mm or short axis diameter ≥ 8 mm) included just 6.5% overdiagnosed pStage I patients and accounted for 52.6% of all pStage III patients. **Methods:** JCOG1509 (UMIN000024065) is designed as a randomized phase III study to confirm the survival superiority of addition of NAC to standard treatment for patients with cT3-4N1-3M0 gastric cancer. In the standard arm, a gastrectomy with D2 lymphadenectomy is performed followed by adjuvant chemotherapy with oral S-1 for 1 year. In the experimental arm, combination of an infusion of oxaliplatin (130 mg/m^2/day, day 1) and oral S-1 (80 mg/m^2/day, days 1–14) is repeated every 3 weeks for 3 courses before gastrectomy, followed by surgery and adjuvant chemotherapy with S-1 for 1 year. The primary endpoint is overall survival. The planned sample size is 470 in total with a 1-sided alpha of 5%, a power of 80%, expecting a 10% increase in the 5-year OS (60% vs 70%). Patients will be enrolled from 58 Japanese institutions over 3.5 years. The study was activated in September 2016 and, as of January 2017, 18 patients were enrolled for the study. Clinical trial information: UMIN000024065.

TPS4135 Poster Session (Board #125a), Sat, 8:00 AM-11:30 AM

Impact of early FDG-PET directed intervention on preoperative therapy for locally advanced gastric cancer: A Cooperative Group random assignment phase II study (Alliance A021302) Impac. *First Author: Manish A. Shah, New York-Presbyterian Hospital, New York, NY*

Background: Gastric cancer is a prevalent and morbid illness for which new treatment strategies are needed. Peri-operative therapy is a standard approach that is associated with only a 15% improvement in overall survival. Early FDG-PET scanning, performed prior to cycle 2, can distinguish patients (pts) responding to chemotherapy from those who are not. FDG-PET non-responding pts have poorer survival. This study addresses the question of salvage therapy in pts who are PET non-responders. Specifically, does salvage chemotherapy with docetaxel /irinotecan improve pt survival in FDG-PET-nonresponding pts with locally advanced gastric cancer. **Methods:** This is a multicenter, cooperative group, NCI supported, randomized phase II study of salvage chemotherapy + surgery versus surgery and post-operative chemoradiotherapy in pts who are FDG-PET non-responders (defined as a decrease in SUV_{max} of the primary tumor of less than 35%). A total of 176 pts with locally advanced, resectable gastric cancer who were FDG-PET non-responders to cycle 1 of platinum/capecitabine based chemotherapy will be randomized in a 1:1 manner to receive either (Arm A) surgery followed by fluoropyrimidine-sensitized radiotherapy (4500 cGy), or (Arm B) salvage chemotherapy with docetaxel / irinotecan (DI) for 2 cycles followed by standard resection and 3 cycles DI post-operatively. DI is administered as D 30 mg/m2, I 50 mg/m2 given on D1, D8 of a 21 day cycle. 416 pts will be screened to yield 162 non-responders (81 FDG-PET non-responders per treatment group). With expected 120 events, the study will have 80% power to detect a hazard ratio of 0.625 for improved survival at the one-sided significant level of 0.15. Pts will be required to provide tissue at the time of resection, as well as whole blood prior to resection for correlative studies associated with platinum sensitivity, FDG avidity, and prognostic markers. This study is available through all cooperative groups (SWOG, ACRIN/ECOG, Alliance, and NRG) and the National Clinical Trials Network. Enrollment began in November 2015. Support: U10CA180821, U10CA180882; Clinical Trial Information: NCT02485834.

TPS4136 Poster Session (Board #125b), Sat, 8:00 AM-11:30 AM

Integrate II: A randomised phase 3 double-blind placebo-controlled study of regorafenib in refractory advanced gastro-oesophageal cancer (AGOC)—An international study organized by the Australasian Gastrointestinal Trials Group (AGITG). *First Author: Katrin Marie Sjoquist, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia*

Background: AGOC has a poor prognosis with no established standard treatment following failure of chemotherapy (CT). Regorafenib (BAY 73-4506)(REG) is an oral multi-kinase inhibitor targeting kinases involved in angiogenesis (VEGFR1-3, TIE-2), tumor microenvironment (PDGFR-β, FGFR), and oncogenesis (RAF, RET and KIT). INTEGRATE (phase 2) demonstrated REG was highly effective in prolonging PFS across a range of AGOC pts, with a positive OS trend. Regional differences were found in magnitude of effect, but REG was effective in all regions/subgroups. The phase 3 INTEGRATE II will explore whether REG is effective in prolonging survival in patients overall, and in the Asian sub-population. **Methods:** International (Australia/New Zealand (NHMRC CTC); Canada (CCTG), Korea, Japan, Taiwan, USA (ACCRU)) randomised phase III, double-blind, placebo-controlled trial with 2:1 (REG:placebo)(PBO) randomisation and stratification by: Location of tumour, Geographic region, prior VEGF inhibitors. Eligible patients (histologically confirmed AGOC), with evaluable metastatic or locally advanced disease refractory to, or relapsed following second line CT, will receive best supportive care plus 160mg REG or matched placebo orally on days 1-21 of each 28 day cycle until disease progression or prohibitive adverse events. Primary endpoint is OS. Secondary endpoints: PFS, response rate, quality of life, safety, identification of prognostic/predictive biomarkers for study endpoints, and REG PK across geographical regions. 350 patients (50% from Asia) randomized in a 2:1 ratio will provide 90% power to detect a hazard ratio (HR) for OS of 0.67 with a 2-sided α of 0.05 assuming PBO median survival is 4.5 mos. The sample size accommodates 2 interim analyses undertaken at 1/3 and 2/3 of required events. As of January 2017, 12 of 28 planned ANZ sites are open, with 4 patients enrolled. Regulatory approval has been received for 12 Canadian sites, and 12 Korean sites. Korean recruitment is expected to commence in February 2017. Regulatory submissions are pending in Taiwan, Japan, and the USA. Clinical trial information: NCT02773524.

TPS4137 Poster Session (Board #126a), Sat, 8:00 AM-11:30 AM

FRACTION (Fast Real-time Assessment of Combination Therapies in Immuno-Oncology)-gastric cancer (GC): A randomized, open-label, adaptive, phase 2 study of nivolumab in combination with other immuno-oncology (IO) agents in patients with advanced GC. *First Author: Praveen Aanur, Bristol-Myers Squibb, Princeton, NJ*

Background: Nivolumab, a fully human IgG4 mAb that targets programmed death-1, alone and in combination with ipilimumab, a fully human IgG1 mAb that targets cytotoxic T-lymphocyte antigen 4, has demonstrated encouraging clinical activity in patients with advanced GC. These data support the rationale that nivolumab in combination with other IO agents or targeted therapies may improve treatment outcomes in patients with advanced GC. Given the rapid development of novel IO agents, traditional studies cannot efficiently evaluate all possible IO-IO and IO-targeted therapy combinations. FRACTION is an innovative clinical trial program with a rolling, adaptive platform design that allows for the addition of new combination regimens, as well as withdrawal of ineffective regimens. Here we describe the study concept, key design components, and the first IO treatment combinations of FRACTION-GC, a phase 2, randomized, open-label, adaptive study in advanced GC (NCT02935634). **Methods:** Patients with advanced GC or gastroesophageal junction (GEJ) cancer will be enrolled based on prior IO treatment and randomized to receive nivolumab plus BMS-986016 (fully human IgG4 mAb that targets lymphocyte activation gene 3) or nivolumab plus ipilimumab. Enrollment is continuous and may offer patients consecutive treatment options based on their treatment exposure and response. The primary endpoints are objective response rate, duration of response, and progression-free survival rate at 24 weeks. The secondary endpoint is safety. Comprehensive biomarker analyses will also be performed. New treatment combinations will be added over time to explore their potential benefits and to provide a continuous flow of treatment options for patients whose cancer progresses on existing treatments. In this way, FRACTION-GC is envisioned to accelerate the development of the next generation of IO combinations for patients with metastatic GC and GEJ cancer. Clinical trial information: NCT02935634.

TPS4138 Poster Session (Board #126b), Sat, 8:00 AM-11:30 AM

A prospective, randomized, double-blinded, placebo-controlled, phase III study to evaluate the efficacy and safety of apatinib plus best supportive care (BSC) compared to placebo plus BSC in patients with advanced or metastatic gastric cancer: The ANGEL study. *First Author: Yoon-Koo Kang, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Apatinib is an orally administered, highly selective tyrosine kinase inhibitor of VEGFR-2 that has been studied in many clinical trials, primarily in China, treating various solid tumors. Based on the results of the Chinese Phase 3 study, apatinib was approved in China for the treatment of advanced gastric cancer (GC), but apatinib has yet to be evaluated in a randomized placebo-controlled study in the rest of the world. ANGEL is a multinational, placebo controlled, Phase 3 study investigating the efficacy and safety of apatinib in advanced GC patients in North America, Europe, and Asia Pacific. **Methods:** Main eligibility criteria include patients with advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction for whom at least 2 prior lines of standard chemotherapy had failed, ECOG performance status ≤ 1, and disease progression < 6 months after last chemotherapy treatment. Approximately 459 patients will be randomized in a 2:1 ratio to receive continuous 28-day cycles of apatinib 700 mg or a matched placebo daily with best supportive care until disease progression, intolerable toxicity or withdrawal of consent. Stratification factors include geographic region (Asia vs. North America/Europe), disease measurability, prior ramucirumab treatment, and treatment therapy line (3^{rd} or 4^{th}). Primary endpoint is overall survival (OS) in the intent-to-treat population, and secondary endpoints are progression free survival (PFS), objective response rate (ORR), disease control rate (DCR), quality of life, and safety. The primary analysis of OS will be conducted in intention-to-treat population using a stratified log-rank test at the two-sided alpha = 0.05 level of significance. If the primary analysis of OS is statistically significant, then PFS and ORR will be analyzed. All other secondary efficacy endpoints will be analyzed using two-sided tests at the alpha = 0.05 level of significance. Enrollment opened Feb 2017. Clinical trial information: NCT03042611.

TPS4139 Poster Session (Board #127a), Sat, 8:00 AM-11:30 AM

A phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of GS-5745 combined with mFOLFOX6 as first-line treatment in patients with advanced gastric or gastroesophageal junction adenocarcinoma. *First Author: Johanna C. Bendell, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: GS-5745 is a monoclonal antibody that inhibits matrix metalloproteinase 9 (MMP9), an extracellular enzyme involved in matrix remodeling, tumor growth, and metastasis. Inhibiting MMP9 blocks paracrine signaling and metastasis and alters the tumor immune microenvironment. GS-5745 (800 mg q 2 weeks) with mFOLFOX6 was examined in a Phase 1b study in 40 patients with gastric and GEJ adenocarcinoma (GS-US-296-0101), and demonstrated encouraging activity without added toxicity (10% CR, median PFS 10.7 mo (Shah et al ASCO GI 2017, a108)). Decreased free MMP9 suggested inhibition of MMP9 enzymatic activity by GS-5745. These data support the hypothesis that GS-5745 treatment inhibits MMP9 activity and that the inhibition may lead to improved clinical outcomes. **Methods:** This phase 3, randomized, double-blind, multicenter study investigates the efficacy and safety of GS-5745 combined with mFOLFOX6 in subjects with untreated gastric and GEJ adenocarcinoma. Total of 430 eligible subjects with advanced gastric and GEJ cancer will be randomized in a 1:1 manner to mFOLFOX6 plus GS-5745 or mFOLFOX6 plus placebo. Stratification factors include ECOG status (0 v 1), geographic region (Latin America v All other countries), and primary tumor site (gastric v GEJ). CT or MRI scans will be performed every 8 weeks to evaluate response to treatment. mFOLFOX6 will be administered on Days 1 and 15 of each 28-day treatment cycle for a total of 6 cycles followed thereafter by leucovorin (LV) and 5-fluorouracil (5-FU) dosing on Days 1 and 15 of each 28-day treatment cycle until disease progression. GS-5745/placebo 800 mg will be infused on Days 1 and Day 15 of each 28 day cycle until disease progression. Primary endpoint is OS, and secondary endpoints include PFS, ORR (RECIST 1.1), and safety. The study is designed to have an 85% power to detect clinically meaningful improvement in overall survival at the one-sided significance level of 0.025. The association of exploratory biomarkers with study drug response will also be evaluated. Enrollment opened Oct. 2015. Clinical trial information: NCT02545504.

TPS4140 Poster Session (Board #127b), Sat, 8:00 AM-11:30 AM

The "RENAISSANCE" Trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction—A phase III trial of the German AIO/CAO-V/CAOGI. *First Author: Daniel Wilhelm Mueller, Institute of Clinical Cancer Research (IKF) at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany*

Background: Recent data indicates that surgical resection may bring a benefit for select patients with metastatic gastric / esophagogastric junction cancer. However, no data obtained in randomized trials is available up to now. The current RENAISSANCE trial investigates this long-lasting question about the role of surgical intervention in limited-metastatic gastric / esophagogastric junction cancer. **Methods:** This is a prospective, multicenter, randomized, investigator initiated phase III trial. In this study, previously untreated patients with limited metastatic stage (retroperitoneal lymph node metastases only or a maximum of one incurable organ site that is potentially resectable or locally controllable with or without retroperitoneal lymph nodes) will receive 4 cycles of FLOT (docetaxel 50 mg/m^2; oxaliplatin 85 mg/m^2; leucovorin 200 mg/m^2; 5-FU 2,600 mg/m^2), and if Her2+ with trastuzumab. Patients without disease progression after 4 cycles are randomized 1:1 to receive additional chemotherapy cycles or surgical resection of primary and metastases followed by subsequent chemotherapy. 271 patients are to be allocated to the trial, of which at least 176 patients will be randomized. The primary endpoint is overall survival; main secondary endpoints are quality of life parameters as assessed by EORTC-QLQ-C30 questionnaire, progression free survival and surgical morbidity and mortality. Recruitment has already started; currently (Feb 2017) 21 patients have been enrolled. EudraCT: 2014-002665-30. Clinical trial information: NCT02578368.

TPS4141 Poster Session (Board #128a), Sat, 8:00 AM-11:30 AM

A phase II, open-label, randomized study to evaluate the efficacy and safety of GS-5745 combined with nivolumab versus nivolumab alone in subjects with unresectable or recurrent gastric or gastroesophageal junction adenocarcinoma. *First Author: Manish A. Shah, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, NY*

Background: GS-5745 is a monoclonal antibody that inhibits matrix metalloproteinase 9 (MMP9), an extracellular enzyme involved in matrix remodeling, tumor growth, and metastasis. Inhibiting MMP9 is expected to block paracrine signaling and metastasis and to alter the immune microenvironment within the tumor. Results from the ATTRACTION-2 Phase III trial showed the PD-1 inhibitor nivolumab significantly improved overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) in patients with heavily pre-treated advanced gastric or gastroesophageal junction cancer. Preclinical studies indicate that selective inhibition of MMP9 can inhibit immune-suppressive myeloid cell polarization, regulatory T cell generation, desmoplasia, and the destruction of ligands for CXCR3 (a critical chemokine receptor that enables effector T cell trafficking). In combination with a checkpoint inhibitor, CD8+, CD4+ and CD44+ cytotoxic T cells are significantly increased in a checkpoint-refractory model, suggesting that MMP9 inhibition could relieve immune suppression. **Methods:** This phase 2, open-label, randomized study investigates the efficacy and safety of GS-5745 combined with nivolumab versus nivolumab alone in patients with unresectable or recurrent gastric or gastroesophageal adenocarcinoma. 120 patients will be randomized to either GS-5745 800mg IV + nivolumab 3mg/kg IV, or nivolumab alone. Treatment will be administered every 2 weeks and stratified by PD-L1 status. CT will be performed every 8 weeks to evaluate response. The primary endpoint of the study is ORR; secondary endpoints include PFS, OS, and occurrence of adverse events. Key inclusion criteria: metastatic or inoperable adenocarcinoma of the stomach or GEJ which has progressed after $\geq$1 prior systemic therapy, ECOG performance status $\leq$1, RECISTv1.1 measureable disease, archival tissue adequate for PD-L1 evaluation. Exploratory biomarkers correlated with study drug response will also be evaluated. Enrollment opened September 2016. Clinical trial information: NCT02864381.

TPS4142 Poster Session (Board #128b), Sat, 8:00 AM-11:30 AM

ClarIDHy: A phase 3, multicenter, randomized, double-blind study of AG-120 vs placebo in patients with an advanced cholangiocarcinoma with an IDH1 mutation. *First Author: Maeve Aine Lowery, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: Advanced cholangiocarcinoma (CC) is a life-threatening disease for which there are limited therapeutic options. Mutations in isocitrate dehydrogenase 1 (mIDH1) occur in up to 25% of intrahepatic CC cases. mIDH1 lead to epigenetic and genetic changes that promote oncogenesis via production of the oncometabolite, D-2-hydroxyglutarate (2-HG). AG-120 is a first-in-class oral inhibitor of the mIDH1 enzyme, and is being tested in a phase 1 study that enrolled 73 patients (pts) with mIDH1 CC who had received a median of 2 prior therapies (range 1–5). AG-120 has demonstrated a favorable safety profile and clinical activity in this study. Among the 72 efficacy evaluable pts ($\geq$1 post-baseline response assessment or discontinued prematurely), 6% (n = 4) had a confirmed partial response and 56% (n = 40) had stable disease. Progression-free survival (PFS) rate at 6 months was 40% as of Dec 16, 2016. The 500 mg once daily (QD) dose of AG-120 was selected for the ongoing phase 3 study in mIDH1 CC described here. **Methods:** ClarIDHy is a global, phase 3, multicenter, double-blind study randomizing 186 pts with mIDH1 CC in a 2:1 ratio to AG-120 (500 mg QD) or matched placebo (NCT02989857). Key eligibility criteria: nonresectable or metastatic CC; documented mIDH1 based on central laboratory testing; ECOG 0–1; measurable disease (RECIST v1.1); documented disease progression following $\leq$2 prior systemic therapies in the advanced setting, including at least 1 gemcitabine- or 5-fluorouracil-containing regimen; and no prior mIDH inhibitor therapy. Crossover from the placebo arm to the AG-120 arm will be permitted. The primary endpoint is PFS as assessed by an independent review. Secondary endpoints include safety, tolerability, overall response rate, overall survival, pharmacokinetic and pharmacodynamic analyses on plasma, and quality of life as assessed by the EORTC QLQ-C30, EORTC QLQ-BIL21, and EQ-5D-5L instruments. An independent data monitoring committee will monitor the data throughout the study. The ClarIDHy study is currently activated at participating sites in the US and will be activated in centers throughout Europe and in South Korea. Clinical trial information: NCT02989857.

TPS4143 Poster Session (Board #129a), Sat, 8:00 AM-11:30 AM

Phase 3, randomized study of pembrolizumab (pembro) vs best supportive care (BSC) for second-line advanced hepatocellular carcinoma (HCC): KEYNOTE-240. *First Author: Richard S. Finn, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: The tyrosine kinase inhibitor sorafenib is the standard of care for first-line HCC; currently, there is no clear standard of care after disease progression on sorafenib or for patients (pts) with intolerance to sorafenib. Because most HCC is driven by inflammation, there is a strong rationale to evaluate immunotherapy in pts with this type of cancer. The randomized, double-blind, placebo-controlled phase 3 KEYNOTE-240 study (ClinicalTrials.gov, NCT02702401) was designed to compare the efficacy and safety of the anti–PD-1 antibody pembro + BSC vs placebo + BSC in pts with previously treated advanced HCC. **Methods:** Eligibility criteria include age ≥ 18 years, histologically or cytologically confirmed diagnosis of HCC, documented progression after stopping treatment with sorafenib or intolerance to sorafenib, disease not amenable to a curative treatmentapproach (eg, transplantation, surgery, or ablation), measurable disease confirmed by central imaging vendor review per RECIST v1.1, Child-Pugh liver score A, ECOG performance status 0-1, and predicted life expectancy > 3 months. Pts will be randomly assigned 2:1 to receive pembro 200 mg IV Q3W + BSC or placebo Q3W + BSC for up to 35 cycles (~2 years) or until disease progression, unacceptable toxicity, or investigator decision. Randomization will be stratified by geographic region, presence of macrovascular invasion, and α-fetoprotein level. BSC will be provided by the investigator per local treatment practices. Response will be assessed every 6 weeks per RECIST v1.1 by central imaging vendor review. Adverse events (AEs) will be assessed throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded per NCI CTCAE v4.0. Primary objectives are comparison of progression-free survival per RECIST v1.1 by central imaging vendor review and overall survival between treatment arms. Secondary objectives are comparison of objective response rate, duration of response, disease control rate, and time to progression per RECIST v1.1 by central imaging vendor review; and evaluation of safety and tolerability. Planned enrollment in KEYNOTE-240 is 408 pts across 26 countries. Clinical trial information: NCT02702401.

TPS4144 Poster Session (Board #129b), Sat, 8:00 AM-11:30 AM

A randomized phase III trial comparing adjuvant chemotherapy with S-1 vs. surgery alone in patients with resectable biliary tract cancer (JCOG1202: ASCOT). *First Author: Masafumi Ikeda, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: No standard adjuvant treatment has been established for patients with curatively resected biliary tract cancer (BTC). S-1, which is one of the oral fluoropyrimidine derivatives, showed promising efficacy with a mild toxicity profiles in patients with advanced BTC, and the survival benefit of adjuvant S-1 therapy has been demonstrated in patients with resected gastric cancer and pancreatic cancer. The aim of this open-label, multicenter, randomized phase III trial is to assess whether adjuvant S-1 would prolong the overall survival in patients with resected BTC. **Methods:** The main eligibility criteria are as follows: 1) curatively resected carcinoma of the extrahepatic bile duct, gallbladder or ampulla of Vater (T2-4, N0, M0 or T1-4, N1, M0), or carcinoma of the intrahepatic bile duct (T1-4, N0-1, M0) (7^{th} UICC classification), 2) histologically confirmed adeno (squamous) carcinoma, 3) R0 or R1 residual disease, 4) age 20 to 80 years, 5) ECOG performance status 0 or 1, 6) no prior chemotherapy or radiotherapy, 7) adequate organ functions, 8) written informed consent. Patients are randomly assigned to the surgery alone arm (arm A) or the adjuvant S-1 arm (arm B) by the minimization method for balancing institution, primary site of cancer and lymph node metastasis between the arms. Patients in arm A do not receive any anti-cancer treatment, while patients in arm B receive 4 cycles of oral S-1 chemotherapy at the dose of 40 mg/m^2 twice daily for 4 weeks followed by 2 weeks of rest. The primary endpoint is overall survival, while the secondary endpoints are relapse-free survival, incidence of (serious) adverse events, and proportion of treatment completion. We assumed a 3-year survival in arm A of 47% and a 10% increase in the 3-year survival in arm B. The sample size was calculated as a total of 350, with a one-side alpha of 5% and power of 70%; planned accrual period is 4 years, and follow-up period, 3 years. Primary analysis will be conducted at 3 years and updated analysis will be conducted at 5 years after closing of accrual. As of Jan 31, 2016, a total of 285 patients have already been enrolled in this trial from Sep 2013. Clinical trial information: UMIN000011688.

TPS4145 Poster Session (Board #130a), Sat, 8:00 AM-11:30 AM

Phase 2, open-label, multicenter study of the efficacy and safety of INCB054828 in patients (pts) with advanced, metastatic, or surgically unresectable cholangiocarcinoma (CCA) with inadequate response to prior therapy. *First Author: Mitesh J. Borad, Mayo Clinic, Scottsdale, AZ*

Background: Dysregulation of fibroblast growth factor receptor (FGFR) signaling by *FGFR* translocations and activating mutations is implicated in many cancers, including CCA. *FGFR2* translocation, the most common *FGFR*alteration, occurs in ~13% of pts with intrahepatic CCA. INCB054828 is a novel, orally available, selective inhibitor of FGFR1, FGFR2, and FGFR3 tyrosine kinase activity (AACR 2015; Abstract 771). **Methods:** This phase 2, open-label trial will evaluate INCB054828 monotherapy in pts with advanced/metastatic or unresectable CCA (NCT02924376). Pts will be prescreened locally or centrally for *FGF/FGFR* status prior to enrollment (Table): *FGFR2* translocation (Cohort A); other *FGF/FGFR* alteration (Cohort B); no *FGF/FGFR* alteration (Cohort C; negative control for effects of *FGF/FGFR* alteration on objective response rate [ORR]). Eligibility criteria include: age ≥18 years; ECOG performance status ≤2; adequate liver and renal function; life expectancy ≥12 wks; disease progression after ≥1 prior systemic therapy; no prior use of selective FGFR inhibitors. Pts will self-administer INCB054828 orally at a starting dose of 13.5 mg QD on a 21-day cycle (2 wks on; 1 wk off); treatment will continue until disease progression or unacceptable toxicity. The primary endpoint will be ORR (complete or partial response, independent radiologic review committee, RECIST v1.1) in pts with *FGFR2* translocation (Cohort A). Secondary endpoints include ORR in pts positive or negative for any *FGF/FGFR*alteration and duration of response, PFS, OS, and safety (all cohorts). The study has currently enrolled 2 pts (recruitment ongoing; estimated primary completion, April 2018). Clinical trial information: NCT02924376.

Study design.

Prescreen	• *FGFR2* translocation → cohort A (n=60) • Other *FGF/FGFR* alteration → cohort B (n=20) • No *FGF/FGFR* alteration → cohort C (n=20)
Screen, enroll and initiate INCB054828	• Oral QD dosing • 21-day cycle (2 wks on; 1 wk off)
Assessments start after cycle 2	• Stable disease/partial or complete response → continue treatment (restaging after cycle 4) • Disease progression → discontinue treatment; safety and survival follow-up

TPS4146 Poster Session (Board #130b), Sat, 8:00 AM-11:30 AM

A multicohort phase II study of durvalumab plus tremelimumab for the treatment of patients (PTS) with advanced neuroendocrine neoplasms (NENs) of gastroenteropancreatic (GEP) or lung origin (the DUNE trial-GETNE1601-). *First Author: Ignacio Matos Garcia, Vall d'Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain*

Background: NENs include a heterogeneous group of tumors with different behavior. Despite immunomodulators such as interferon are approved for the management of grade 1-2 NENs, the low mutation tumor load and PD-1/PDL-1 expression have limited the development of immune check-point inhibitors in this setting. The rational for immunotherapy in high grade NENs is stronger compared with low grade NENs based on the results observed in small cell lung cancer. However, the combination of an antiPDL-1 and antiCTLA-4 could increase the probability of success regardless of tumor growth rate, mutational tumor load or PDL-1 expression in low grade NENs. **Methods:** This prospective, multi-center, open label, phase II study (EudraCT:2016-002858-20) will evaluate the efficacy and safety of durvalumab plus tremelimumab in 126 pts within four different cohorts, including well-moderately differentiated lung NENs (Cohort 1), grade 1-2 gastrointestinal NENs (Cohort 2), grade 1-2 pancreatic NENs (Cohort 3) and grade 3 GEP NENs (Cohort 4). To optimize the efficacy of immunotherapy in low grade NENs, pts included in the trial must have progressed to all standard approved therapy in each setting, including somatostatin analogues, targeted agents and chemotherapy for lung and GEP grade 1-2 NENs up to 4 prior lines. For pts included in cohort 4, progression to standard platinum-based chemotherapy is mandatory. All pts will receive durvalumab 1500 mg every 28 days for 12 months, and tremelimumab 75 mg Q4W up to 4 doses/cycles. Retreatment is allowed after disease progression in the follow-up period. The primary endpoint of the study for cohorts 1-3 is disease control rate at 9 months including the percentage of pts achieving complete response, partial response, or stable disease according to RECIST v1.1; Median overall survival will be the primary endpoint for cohort 4. Primary endpoints will be assessed by investigators and confirmed by central radiological review. Secondary endpoints include median progression-free survival, safety and tolerability and a wide panel of biomarkers in blood samples and tumor tissue. Clinical trial information: 2016-002858-20.

TPS4147 Poster Session (Board #131a), Sat, 8:00 AM-11:30 AM

Randomized phase II study of 2nd-line FOLFIRI versus modified FOLFIRI with PARP inhibitor ABT-888 (veliparib) (NSC-737664) in metastatic pancreatic cancer (mPC): SWOG S1513. *First Author: E. Gabriela Chiorean, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: PC is characterized by multiple DNA repair defects, including in *BRCA1/2*, and other homologous recombination (HR) genes such as *FANC*, *ATM, ATR* (Waddell N, Nature 2015). Folinic acid/5-fluorouracil/irinotecan (FOLFIRI) is a 2nd line therapy option in mPC, but overall survival (OS) averages only 6 mos (Yoo C, Br J Cancer 2009). It is known that PARP facilitates repair from topoisomerase 1-associated DNA damage, and that preclinically PARP inhibitors (PARPi) increase DNA breaks from camptothecins, resulting in synergistic antitumor effects (Smith LM, Clin Cancer Res 2005, Davidson D, Invest New Drugs 2013). PARPi are active in mPC harboring *BRCA1/2* mutations. Given the preclinical synergism between ABT-888 with irinotecan, and the safety and preliminary efficacy noted in a phase I trial (Berlin J, J Clin Oncol 2014; abstr 2574), we designed a randomized phase II study of mFOLFIRI /ABT-888 vs FOLFIRI alone for 2nd line mPC patients (pts). Blood and tumor samples are collected at baseline to retrospectively analyze biomarkers related to DNA repair capacity, including the HRD assay and BROCA-HR, a targeted multi-gene sequencing to detect alterations within the Fanconi Anemia-BRCA (HR), non-homologous end joining (NHEJ), and DNA mismatch repair pathways, and correlate with efficacy. **Methods:** Phase II study in 143 pts randomized (1:1) to mFOLFIRI/ABT-888 or FOLFIRI. For optimal PARP inhibition, ABT-888 is dosed Days (D) 1-7 and mFOLFIRI (no 5-FU bolus) D3-5 in 14D-cycles. In the control arm, FOLFIRI is dosed D1-3 in 14D-cycles. Primary endpoint: compare OS between treatment arms; secondary endpoints: safety, progression-free survival, response rates; translational: correlate germline/somatic *BRCA1/2* mutations, and other DNA repair biomarkers with efficacy in each arm. Standard eligibility criteria apply. Assuming that the addition of ABT-888 will increase OS from 6 to 9 mos, 128 eligible pts (143 pts total) are required, based on a one-sided type 1 error of 10%, and 80% power. Kaplan-Meier methodology will be used to estimate median OS for each treatment arm. This study is open to accrual (NCT02890355). Clinical trial information: NCT02890355.

TPS4148 Poster Session (Board #131b), Sat, 8:00 AM-11:30 AM

CanStem111P trial: A phase III study of napabucasin (BBI-608) plus nab-paclitaxel (nab-PTX) with gemcitabine (gem) in adult patients with metastatic pancreatic adenocarcinoma (mPDAC). *First Author: Tanios S. Bekaii-Saab, Mayo Clinic Cancer Center, Phoenix, AZ*

Background: Cancer stem cells are considered to be fundamentally important for resistance to therapy, recurrence and metastasis. Napabucasin is a first-in-class cancer stemness inhibitor identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells (Li et al, PNAS 112(6):1839, 2015). Preclinical studies suggest that napabucasin sensitizes heterogeneous cancer cells to chemotherapeutic agents, including nab-PTX and gem. Encouraging anticancer activity in mPDAC was observed in a phase Ib (El-Rayes et al, ASCO 2016) study of 37 pts, reporting 93% (28/30) disease control rate (DCR) and 50% (15/30) overall response rate (ORR), with 1 complete and 14 partial responses and prolonged disease control ($>$ 24 wks) in 57% (17/30) of pts who have had a RECIST evaluation. On the basis of these data, a phase III trial is being conducted in North America, Europe, Australia and Asia. **Methods:** This study (ClinicalTrials.gov NCT02993731) will assess the efficacy of napabucasin+nab-PTX+gem *vs* nab-PTX+gem in pts with mPDAC (n = 1132). Pts must have been diagnosed with mPDAC $<$ 6 weeks prior to randomization and not have received treatment for metastatic disease. Pts are randomized in a 1:1 ratio to receive napabucasin 240 mg PO twice daily continuously plus nab-PTX +gem IV weekly for 3 out every 4 weeks, or nab-PTX+gem IV weekly for 3 out every 4 weeks. Pts will be stratified by geography, performance status and presence of liver metastases. Treatment will continue until disease progression, death, intolerability or patient/investigator decision to stop. Primary endpoint is overall survival (OS) in the general study population (HR 0.80 for OS improvement from 8.5 to 10.63 months); secondary endpoints include progression free survival (PFS), OS and PFS in the biomarker positive sub-population, ORR and DCR, safety and quality of life. In addition, blood and tumor archival tissue will be assessed for pharmacokinetic and biomarker analyses. Global enrollment is underway. Clinical trial information: NCT02993731.

TPS4149 Poster Session (Board #132a), Sat, 8:00 AM-11:30 AM

The CCTG PA.7 trial: A randomized phase II study of gemcitabine and nab-paclitaxel vs. gemcitabine, nab-paclitaxel, durvalumab, and tremelimumab as 1st line therapy in metastatic pancreatic ductal adenocarcinoma (PDAC). *First Author: Daniel John Renouf, BC Cancer Agency, Vancouver, BC, Canada*

Background: Gemcitabine (GEM) and Nab-Paclitaxel (Nab-P) has become a standard 1st line therapy for advanced PDAC based on the MPACT Trial. Durvalumab (D) is a human monoclonal antibody (mAb) that inhibits binding of programmed cell death ligand 1 (PD-L1) to its receptor (PD-1). Tremelimumab (T) is a mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Monotherapy with immune checkpoint inhibitors has thus far demonstrated limited activity in PDAC. This may be partly related to the activity of cancer associated fibroblasts (CAF) in promoting an immunosuppressive tumoural microenvironment in PDAC. GEM and Nab-P treatment may deplete stroma and CAFs, release neo-antigens and increase the immunogenicity of PDAC. This study is designed to evaluate whether the addition of PD-L1 and CTLA-4 inhibition to GEM/Nab-P increases treatment efficacy. **Methods:** This randomized phase II study (ClinicalTrials.gov NCT02879318) will assess the efficacy and safety of GEM/Nab-P vs. GEM/Nab-P/D/T in patients (pts) with metastatic PDAC (n = 190). Good performance status pts (ECOG $<$ 2) with untreated metastatic PDAC will be eligible. Prior adjuvant therapy is allowed provided recurrence is $>$ 6 months post-completion. There is a safety lead in of 10 pts receiving GEM/Nab-P/D/T. Assuming no safety concerns the study will go on to randomize pts in a 2:1 ratio to receive GEM (1000mg/m^2 D1, 8, 15)/Nab-P (125mg/m^2 D1, 8, 15) with/without D (1500 mg) D1 q 28 days and T (75 mg) D1 for first 4 cycles. Treatment will continue until disease progression, death, intolerable toxicity, or patient/investigator decision to stop. Primary endpoint is overall survival; secondary endpoints include progression free survival, safety, overall response rate and quality of life. Analysis will be according to randomized group stratified by ECOG PS and receipt of prior adjuvant chemotherapy. Blood, plasma, and archival tissue will be collected and assessed for potential prognostic and predictive biomarkers. As of February 1 2017, 11 pts have been enrolled and the initial safety analysis is ongoing. Clinical trial information: NCT02879318.

TPS4150 Poster Session (Board #132b), Sat, 8:00 AM-11:30 AM

A phase II study of abemaciclib as a monotherapy and in combination with other agents in patients with previously treated metastatic pancreatic ductal adenocarcinoma (PDAC). *First Author: E. Gabriela Chiorean, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: PDAC is a lethal tumor with unusual resistance to cytotoxic and targeted therapies, and pathogenesis frequently associated with hyperactive CDK 4&6 signaling. Pre-clinical models have demonstrated anti-proliferative activity with CDK 4&6 inhibitors alone, however, synergistic effects have been observed when combined with a PI3K/mTOR or TGF- βR1 inhibitor. Abemaciclib is a selective inhibitor of CDK 4&6 with an acceptable safety profile in clinical studies.This study will evaluate the safety and efficacy of abemaciclib alone or in combination with LY3023414, a PI3K/mTOR dual inhibitor, or galunisertib, a TGF-βR1 inhibitor, versus standard of care (SOC) in pateints (pts) with metastatic PDAC. **Methods:** Design: Study JPCJ is an adaptive, open-label, randomized, Phase 2 study in pts with previously treated metastatic PDAC. Pts will be stratified based on number of prior systemic therapies (1 or 2), and in Stage 1 (25 pts/arm) will be randomized in a 1:1:1:1 ratio to 4 treatment arms: abemaciclib; abemaciclib+LY3023414; abemaciclib + galunisertib; SOC treatment gemcitabine or capecitabine. Investigational arms demonstrating evidence of disease control rate (DCR) comparable to or better than the SOC will advance to Stage 2 (additional 50 pts/arm). Eligibility: Pts must have metastatic PDAC with disease progression following 1 or 2 prior lines of therapy, measurable disease, ECOG PS $\leq$1, no prior treatment with any CDK 4&6, TGF-β, or PI3K and/or mTOR inhibitors, no severe cardiac disorders, and must not have insulin-dependent diabetes. Objectives: The primary endpoint is to evaluate the DCR (Stage 1) and progression-free survival (PFS [Stage 2]). Secondary objectives include response rate, overall survival, safety, pharmacokinetics, biomarkers related to the CDK 4&6 pathway, and quality of life. Statistics: Assuming a hazard ratio of 0.65 in PFS (median PFS of 2.3 months in abemaciclib containing arms vs. 1.5 months in the SOC arm), the study has approximately 76% power to detect superiority of the abemaciclib-containing arm using a 2-sided log-rank test at 0.10 significance level. Accrual began on 01/12/2017. Clinical trial information: NCT02981342.

TPS4151 Poster Session (Board #133a), Sat, 8:00 AM-11:30 AM

Alliance for clinical trials in oncology trial A021501: Preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. *First Author: Matthew H. G. Katz, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Borderline resectable pancreatic cancers infiltrate into adjacent vascular structures to an extent that makes an R0 resection unlikely when pancreatectomy is performed *de novo*. In a pilot study, Alliance for Clinical Trials in Oncology Trial A021101, the median survival of patients who received chemotherapy and radiation prior to anticipated pancreatectomy was 22 months, and an R0 resection was achieved in 64% of operations. However, the individual contributions of preoperative chemotherapy and radiation therapy are poorly defined.This study, Alliance for Clinical Oncology Trial A021501, will help define a standard preoperative treatment regimen for borderline resectable pancreatic cancer and position the superior arm for further evaluation in future phase III trials. **Methods:** In this recently activated randomized phase II trial, 134 patients with a biopsy-confirmed pancreatic ductal adenocarcinoma that meets centrally-reviewed radiographic criteria for borderline resectable disease are randomized to receive either 8 cycles of modified FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 for 4 cycles) or to 7 cycles of modified FOLFIRINOX followed by stereotactic body radiation therapy (33-40 Gy in 5 fractions). Patients without evidence of disease progression following preoperative therapy undergo pancreatectomy and subsequently receive 4 cycles of postoperative modified FOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 for 4 cycles). The primary endpoint is the 18-month overall survival rate of patients enrolled into each of the two treatment arms. An interim analysis of the R0 resection rate within each arm will be conducted to assess treatment futility after accrual of 30 patients. Secondary endpoints include rates of margin-negative resection and event-free survival. The trial is activated nationwide and eligible to be opened for accrual at any National Clinical Trials Network cooperative group member site. Clinical trial information: NCT02839343.

TPS4152 Poster Session (Board #133b), Sat, 8:00 AM-11:30 AM

SWOG S1505: A randomized phase II study of perioperative mFOLFIRINOX vs. gemcitabine/nab-paclitaxel as therapy for resectable pancreatic adenocarcinoma. *First Author: Davendra Sohal, Cleveland Clinic, Cleveland, OH*

Background: Clinical outcomes after curative therapy for resectable pancreatic ductal adenocarcinoma (PDA) remain suboptimal. Series show that 70-85% of patients die of systemic recurrence. Improved overall survival (OS) in the metastatic setting with the use of multi-agent chemotherapy regimens (FOLFIRINOX, gemcitabine/nab-paclitaxel) holds the promise of progress in the curative setting as well. However, aggressive systemic therapy is usually not feasible after major pancreatic surgery. Therefore, early control of systemic disease by increased preoperative chemotherapy may improve outcomes. Furthermore, the perioperative platform facilitates early identification of patients with chemotherapy-resistant tumors and allows prospective biomarker studies in the future. **Methods:** This is a randomized phase II study intended to choose the most promising perioperative regimen to test in a larger trial. Eligibility requirements include adult patients with an ECOG PS of 0 or 1, a confirmed histopathologic diagnosis of PDA, and resectable disease as confirmed by central radiology review: no involvement of the celiac, common hepatic, or superior mesenteric arteries (and, if present, variants); no involvement, or $< 180°$ interface between tumor and vessel wall, of the portal or superior mesenteric veins; patent portal vein/splenic vein confluence; no metastases. Treatment includes 12 weeks [either 6 doses of mFOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin – without bolus 5-FU and leucovorin), or 9 doses of gemcitabine/nab-paclitaxel, on standard schedules] of preoperative chemotherapy, followed by surgical resection and 12 weeks of identical postoperative chemotherapy. Primary outcome is 2-year OS, using a "pick the winner" design with minimum two-year OS of 40% assuming a 58% alternative hypothesis, 88% power, and a 1-sided α of 0.05, providing 90% probability of selecting the better regimen with a total sample size of 118 patients. Correlative studies are planned. The study opened through the National Clinical Trials Network (NCT02562716), and is supported by NIH/NCI/NCTN grants CA180888, CA180819, CA180821, CA180833. Clinical trial information: NCT02562716.

TPS4153 Poster Session (Board #134a), Sat, 8:00 AM-11:30 AM

A phase III, double-blind, randomized clinical trial comparing S-1 in combination with DC vaccine loaded with WT1 peptides (TLP0-001) or placebo for the patients with advanced pancreatic cancer refractory to standard chemotherapy. *First Author: Masahiro Katsuda, Second Department of Surgery, Wakayama Medical University, Wakayama, Japan*

Background: The development of new potent therapeutic is strongly called for treating pancreatic cancer. Dendritic cells (DCs) are a type of antigen-presenting cells that play an important role in adaptive immune system, and this property has prompted their recent application to therapeutic cancer vaccines. DCs loaded with tumor antigen ex vivo and administered as a cellular vaccine have been found to induce therapeutic anti-tumor immunity. Wilms' tumor gene WT1 is expressed in various kinds of cancers including pancreatic cancer. In pilot clinical trials of DC vaccination loaded with WT1 peptides for patients with advanced pancreatic cancer, induction of anti-tumor WT1 specific immune responses and tumor regressions have been observed (Kimura et al, Pancreas, 2012 / Kobayashi et al, Cancer Immunol Immunother, 2014 / Mayanagi et al Cancer Sci, 2015). TLP0-001 is activated Dendritic cells loaded with epitope peptides derived from WT-1. **Methods:** This is an investigator initiated, phaseIII, multicenter, double-blind, randomized trial of TLP0-001+S-1 versus placebo+S-1 for the patients with locally advanced or metastatic pancreatic cancer refractory to standard chemotherapy. Patients are allocated to either DC vaccine (TLP0-001) + S-1 group or placebo + S-1 in 1:1 ratio by dynamic allocation method. The primary endpoint is overall survival. Sample size is estimated presuming the effects will be observed from the time point of 50% cumulative survival rate. Assuming a type I error alpha (two-sided) level of 5% and a power of 80% or more for hazard ratio 0.644, sample size necessary is estimated as 174 patients. When the first 6 patients are administerd TLP0-001, the independent Data Monitoring Commitee checks safety data to assess continuation of the study. Enrollment begins in March 2017.

TPS4154 Poster Session (Board #134b), Sat, 8:00 AM-11:30 AM

Phase II study of GM-CSF secreting allogeneic pancreatic cancer vaccine (GVAX) with PD-1 blockade antibody and stereotactic body radiation therapy (SBRT) for locally advanced pancreas cancer (LAPC). *First Author: Valerie Lee, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Optimal treatment strategy beyond systemic chemotherapy for LAPC remains undefined. SBRT improves local control, but distant metastasis free survival (DMFS) is only 7.7 months. Checkpoint inhibitors are poor monotherapies in pancreas cancer, but may be primed by SBRT via absocopal effect and GVAX, which induces novel lymphoid infiltrates and increased effector T-cells in tumor microenvironment. **Methods:** This is a single-arm, single-institution, open-label study for pts with LAPC. Eligibility: surgically unresectable LAPC, predominant adenocarcinoma at diagnosis, with ECOG 0-1, who remain metastases free after 4-8 cycles of FOLFIRINOX or gemcitabine/abraxane based-chemotherapy. Exclusion: those off chemotherapy $>$ 49 days prior to study treatment, prior immunotherapy, active immunosuppressive use, autoimmune disease, HIV, HBV, or HCV infection, and non-oncology vaccines within 28 days of study treatment. Pts receive cyclophosphamide (200mg/m2 IV) and pembrolizumab (200mg IV) on day 1, followed by GVAX (six intradermal injections) on day 2 every three weeks for two cycles, with cycle 2 initiating concurrently with five days of SBRT. If non-metastatic, pts undergo surgical resection, nano-knife, or EUS guided biopsy (if non-surgical). Pts receive two further cycles of chemotherapy, and if remain free of metastases, receive q3 week cyclophosphamide, pembrolizumab, and GVAX for six cycles, then are monitored for two years. The primary endpoint is DMFS. Secondary endpoints include overall survival, surgical resectability, pathologic response, quality of life, and toxicity. Exploratory objectives of peripheral antigen specific t-cell responses, and changes in immune parameters of tumor microenvironment. 11 of 54 pts have been enrolled since July 2016. Clinical trial information: NCT02648282.

4500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Comprehensive molecular characterization and analysis of muscle-invasive urothelial carcinomas. *First Author: Seth P. Lerner, Baylor College of Medicine, Houston, TX*

Background: We reported the integrated molecular analysis of 131 tumors in 2014 (Nature 507:315, 2014) and now report on the entire cohort of 412 tumors from the TCGA project in chemotherapy-naïve, muscle-invasive urothelial bladder cancer. **Methods:** Following strict clinical and pathologic quality control, tumors were analyzed for DNA copy number variants, somatic mutations (WES), DNA methylation, mRNA, non-coding RNA (lncRNA and miRNA) and (phospho-) protein expression, gene fusions, viral integration, pathway perturbation, clinical correlates, outcomes, and histopathology. **Results:** There was a high overall somatic mutation rate (8.2/Mb), as previously reported. There were 58 significantly mutated genes (SMGs) (MutSig_2CV), increased from 32 in the original report. We identified 5 mutation signatures including APOBEC-a and b, ERCC2, C > T_CpG, and a single ultra-mutated sample with a functional POLE mutation. APOBEC mutagenesis explained 70% of the mutation burden and was associated with survival (p = 0.0013). High mutation burden and neoantigen load were also associated with improved outcome (p = 0.00014 and 0.00078). The previously identified four mRNA subtypes were predicted on the larger set and also identified a novel poor-survival 'neuronal' subtype that nevertheless lacked small cell or neuroendocrine histology. Clustering converged for mRNA, lncRNA and miRNA expression, and for inferred activity of gene sets associated with regulator expression. We identified subsets with differential epithelial-mesenchymal transition scores, carcinoma-in-situ scores, and survival, with implications for distinct therapeutic potential. **Conclusions:** This integrated analysis of 412 TCGA patient samples validates and extends observations from the first 131 patients and significantly increases our power to detect additional low-frequency aberrations. The results provide unique insights into mechanisms of bladder cancer development, and identify novel subsets of MIBC that may benefit from differential treatment approaches.

4501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Planned survival analysis from KEYNOTE-045: Phase 3, open-label study of pembrolizumab (pembro) versus paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial cancer (UC). *First Author: Dean F. Bajorin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Second-line chemotherapies (chemo) for advanced UC have limited clinical benefit (OS, 7-9 mo). Data from the open-label, phase 3 KEYNOTE-045 study (NCT02256436) showed significantly longer OS with pembro v chemo (median, 10.3 v 7.4 mo; hazard ratio [HR], 0.73; P = 0.002) in recurrent, advanced UC. Data from a planned survival analysis are presented. **Methods:** Pts had histologically or cytologically confirmed UC, progression after platinum, ECOG PS 0-2, measurable disease (RECIST v 1.1), and ≤2 lines of systemic therapy. Pts were randomly assigned 1:1 to pembro 200 mg Q3W or investigator's choice of paclitaxel 175 mg/m^2 Q3W, docetaxel 75 mg/m^2 Q3W, or vinflunine 320 mg/m^2 Q3W. Primary efficacy end points were OS and PFS (RECIST v1.1, blinded central review). ORR (RECIST v1.1, blinded central review) was a secondary end point. **Results:** 542 pts were enrolled (pembro, 270; chemo, 272). Baseline characteristics were generally similar between arms. As of Jan 18, 2017, median follow-up was 18.5 mo (range, 14.2-26.5). Median OS was significantly longer with pembro v chemo (10.3 v 7.4 mo; HR, 0.70; P < 0.001), and significance was maintained regardless of PD-L1 expression as measured by combined positive score (HR: CPS < 1%, 0.84; CPS ≥1%, 0.59; CPS < 10%, 0.76; CPS ≥10%, 0.57). OS benefit with pembro v chemo was seen regardless of age, ECOG PS, prior therapy, liver metastases, histology, and choice of chemo. The 18-mo OS rate (95% CI) was 36.1% (30.1%-42.0%) with pembro v 20.5% (15.2%-25.8%) with chemo (KM estimate). PFS was not different between arms. ORR was higher with pembro v chemo (21.1% v 11.0%), and median (range) duration of response was longer (not reached [1.6+-20.7+ mo] v 4.4 mo [1.4+-20.3]). 69% (pembro) v 36% (chemo) of responses lasted ≥12 mo. Fewer pts experienced a treatment-related AE with pembro v chemo (any grade, 61.3% v 90.2%; grade ≥3, 16.5% v 49.8%). **Conclusions:** The OS benefit and superior safety profile of pembro over chemo are maintained with longer follow-up. Combined, these results support the potential of pembro as a new standard of care for patients with UC who previously received platinum. Clinical trial information: NCT02256436.

4502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Biomarker findings and mature clinical results from KEYNOTE-052: First-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). *First Author: Peter H. O'Donnell, The University of Chicago Medical Center, Chicago, IL*

Background: Comorbidities and renal impairment preclude many with advanced UC from receiving chemotherapy. Initial results from the phase 2 KEYNOTE-052 (NCT02335424) trial suggested first-line pembro is active and safe in cisplatin-ineligible advanced UC. We present updated efficacy and safety data (all pts have ≥6 mo follow-up) and evaluate biomarkers correlated with outcomes. **Methods:** Eligibility criteria included cisplatin-ineligible (ECOG PS 2, CrCl ≥30- < 60 mL/min, grade ≥2 neuropathy/hearing loss, NYHA Class 3 heart failure), advanced UC, and no prior systemic chemotherapy. Pts received pembro 200 mg IV Q3W. Imaging was performed at wk 9, then Q6W for the first year, and Q12W thereafter. Primary end point was confirmed ORR (RECIST v1.1, independent review). Efficacy and safety were assessed in the 370 pts with ≥1 pembro dose. The associations of an 18-gene expression profile (GEP) and IHC PD-L1 combined positive score (CPS) with ORR were evaluated. **Results:** As of the Dec 19, 2016, data cutoff, ORR was 29% (95% CI, 24-34): 25 (7%) and 81 (22%) pts achieved complete and partial responses. Another 69 pts (19%) had stable disease as best response, for a clinical benefit rate of 47%. Median time to response was 2 mo (range, 1-5). At a median follow-up of 8 mo (range, 0.1-20) across all pts, median duration of response was not reached (range, 1+-18+ mo). 74% of responses were ongoing. Any-grade and grade ≥3 drug-related AEs occurred in 239 (65%) and 68 (18%) pts. Immune-mediated AEs occurred in 76 (21%) pts. Evidence supporting a positive association with response was seen in the first 100 pts for both biomarkers (GEP, n = 72, P = 0.007, ROC AUC 0.69; CPS, n = 96, P = 0.111, ROC AUC 0.58); biomarker data for all pts will be presented. ORR in the 110 pts with CPS ≥10% was 47% (95% CI, 38-57). **Conclusions:** Results confirm that pembro elicits clinically meaningful, durable responses in cisplatin-ineligible advanced UC. Consistent with PD-1 pathway biology, biomarkers (GEP and CPS) showed the expected trends of positive association with response to pembro. Pembro was well tolerated across cisplatin-ineligible pts, including elderly and pts with poor performance status. Clinical trial information: NCT02335424.

4503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Epacadostat plus pembrolizumab in patients with advanced urothelial carcinoma: Preliminary phase I/II results of ECHO-202/KEYNOTE-037. *First Author: David C. Smith, University of Michigan, Ann Arbor, MI*

Background: Pembrolizumab (P), a PD-1 inhibitor, is active and well tolerated in platinum-treated, advanced urothelial carcinoma (UC). Epacadostat (E) potently and selectively inhibits indoleamine 2,3-dioxygenase 1 (IDO1), a tryptophan-catabolizing enzyme that suppresses T-cell–mediated immune surveillance. IDO1 overexpression is associated with tumor progression and shortened patient (pt) survival. ECHO-202/KEYNOTE-037 is an open-label, phase I/II study of E + P in pts with advanced tumors. We report phase I/II efficacy and safety outcomes for the UC cohort at an October 29, 2016 data cutoff. **Methods:** Adult pts with advanced UC, prior platinum therapy (adjuvant or advanced disease setting) or alternative therapy (if platinum was not appropriate), and no prior checkpoint inhibitor therapy were eligible to participate. In phase I, pts received E (25, 50, 100, or 300 mg PO BID) + P (2 mg/kg or 200 mg IV Q3W); MTD was not exceeded. E (100 mg BID) + P (200 mg Q3W) dosing was selected for phase II. Response was assessed in RECIST 1.1–evaluable pts. Safety was assessed in pts receiving ≥1 E + P dose. **Results:** A total of 40 pts (phase I, n = 5; phase II, n = 35) were evaluated. Median age was 67 years, 75% were men, 88% were white, 100% had prior platinum therapy, and 75% had 0–1 prior line of therapy for advanced disease. Preliminary ORR (CR+PR) and DCR (CR+PR+SD) for all efficacy-evaluable pts were 35% (13/37; all PR) and 57% (21/37; 13 PR, 8 SD), respectively; for pts with 0–1 prior line of therapy for advanced disease, ORR and DCR were 37% (10/27) and 63% (17/27). At data cutoff, 12/13 responses were ongoing (range, 1+ to 652+ days). PFS and biomarker analyses are ongoing. The most common TRAEs (≥10% of 40 pts) were fatigue (28%), rash (18%), and increased amylase (10%; asymptomatic). Grade ≥3 TRAEs occurred in 20% of pts (rash was the only grade ≥3 TRAE to occur in > 1 pt [n = 3]). Three pts discontinued due to TRAEs (grade 3 rash [n = 1]; grade 3 COPD exacerbation [n = 1], grade 2 diarrhea [n = 1]). **Conclusions:** E + P was generally well tolerated and associated with increased response compared with previously reported PD-1 inhibitor monotherapy in pts with advanced UC. A phase III UC study is planned. Clinical trial information: NCT02178722.

4504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

First-line avelumab + axitinib therapy in patients (pts) with advanced renal cell carcinoma (aRCC): Results from a phase Ib trial. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA*

Background: Combining an immune checkpoint inhibitor with a targeted antiangiogenic agent may leverage complementary mechanisms of action for treatment of aRCC. Avelumab is a fully human anti–PD-L1 IgG1 antibody with clinical activity in various tumor types; axitinib, a VEGF receptor inhibitor, is approved for second-line treatment of aRCC. JAVELIN Renal 100 (NCT02493751) is a phase Ib study evaluating safety and clinical activity of avelumab + axitinib in treatment-naïve pts with aRCC; updated results are reported here. **Methods:** Eligible pts had confirmed clear-cell aRCC, ≥1 measurable lesion, fresh or archival tumor specimen, ECOG PS ≤1, and no prior systemic therapy. Pts received avelumab 10 mg/kg IV Q2W + axitinib 5 mg orally BID until progression, unacceptable toxicity, or withdrawal. Endpoints included safety (NCI CTCAE v4.03) and objective response (RECIST v1.1). **Results:** As of Dec 30, 2016, 55 pts (median age 60.0 yrs [range 42.0–76.0]; 76.4% male; 34.5% ECOG PS = 1) were enrolled. 54 pts were treated with avelumab for a median of 24.1 wks (range 2.0–62.0); 55 pts were treated with axitinib for a median of 25.3 wks (range 3.0-61.0). 51 pts (92.7%) had an avelumab-related adverse event (AE) with the therapy combination, the most common (≥30% any grade) were fatigue and diarrhea (30.9% each). 10 pts (18.2%) had a max grade 3 and 1 pt (1.8%) had a max grade 4 avelumab-related AE. 52 pts (94.5%) had an axitinib-related AE with the therapy combination; the most common (≥30% any grade) were diarrhea (52.7%), hypertension (45.5%), dysphonia (43.6%), and fatigue (43.6%). 24 pts (43.6%) had a max grade 3 and 5 pts (9.1%) had a max grade 4 axitinib-related AE. 2 deaths occurred in the study during the reporting period: 1 due to progression and 1 related to both treatments (myocarditis). An AE led to discontinuation of avelumab in 5 pts (9.1%) and axitinib in 4 pts (7.3%). Confirmed ORR was 54.5% (95% CI 40.6–68.0) based on 2 CR and 28 PR. Unconfirmed ORR was 60.0% (95% CI 45.9–73.0). **Conclusions:** The safety profile of the combination of avelumab + axitinib appears manageable and consistent with those agents administered as monotherapy, and early encouraging antitumor activity was observed. Follow-up is ongoing. Clinical trial information: NCT02493751.

4505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

IMmotion150: A phase II trial in untreated metastatic renal cell carcinoma (mRCC) patients (pts) of atezolizumab (atezo) and bevacizumab (bev) vs and following atezo or sunitinib (sun). *First Author: Michael B. Atkins, Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC*

Background: While inhibiting VEGF improves outcomes in mRCC pts, most develop resistance, often within a year. Here, we report results from a Ph II study of atezo (anti–PD-L1) and bev (anti-VEGF) vs and following atezo or sun (TKI) in mRCC pts. **Methods:** Pts with untreated mRCC were enrolled in the hypothesis generating IMmotion150 study (NCT01984242) and randomized to atezo 1200 mg IV q3w + bev 15 mg/kg IV q3w, atezo alone or sun 50 mg PO QD 4 wk on/2 wk off. After progression on atezo or sun, crossover to atezo + bev was allowed. PD-L1 status was scored on tumor-infiltrating immune cells (IC, SP142 IHC assay). The primary analysis was modified prior to final analysis to reflect the coprimary endpoints of IRF-assessed PFS (RECIST v1.1) in ITT pts and pts with PD-L1 expression on ≥ 1% of IC (PD-L1+). **Results:** 54% of pts were PD-L1+. In PD-L1+ pts 1L treatment resulted in a PFS hazard ratio (HR) of 0.64 for atezo + bev vs sun (table). After 1L treatment, 78% of sun and 60% of atezo pts who progressed subsequently received atezo + bev and achieved ORRs of 28% and 24%, respectively (table). Safety was comparable to the known individual profiles of atezo and bev. Additional clinical, safety and biomarker data will be presented. **Conclusions:** Atezo + bev resulted in encouraging antitumor activity in 1L pts with PD-L1+ mRCC. Preliminary activity in the 2L setting was demonstrated in pts who crossed over to atezo + bev, regardless of prior therapy. 1L atezo + bev vs sun is being evaluated in the ongoing Ph III study IMmotion151 (NCT02420821). Clinical trial information: NCT01984242.

	Atezo + Bev n = 101	Atezo n = 103	Sun n = 101	Atezo + Bev vs Sun	Atezo vs Sun
	mPFS (95% CI), mo [a]			HR (95% CI)	
ITT n = 305	11.7 (8.4, 17.3)	6.1 (5.4, 13.6)	8.4 (7.0, 14.0)	1.00 (0.69, 1.45) *P* = .982	1.19 (0.82, 1.71) *P* = .358
PD-L1+ n = 164	14.7 (8.2, 25.1)	5.5 (3.0, 13.9)	7.8 (3.8, 10.8)	**0.64 (0.38,1.08)** *P*= .095	1.03 (0.63, 1.67) *P* = .917
	ORR (confirmed), n (%)[a] (95% CI)				
ITT	32 (32%) (23, 42)	26 (25%) (17, 35)	29 (29%) (20, 39)	–	–
PD-L1+	23 (46%) (32, 61)	15 (28%) (16, 42)	16 (27%) (16, 40)	–	–
	ORR post crossover to atezo + bev (confirmed), n (%)[b] (95% CI)				
ITT	–	n = 44 10 (24%) (12, 40)	n = 57 15 (28%) (16, 42)	–	–

[a] IRF assessed; [b] Investigator assessed *P* values for descriptive purposes only

4506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

A phase I/II study to assess the safety and efficacy of pazopanib (PAZ) and pembrolizumab (PEM) in patients (pts) with advanced renal cell carcinoma (aRCC). *First Author: Simon Chowdhury, Sarah Cannon Research Institute, London, United Kingdom*

Background: PAZ is indicated for the treatment of aRCC. The combination of an antiangiogenic agent and immunotherapy may improve anti-tumor activity. We report preliminary safety and efficacy results of the phase I part of the study. **Methods:** Twenty pts were originally enrolled in cohorts A and B assessing PAZ 800 mg and 600 mg, respectively, both with 2mg/kg (Q2W and then Q3W) PEM to determine the maximum tolerated dose. Due to dose limiting liver toxicity, cohort C was opened to assess if the sequential schedule of 9 weeks PAZ run-in followed by PAZ+PEM would improve safety. Strict safety criteria for initiating PAZ+PEM were set. The data from this ongoing study are presented given the limited information available on the combination of TKI + PD-1 inhibitors in RCC. **Results:** Overall, 35 pts were treated; 5 out of 15 pts in cohort C received PAZ+PEM at the data cut-off. Three dose-limiting toxicities (DLT) occurred in cohort C in pts receiving PAZ+PEM; updated DLTs in all cohorts are reported in Table. G3/4 AEs were observed in 90% of pts in cohorts A and B and in 80% of pts in cohort C receiving PAZ+PEM. No G3/4 ALT/AST elevation was reported in cohort C PAZ+PEM while they were observed in 70% and 60% in cohorts A and B, respectively. Best overall response (CR+PR) was reported in 6, 2 and 1 pts receiving PAZ+PEM in cohorts A, B and C, respectively. **Conclusions:** Results from cohorts A and B showed significant hepatotoxicity. The sequential schedule PAZ → PAZ+PEM has shown reduced hepatotoxicity and preliminary signs of efficacy but overall limited tolerability. PAZ+PEM is not suitable to test in a larger cohort. Clinical trial information: 2013-003785-14.

	Cohort A	Cohort B	Cohort C PAZ+PEM post run-in
Pts (n)	10	10	5*
DLTs (n)	2	5	3
	• ALT G3; AST G3; Bilirubin G3 • ALT G3; AST G3	• AST G3 • ALT G3 • ALT G4; AST G3 • ALT G2; AST G3 • Lipase G3	• Pneumonitis G3 • Bowel perforation G3 • Lipase G4
Grade 3/4 (%)	90	90	80
AEs leading to dose interruption or reduction (%)	90/70	90/50	80/40
AEs leading to permanent discontinuation (%)	50	80	20

* N = 15 enrolled in cohort C.

4507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT). *First Author: Robert J. Motzer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: PROTECT (NCT01235962) evaluated the efficacy and safety of pazopanib (PAZ) versus placebo in patients (pts) with locally advanced renal cell carcinoma (RCC) post nephrectomy. **Methods:** 1538 pts with resected pT2 (high grade), pT3 or greater clear cell RCC were randomly assigned to PAZ or placebo for 1 year. The starting dose (800 mg) following treatment of 403 pts was lowered to 600 mg to improve tolerability and primary endpoint was changed to disease-free survival (DFS) with PAZ 600 (N = 1135). Primary analysis was performed after 350 DFS events in intent-to-treat (ITT) PAZ 600, and DFS follow-up analysis was performed after an additional 12 months. Secondary endpoints included DFS with ITT PAZ 800 and ITT ALL, and safety. **Results:** Disease characteristics were similar between arms. The primary analysis results of DFS ITT 600 were not significant [HR: 0.862; 95% CI, 0.699, 1.063; p = 0.165] (Table). The secondary endpoint of DFS in ITT PAZ 800 and ITT ALL yielded 31% and 20% risk reduction, respectively. Updated DFS analysis in ITT 600 showed a higher HR with longer follow up. Increased ALT and AST were the most common adverse events leading to treatment discontinuation in the PAZ 600 (ALT 16% and AST 5%) and PAZ 800 (ALT 18% and AST 7%) groups. **Conclusions:** The study did not meet the primary DFS endpoint in ITT 600; however, a 31% decrease in the risk of recurrence was observed in ITT 800. The safety profiles in the 600 mg and 800 mg groups were similar and consistent with PAZ prior experience. Clinical trial information: NCT01235962.

	ITT 600		ITT 800		ITT ALL	
	Pazopanib N = 571	Placebo N = 564	Pazopanib N = 198	Placebo N = 205	Pazopanib N = 769	Placebo N = 769
DFS—Primary analysis, HR (95% CI)	0.862 (0.699, 1.063); p = 0.165*		0.693 (0.510, 0.943)		0.802 (0.675, 0.954)	
DFS—Follow up analysis, HR (95% CI)	0.936 (0.769, 1.140)		0.663 (0.491, 0.895)		0.842 (0.714, 0.993)	
DFS rate at 3 years, % (95% CI)	67 (62, 71)	64 (60, 68)	66 (58, 72)	56 (48, 62)	66 (63, 70)	62 (58, 65)
DFS rate at 5 years, % (95% CI)	NA	NA	61 (53, 68)	48 (40, 55)	58 (53, 62)	54 (48, 58)

*Stratified log-rank test, two sided.

4508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase III trial of adjuvant sunitinib in patients with high-risk renal cell carcinoma (RCC): Validation of the 16-gene Recurrence Score in stage III patients. *First Author: Bernard J. Escudier, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Adjuvant therapy with sunitinib (SU) compared with placebo (PBO) prolonged disease-free survival (DFS) in 615 patients (pts) with high-risk RCC (hazard ratio [HR] 0.76; *P*= 0.03) in the S-TRAC trial. The 16-gene Recurrence Score (RS) was developed and validated to predict risk of recurrence of RCC after nephrectomy in 2 cohorts of stage I–III pts (Rini et al., *Lancet Oncol* 2015;16:676-85). We present further validation of RS results in high-risk stage III pts from S-TRAC. **Methods:** The study was prospectively designed with prespecified genes, algorithm, endpoints, analytical methods, and analysis plan using primary RCC tissues from 212 evaluable pts with informed consent. Gene expression was quantitated by RT-PCR; primary analysis focused on stage III (n = 193 pts). Time to recurrence (TTR) and DFS were analyzed using Cox proportional hazard regression. **Results:** Baseline characteristics were similar in SU and PBO arms and in pts with and without gene expression data; effect of SU was numerically similar to that in the entire trial (DFS HR 0.78, 95% CI 0.48–1.24; *P*= 0.29). RS predicted TTR and DFS in both treatment arms with the strongest results observed in PBO arm where high RS group had significantly higher risk (Table). Interaction of RS with treatment was not significant (TTR *P*= 0.192; DFS *P*= 0.219); however, the number of events was relatively low. **Conclusions:** The prognostic value of the 16-gene assay was confirmed in S-TRAC. RS is now validated with consistent results in 2 separate studies (level IB evidence). RS results may help identify patients at high risk who could derive higher absolute benefit from adjuvant treatment. The predictive value of RS to select patients for adjuvant SU requires further investigation in independent adjuvant trials.

Statistics	PBO, n = 90	SU, n = 103
TTR*	4.24 (2.31–7.80), < 0.001	2.53 (1.29–4.97), 0.008
DFS*	3.75 (2.13–6.60), < 0.001	2.31 (1.20–4.43), 0.014
High vs low RS group, n	42 vs 20	48 vs 16
TTR#	9.18 (2.15-39.24), < 0.001	1.86 (0.68-5.06), 0.201
DFS#	5.17 (1.78-14.99), < 0.001	1.87 (0.69-5.07), 0.255

* HR (95% CI), p value, per 25-units increase of RS # HR (95% CI), p value, high vs low RS group.

4509 Clinical Science Symposium, Fri, 2:45 PM-4:15 PM

DNA damage repair and response (DDR) gene alterations (alt) and response to PD1/PDL1 blockade in platinum-treated metastatic urothelial carcinoma (mUC). *First Author: MinYuen Teo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Somatic DDR alts are associated with increased mutation load (ML) and improved clinical outcomes for platinum-treated mUC (Teo et al, CCR 2017). We examined the relationship between DDR alts and response to PD1/PDL1 blockade. **Methods:** mUC pts enrolled to phase 2 trials of atezolizumab or nivolumab who had targeted exon sequencing of 410 genes (MSK-IMPACT) were identified. Pts were dichotomized based on presence of alts in a panel of 34 DDR genes. Analyses were performed based on: (1) any DDR alts and (2) deleterious DDR alts (frameshift, splice site, nonsense or Hotspot point mutations). Study endpoint was overall response (OR) per RECIST. ML was defined as total number of nonsynonymous mutations by MSK-IMPACT. Fisher exact, Wilcoxon rank sum, and stratified logistic regression were used. **Results:** Fifty two pts were identified (atezo: n=18, nivo: n=34). Median age was 67 years (range: 32 – 84) and majority (44) was male. Median platinum-free interval was 10.2 months (range: 0.3 – 150.4). DDR and deleterious DDR were seen in 25 (48.1%) and 14 (26.9%) pts (including 2 MSI and 1 POLE). OR rate was 46.2%. Responses were associated with DDR alts but not with age, gender, treatment, platinum-free interval or ML (table). In univariate logistic regression model, DDR status was associated with OR (p<.001) while a trend was observed with ML as a continuous variable (p=.051). While DDR alts were associated with higher ML (all: p=.001, deleterious: p=.004), the effect of DDR alts on OR remained significant regardless of ML (>median: p=.027; ≤median: p=.023), indicating that the effect of DDR was independent of ML. **Conclusions:** DDR alts appeared to be associated with OR to PD1/PDL1 blockade and should be integrated into future validation efforts along with other potential predictors of response.

Response		No	Yes	p
Age, years	Median (range)	68 (46-81)	66 (32-84)	.80
Gender	Female	5 (18)	3 (13)	.71
	Male	23 (82)	21 (87)	.
Agent	atezo	11 (39)	7 (29)	.58
	nivo	17 (61)	17 (71)	.
Plat-free interval, months	Median (range)	9.9 (0.3 - 150.4)	10.4 (0.9 - 121.4)	.77
DDR	0	21 (75)	6 (25)	.0007
	1	7 (25)	18 (75)	.
Deleterious DDR	0	25 (89.3)	13 (54.2)	.0058
	1	3 (10.7)	11 (45.8)	.
ML	Median (range)	7 (0-20)	10 (1-80)	.12

4510 Clinical Science Symposium, Fri, 2:45 PM-4:15 PM

Cancer predisposing germline mutations in patients (pts) with urothelial cancer (UC) of the renal pelvis (R-P), ureter (U) and bladder (B). *First Author: Maria Isabel Carlo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Urothelial cancers (UC) are suspected to have a substantial hereditary component, but other than highly penetrant genes such as those in mismatch-repair pathway (e.g. *MSH2*) typically associated with R-P/U primaries, heritable gene mutations have not been systematically studied. We sought to investigate the prevalence of known cancer pre-disposing germline mutations in pts with UC originating from all sites within the urinary tract. **Methods:** Pts with R-P, U and B primaries, unselected for suspicion of inherited cancer syndrome, were prospectively enrolled from medical oncology and urology clinics to a germline sequencing protocol from June 2016 to January 2017. Germline gene analysis was performed in a CLIA-certified lab using a next generation sequencing (NGS) platform (MSK-IMPACT) that analyzes tumor-normal DNA pairs. The germline gene panel consisted of 76 genes associated with hereditary cancer predisposition. **Results:** As of January 24, 2017, 101 pts have NGS results available, with median age 63 (31-87), 76% male, 24% female. Primary sites were B (67%), R-P/U (31%), or both (3%). 73% had organ-confined disease and 27% had metastases. 8% had early onset (≤45 yrs at diagnosis), 10% had a family history of UC, 25% had documented non-UC cancers. 25 pathogenic or likely pathogenic (P-LP) mutations were identified in 22 patients. P-LP mutations were present in 29% of pts with R-P/U primaries and 18% of pts with B primaries. 12 DNA damage response gene alterations were found (4 *CHEK2*, 3 *BRCA1*, 2 *BRCA2*, 1 *ATM*, 1 *BRIP1*, 1 *NBN*) and 8 in Lynch syndrome associated genes (5 *MSH2*, 2 *MSH6*, 1 *MLH1*). Other mutations include 2 *APC*, 1 *TP53*, and 1 *FH*. Notably 3 pts had 2 alterations each (*MSH6*/*APC*, *BRCA2*/*APC*, *BRCA1*/*CHEK2*). 9/22 pts with P-LP mutations did not meet American College of Medical Genetics criteria for genetic screening. **Conclusions:** 22% of UC pts had a germline mutation in a cancer-associated gene. There was an unexpectedly high frequency of pts with DNA-repair pathway mutations. Active accrual is ongoing to define the full spectrum of alterations. These results have profound implications for genetic counseling and screening and further studies are warranted.

4511 Clinical Science Symposium, Fri, 2:45 PM-4:15 PM

Mismatch repair (MMR) detection in urothelial carcinoma (UC) and correlation with immune checkpoint blockade (ICB) response. *First Author: Gopa Iyer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: High mutation burden correlates with response to ICB in UC. Loss of function alterations or epigenetic silencing of MMR genes results in MMR deficient (MMR-D) UC, leading to a microsatellite instability (MSI) mutation signature. We used a CLIA-certified pipeline (MSISensor) to interrogate Next Generation sequencing (NGS) data from UC tumors to identify MMR-D patients (pts). We correlated MMR-D with mutation load and response to ICB. **Methods:** 447 tumors from 424 UC pts underwent prospective NGS using the MSK-IMPACT exon capture assay and genomic interrogation of microsatellite (MS) sites using MSIsensor, which assesses the number/length of MS within the targeted regions of tumor-normal sample pairs. Loci are considered unstable (somatic) if k-mer distributions are significantly different between tumor and matched normal using a standard multiple testing correction of $\chi 2$ p-values. The fraction of unstable sites is reported as an MSIsensor score. MSI high tumors have scores >10 while <3 are denoted MS stable. Scores from 3-10 were categorized as MS intermediate. **Results:** Thirteen pts (3%) had an MSI score >10 and a median mutation count of 52 (36.5-73.5) vs 8 (5-13) in 410 non-MMR-D pts (p<0.01). Ten pts (71%) had upper tract UC. Of 9 pts with germline sequencing performed, 8 (89%) had heritable loss of function mutations in MMR proteins (Lynch syndrome, LS). One pt had a somatic MSH2 mutation. Fifteen pts had MS scores from 3-10: 3 had LS, one a BRCA1 germline alteration, and 9 did not have germline testing available. Two pts with MSI scores <3 had extremely high mutation loads (213 and 414) and both had POLE mutations. Five pts received ICB therapy for metastatic and all achieved near-complete or complete responses. No MMR-D pt has died at 27 months follow-up vs 125 non-MMR-D pts (p=0.014). **Conclusions:** The MSI Sensor assay can discriminate MSI high from MMR proficient UC. While rare, MMR-D UC is characterized by a high mutation load, strong association with Lynch syndrome, and durable responses to ICB, similar to data in colon cancer. An MMR-D signature should trigger genetic testing for Lynch syndrome. ICB should be considered early in the treatment course of patients with MMR-D metastatic UC.

4512 Clinical Science Symposium, Fri, 2:45 PM-4:15 PM

Subclonal mutational heterogeneity and survival in cisplatin-resistant muscle-invasive bladder cancer. *First Author: David Liu, Dana-Farber Cancer Institute, Boston, MA*

Background: Biomarkers of survival and resistance in chemotherapy-resistant muscle-invasive bladder cancer (MIBC) are not well-characterized, but may inform management in this setting. **Methods:** Matched pre- and post-neoadjuvant cisplatin-based chemotherapy (NAC) tumor samples were obtained from 30 MIBC patients with gross residual disease (≥ pT2) at cystectomy, followed by whole exome sequencing of these "trios" (pre- and post-NAC tumor with matched germline samples). Phylogenetic analysis of matched tumor samples was performed to identify subclones, their associated mutations, and the corresponding enrichment in post-treatment tumors. Intratumoral heterogeneity was assessed by the proportion of mutations that were subclonal; the number of inferred subclones; and associated with overall survival using a Cox Proportional Hazards model. **Results:** Increased proportion of subclonal mutations in post-treatment tumors was associated with worse overall survival (HRR 1.86 [95% CI 1.12-3.06], p = 0.02), whereas pre-treatment proportion of subclonal mutations was only borderline statistically significant (HRR 1.48 [95% CI 0.99-2.20], p = 0.052). The total number of inferred tumor subclones in pre- or post-treatment tumor (or both) was associated with overall survival (HRR 1.60 [95% CI 1.05-2.43], p = 0.03), interpreted as a 60% increase in death rate per additional inferred subclone. While no single gene was statistically significantly enriched for new alterations in the post-chemotherapy resistant samples, we observed new post-treatment amplifications in cell-cycle genes (*E2F3*, *c-JUN*), biallelic events in cell-cycle regulators (*FBXW7*), and amplification of immune checkpoint genes (*PDL1/2*). **Conclusions:** These results suggest that intratumoral heterogeneity (particularly post-therapy) predicts survival in a chemotherapy-resistant cohort. Further, alterations in cell cycle regulation may contribute to the mechanism of chemotherapy resistance. Finally, we observe evidence of immune checkpoint gene amplification post-treatment, suggesting that testing immune checkpoint blockade during NAC or, in high risk patients, following NAC may be warranted.

4513 Poster Discussion Session; Displayed in Poster Session (Board #191), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Phase II study of alternate sunitinib schedule in patients with metastatic renal cell carinoma. *First Author: Eric Jonasch, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Sunitinib is an antiangiogenic agent indicated for the treatment of metastatic renal cell carcinoma (mRCC). Sunitinib is given in a 4 week on, 2 week off (4/2) schedule. Significant toxicities are observed in patients in the 3rd and 4th weeks of therapy. We hypothesized that a 2 week on, 1 week off (2/1) schedule would provide improved toxicity without compromising efficacy. **Methods:** A multicenter, single arm study was performed, with patients initiating sunitinib 50mg on a 2/1 schedule. Schedule and dose alterations were performed if grade > 3 toxicities were observed. The primary objective was to determine the percentage of patients who experienced grade > 3 fatigue, diarrhea, or HFS. The sample size of 60 patients was selected to ensure the upper bound of a 95% confidence would fall below standard schedule rate of 25%-30% if sample rate was 10%-15%, respectively. Secondary outcomes included response rate (RR), progression free survival (PFS) and dose reductions. **Results:** Between August 2014 and April 2016, 60 patients were enrolled, and 59 treated. Patients had a median age of 65.5 years (ranging from 45-92). 24% of patients (14/59) had grade 3 or higher fatigue, diarrhea, or HFS (95% CI: 13.6%, 36.6%). This is similar to the average of the 4 week on, 2 week off schedule of 25%-30%, and the lower bound of the confidence interval is in the center of our target rate of 10%-15%. Among events at least possibly related to study drug, patients were most likely to experience the expected events of diarrhea (75% with 5 grade 3 events), fatigue (71% with 6 grade 3 events), and HFS (54% with 3 grade 3 events). 22 (37%) patients responded (25.0%, 50.9%). Among patients with secondary endpoint data available, median PFS was 19.3 months (95% CI: 8.2, NR) and 33/56 (59%) of patients underwent dose reduction. **Conclusions:** Sunitinib administered in a 2/1 schedule in this study did not result in a lower rate of grade 3 or higher fatigue, diarrhea or HFS when compared to historical data from trials employing a 4/2 schedule. However, efficacy data showed robust response rate and a prolonged PFS, suggestive of long-term tolerability in patients receiving sunitinib on a 2/1 schedule. Evaluation of toxicity kinetics and patient quality of life is ongoing. Clinical trial information: NCT02060370.

4514 Poster Discussion Session; Displayed in Poster Session (Board #192), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Phase II study of individualized sunitinib (SUN) as first-line therapy for metastatic renal cell cancer. *First Author: Georg A. Bjarnason, Sunnybrook Research Institute, Toronto, ON, Canada*

Background: Higher SUN exposure is associated with better outcomes. Patients (pts) with minimum toxicity on the standard schedule do worse than pts needing dosing changes for toxicity. **Methods:** It was hypothesized that toxicity-driven dose/schedule individualization would improve the primary endpoint (PFS) from 8.5 (EFFECT trial) to 14 months (mo), with 99 pts required to detect this with 90% power and 2-sided alpha = 0.05. In a prospective phase II study (eligibility as EFFECT) pts start on 50 mg/day (d) for 28 d with treatment (Rx) breaks reduced to 7 d. If grade-2 toxicity develops before d 28, pts stay on a 50 mg on the next cycle with the number of d on Rx individualized aiming for ≤ grade-2 toxicity. Dose is reduced to 37.5 mg and then 25 mg if pts do not tolerate a 50 mg or 37.5 mg dose respectively for at least 7 d. Pts with minimum toxicity on d 28 are escalated to 62.5 mg and then 75 mg. **Results:** 117 pts were enrolled in 12 centers. Nine non-evaluable pts came off early due to toxicity (5), non-compliance (2) and global deterioration (2). Of 108 pts evaluable for response (IMDC favorable 31.5%, intermediate 58.3%, poor 10.2%. Bone mets 19%, Nephrect 83%), 10 are still on Rx. Dose was escalated in 20 pts (18.5%) to 62.5 mg (12 pts) and then to 75 mg (8 pts). In 49 pts (45.4%) eligible for dose reduction by standard criteria, a 50 mg dose was maintained but for 7 - 24 d, while 7 pts (6.5%) stayed on a 28 d schedule. Dose was reduced to 37.5 mg in 22 pts (20.4% vs. 36 - 63% in 4 large SUN trials) and to 25 mg in 10 pts (9.3% vs. 27 - 43% in 4 trials). Rx was stopped due to toxicity in 10/117 pts (9.3% vs. 15 - 19% in 4 trials). See table for response (ORR, 108 pts) and survival (117 pts) data vs. EFFECT (146 pts). The median followup is 15.5 mo (0.6 -37.9) for PFS and 24.5 mo (4.4 - 47.7) for OS. **Conclusions:** The null hypothesis of the PFS being 8.5 mo can be rejected with a p < 0.001. Individualized dosing is safe and feasible in a multicenter setting and associated with improved dose intensity and one of the best ORR, PFS and OS reported for a TKI. Clinical trial information: NCT01499121.

	Current study	EFFECT 4/2 arm
CR%	2.8 (n = 3)	0
PR%	47.2 (n = 51)	32
CR + PR%	50.0 (n = 54)	32
SD%	40.7 (n = 44)	43
CR+PR+SD%	90.7 (n = 98)	75
PD%	9.2 (n = 10)	25
PFS (mo), (95% CI)	11.9 (9.3-16.5)	8.5 (6.9-11.1)
OS (mo) (95% CI)	35.9 (27.4- not reached)	23.1 (17.4-25.4)

4515 Poster Discussion Session; Displayed in Poster Session (Board #193), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Epacadostat plus pembrolizumab in patients with advanced RCC: Preliminary phase I/II results from ECHO-202/KEYNOTE-037. *First Author: Primo Lara, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Epacadostat (E) is a potent oral inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1), a tryptophan-catabolizing enzyme that induces immune tolerance by T-cell suppression. Preclinical and clinical data suggest that epacadostat has antitumor activity when combined with checkpoint inhibitors, including the PD-1 inhibitor pembrolizumab (P). ECHO-202/KEYNOTE-037 is an ongoing open-label, phase 1/2 (P1/2) study evaluating E + P in multiple tumor types. We report preliminary P1/2 efficacy and safety data for the advanced renal cell carcinoma (RCC) cohort as of a 29OCT2016 data cutoff. **Methods:** Eligible patients (pts) had advanced clear-cell RCC, prior antiangiogenic therapy (tx), and no prior checkpoint inhibitor tx. In P1 dose escalation (3+3+3), pts received E (25, 50, 100, or 300 mg PO BID) + P (2 mg/kg or 200 mg IV Q3W); MTD was not exceeded. E (100 mg BID) + P (200 mg Q3W) dosing was selected for P2 cohort expansion. Response was assessed in RECIST 1.1 evaluable pts. Safety/tolerability was assessed in pts receiving ≥1 E + P dose. **Results:** 33 pts (P1, n = 11; P2, n = 22) were enrolled (median age, 63 years; 70% men; 97% white; MSKCC criteria of favorable, intermediate, and poor in 6%, 64%, and 12% of pts, respectively). Of 30 efficacy-evaluable pts, 63% (n = 19) had 0–1 prior tx and 37% (n = 11) had ≥2 prior tx for advanced disease. ORR (CR+PR) and DCR (CR+PR+SD) for pts with 0–1 prior tx was 47% (9/19; 1 CR, 8 PR) and 58% (11/19; 1 CR, 8 PR, 2 SD), respectively; for pts with ≥2 prior tx, ORR and DCR were 0% and 36% (4/11; all SD). At data cutoff, 9/9 responses were ongoing (range, 1+ to 372+ days). PFS and biomarker analyses are ongoing. TRAEs occurring in ≥10% of the 33 pts included fatigue and rash (36% each); and arthralgia, diarrhea, pruritus, and pyrexia (12% each). Grade ≥3 TRAEs occurred in 15% of pts (none in > 1 pt). Two pts discontinued due to TRAEs (grade 3 autoimmune hepatitis, n = 1; grade 3 aseptic meningitis/headache/nausea/vomiting/anxiety, n = 1). **Conclusions:** E + P was generally well tolerated and associated with encouraging response outcomes in advanced RCC pts with 0–1 prior line of tx. E + P represents a novel immunotherapeutic strategy. A phase 3 RCC study is planned. Clinical trial information: NCT02178722.

4516 Poster Discussion Session; Displayed in Poster Session (Board #194), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Phase II study of pazopanib in patients with von Hippel-Lindau disease. *First Author: Eric Jonasch, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Von Hippel-Lindau disease (VHL) is an autosomal dominant inherited disorder. Affected individuals develop vascular neoplastic lesions in multiple sites including eye, brain, pancreas, adrenal and kidney. Standards of care include surveillance imaging and surgical intervention. We hypothesized that treatment of VHL related lesions with an antiangiogenic agent would result in shrinkage of all lesion types. We chose the multikinase inhibitor pazopanib to test this hypothesis. **Methods:** After obtaining IRB approval, patients with clinical features or genetic confirmation of VHL disease and with measurable lesions were treated with pazopanib 800mg PO daily for two 12-week cycles. Efficacy was determined by RECIST after two cycles. Patients had the option to continue therapy if considered in patient's best interest. Continuous monitoring for any lesion progression and drug discontinuation due to toxicity during the whole period of the treatment was planned. **Results:** Patients were enrolled (N=32) and treated (N=31) between 1/2012 and 6/2016. Median age was 37 (range 19-67). 23 patients had genomically confirmed VHL disease; four had family and personal history but had not undergone genetic testing, and five patients had clinical features of VHL disease and negative genetic testing. A median of two cycles (range 1-12) of therapy was administered. Of 31 evaluable patients, 13 (42%) showed a response, 18 patients had stable disease and no patients had PD as best response. Responses were seen in renal (2 CR and 29 PR/59 total), pancreatic (9 PR/17 total) and CNS 2 PR/49 total) target lesions. The most common side effect was diarrhea (grades 1 and 2) experienced in 14 patients. Twelve patients dose reduced to 600 mg and 6 to 400 mg pazopanib PO daily. Eight patients discontinued therapy due to adverse events of whom 4 experienced transaminitis. One patient experienced a grade V CNS hemorrhage. **Conclusions:** This is the largest prospective VHL disease specific therapeutic study performed to date. Pazopanib resulted in significant and sustained disease control for the majority of VHL patients enrolled on the study, with an acceptable safety profile. This agent may be considered as an alternative to surgical intervention in patients with VHL disease. Clinical trial information: NCT01436227.

4517 Poster Discussion Session; Displayed in Poster Session (Board #195), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Comprehensive genomic profiling (CGP) of advanced papillary renal cell carcinoma (PRCC) to reveal distinctions from TCGA dataset. *First Author: Sumanta K. Pal, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Biologic characterization of PRCC by TCGA reveals alterations in *MET* in type 1 disease, and *CDKN2A*silencing, *SETD2* mutations and *TFE3* fusions in type 2 disease. A limitation of TCGA data is that of 161 pts analyzed, 73% and 3% had M0 and M1 disease, respectively. We present the gene alterations (GA) identified in pts with advanced PRCC.**Methods:** FFPE tissue was obtained from 169 patients with PRCC. Diagnosis and PRCC subtyping was centrally confirmed by 2 board-certified pathologists. DNA was extracted and comprehensive genomic profiling (CGP) was performed (median coverage, 648X) in a CLIA-certified central laboratory. **Results:** Of 169 pts with advanced PRCC, 39 (23%) were type 1, 108 (64%) were type 2 and 22 (13%) were unclassified. 66 samples (39%) were from a metastatic site biopsy, and 103 were from the kidney (61%). An average of 2.4 GA/tumor were detected. In type 1 pts, commonly altered genes were *MET* (33%: 8 activating mutations, 5 amplifications), *TERT* (30%), *CDKN2A/B* (13%), and *EGFR* (8%). In type 2 pts, commonly altered genes were *CDKN2A/B* (18%), *TERT* (18%), *NF2* (13%) and *FH* (13%); *MET*GAs (5 mutations, 3 amplifications) were observed in 7.4% of type 2 pts. *MET* GA was significantly associated with type 1 PRCC (p = 0.0002) and *NF2* GA and alterations in SWI/SNF complex genes were both significantly associated with type2 PRCC (p = 0.02 and p = 0.007, respectively). Overall, frequent alterations were found in genes involved in SWI/SNF complexes (25%), chromatin modification (23%) and cell cycle regulation (22%). RAS/RAF pathway (9%) and PI3K/mTOR pathway (8%). Notable differences with TCGA include higher frequencies of *MET* and *NF2* GAs, association of GAs in the SWI/SNF with type 2 PRCC, and frequent *CDKN2A/B* alteration in both type 1 and type 2 disease. *MET* alteration was lower in metastases vs primary (type 1: 15% vs 38%; type 2: 4% vs 10%). **Conclusions:** In a cohort of PRCC patients slightly larger than the TCGA experience, key differences in CRGA frequency were observed. These likely underscore the marked difference in stage distribution between datasets. Results of this study may inform trials of relevant targeted therapy in metastatic PRCC.

4518 Poster Discussion Session; Displayed in Poster Session (Board #196), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Multiregion sequencing of penile cancer to reveal distinct patterns of heterogeneous actionable mutations. *First Author: Simon Rodney, University College London, London, United Kingdom*

Background: Penile cancer is a rare but mutilating disease. Due to its rarity few studies have investigated the molecular oncogenic changes. There is a huge need to improve the poor outcome of metastatic disease by advancing the standard practice of platinum based therapies. Treatment based on actionable mutations and the potential of immunotherapies may improve clinical outcomes. We present the first analysis of intra-tumour heterogeneity within penile cancer. **Methods:** Tissue samples, greater than 80% purity, were collected from four spatially distinct tumor regions together with matched normal and metastatic tissue. Deep whole exome sequencing was performed on the resulting 48 samples from eight patients. Mutations were called by using Mutect2 and annotated with Annovar. Copy number changes were estimated using Sequenza and phylogenetic trees created using pyclone. **Results:** A mean of 650 single nucleotide variants and insertion/deletion events were discovered per tumor sample. Extensive intra-tumor heterogeneity was found with a wide range of different predicted subclonal architectures. Two distinct patterns were noted: either the acquisition of mutations by the lymph node metastasis was an early event with a lower mutational load, or it was a later event with a high mutational load. In the two instances where patients were negative for human papillomavirus infection, the lymph node metastasis evolved at a later date. However in 5/6 cases of HPV infection, an early subclone developed which potentially led to the lymph node metastasis. Driver mutations in *p53*, *cMET* or *FAT1* were found to be truncal early events in 80% of cases. Actionable mutations in *PIK3CA* and *EGFR* were found to be subclonal in two further samples. **Conclusions:** There is extensive intra- and inter-tumour heterogeneity within penile cancer. The main truncal drivers in penile cancer are *cMET*, *FAT1* and *p53*. Samples infected with human papillomavirus appeared to have a distinct signature in terms of both copy number changes and clonal architecture. Actionable mutations *PIK3CA* and *EGFR* were found to be subclonal in origin. This may have profound effects on the clinical utility of targetable treatments such as tyrosine kinase inhibitors.

4519 Poster Discussion Session; Displayed in Poster Session (Board #197), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Infusional gemcitabine + docetaxel/melphalan/carboplatin (GemDMC) ± bevacizumab (BEV) as an effective high-dose chemotherapy (HDC) regimen for refractory of poor-risk relapsed germ-cell tumors (GCT). *First Author: Yago Nieto, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tandem HDC with carbo/etoposide (CE) is curative for a portion of relapsed GCT pts. However, outcomes of refractory or high-risk relapsed pts remain poor. We tested a new HDC regimen of GemDMC, based on DNA damage repair inhibition. We combined BEV with HDC given their potential synergy and the high vascularity of GCT metastases. **Methods:** Eligibility: Intermediate (int)/high-risk (Beyer Model), creatinine ≤1.8 mg/dL and adequate organ function. HDC included BEV (5 mg/kg) preceding GemDMC (HDC #1) and ifosfamide/CE (ICE) (HDC #2). Following accrual of 42 pts, we amended the trial omitting BEV. The trial was powered to distinguish a target 50% 2-yr RFS from an expected 25% in this population. **Results:** We enrolled 69 male pts in cohorts 1 (BEV, N=42) and 2 (no BEV, N=27) (Table). Pts were heavily pretreated and most had refractory tumors. Main AE: mucositis and renal (4 HDC-related deaths in cohort 1, 1 in cohort 2). Tumor markers normalized in 90% pts with active tumors at HDC. After HDC, 19 pts were in CR and 28 in PRm- (of these, 22 had residual lesions resected with no viable tumor found in 20/22, 2 xRT, 4 monitored). Median f/u = 39 (2-105) mo. The 2-yr RFS rates in cohorts 1 and 2 = 52% and 78%, respectively. Their respective 2-yr OS rates = 55% and 81%. **Conclusions:** Sequential HDC with GemDMC–ICE shows encouraging outcomes in heavily pretreated and refractory GCT, exceeding the anticipated results. Addition of BEV increases toxicity but not tumor control. Clinical trial information: NCT00936936.

	BEV (N=42)	No BEV (N=27)	P
Median age (range)	30 (20 - 49)	28 (19-56)	.9
1◦ testis / mediast / retroperit (%)	76 / 14 / 10	85 / 11 / 4	.7
Median # prior regimens	4 (2 - 9)	4 (2-8)	.7
Tumor markers at rel/PD: median (range)			
AFP (N=29)	395 (25–377,426)	1,942 (17-750,303)	.4
B-HCG (N=34)	344 (26–89,000)	1,482 (22-24,579)	.5
Prior progression-free interval (%)			
≤3 mo	90	89	.9
>3 mo	10	11	
# prior rel/PD (%)			
1	24	37	.2
2	18	30	
3-6	58	33	
Cisplatin sensitive (%):			
Absol refr	39	29	.2
Refr	45	39	
Sensit	16	32	
% prior surgery of mets	60	67	.6
% prior xRT	21	30	.6
Resp at HDC #1 (%):			
No resp (PD / SD)	58 (53 / 5)	32 (26 / 6)	.02
PRm+	18	55	
PRm-	13	10	
CR	11	3	
Risk (%):			
Beyer: Int / high	48 / 52	62 / 38	.3
IPS: Int / high / very high	5 / 14 / 81	7 / 22 / 70	.9

4520 Poster Discussion Session; Displayed in Poster Session (Board #198), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Phase II trial of pembrolizumab in patients (pts) with incurable platinum refractory germ cell tumors (GCT). *First Author: Nabil Adra, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Despite remarkable results with salvage standard-dose (SDCT) or high-dose chemotherapy (HDCT), about 15% of pts with relapsed GCT are incurable. Immune therapy with Pembrolizumab is a novel approach for salvage in pts with metastatic GCT. **Methods:** Single arm phase 2 trial investigating pembrolizumab 200mg IV Q3weeks until disease progression in pts with relapsed GCT and no curable options. Pts age≥18 with metastatic GCT who progressed after first line cisplatin-based chemotherapy and after at least 1 salvage regimen (HDCT or SDCT) were eligible. Centrally assessed PD-L1 on tumor infiltrating immune cells using PD-L1 (22C3) assay was scored as 0, 1, 2, 3 along with PD-L1 expression score (H-score) incorporating intensity of staining. Pts were eligible irrespective of PD-L1 expression status. The primary endpoint was overall response rate using immune-related response criteria. Simon's 2-stage design required response in ≥ 1/12 pts to proceed to stage 2 enrolling 8 more pts for a total of 20. **Results:** 12 male pts were enrolled. Median age 38 (range, 27-55). All pts had non-seminoma. Primary tumor site was testis in 11 pts and mediastinum in 1. Median AFP 615 (range, 1-32,760) and hCG 4 (range, 0.6-37,096). 5 pts had late relapse (> 2years). Median number of previous chemotherapy regimens was 3 (range, 1-6). 6 pts received prior HDCT. 2 pts had positive PD-L1 staining (H-score 90 and 170). Median number of deliverable pembrolizumab doses was 2 (range, 1-8). There were 5 grade 3 adverse events, with 3 events possibly related to study treatment (chest pain, hyperglycemia, abdominal pain). No partial or complete responses were observed. 2 pts achieved stable disease for 12 and 9 weeks respectively; 10 pts had progression of disease as their best response. The 2 pts with stable disease had continued rising AFP level despite radiographic stability; both had negative PD-L1 staining. **Conclusions:** This is the first reported trial evaluating immune checkpoint inhibitors in GCT. Although 2 pts had stable disease, each had rising tumor markers suggesting continued treatment resistance. Pembrolizumab is well tolerated but does not appear to have clinically meaningful single-agent activity in refractory GCT. Clinical trial information: NCT02499952.

4521 Poster Discussion Session; Displayed in Poster Session (Board #199), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

FDG PET scan (PET) positive residual lesions after chemotherapy (chemo) for metastatic seminoma: Results of an International Global Germ Cell Cancer Group (G3) registry. *First Author: Richard Cathomas, Kantonsspital, Chur, Switzerland*

Background: Residual disease is a frequent finding after chemo for metastatic seminoma. Watchful waiting is recommended for residual lesions < 3 cm or lesions ≥3 cm with negative PET. Data on the optimal management of PET positive residual lesions is lacking. **Methods:** A retrospective analysis within the G3 Group identified 91 patients (pts) from 9 countries with metastatic seminoma and residual PET positive lesions after chemo. Pts with elevated AFP (> 2xULN) or non-seminomatous components at diagnosis were excluded. We analyzed the post PET management chosen and its impact on relapse and survival. **Results:** Median follow-up was 29 (IQR 10 – 64) months. Median age at diagnosis was 41 (range 19 – 69) years. The primary tumor was gonadal in 68 pts (76%), retroperitoneal in 12 pts (13%) and mediastinal in 10 pts (11%). Prior to chemo the median size of the largest metastasis was 10 (range 1.4 – 23) cm, 67 pts (74%) had elevated LDH and 51 pts (57%) elevated HCG. Median diameter of the largest residual mass was 4.8 (range 1.1 – 14) cm mainly located in the retroperitoneum (77%), pelvis (15%), mediastinum (16%) or lung (4%). Median time from last day of chemo to PET was 7 (IQR 4 – 10) weeks. Post PET management was repeated imaging in 46 pts (51%), resection in 32 pts (35%), biopsy in 9 pts (10%) and radiotherapy in 4 pts (4%). Histology of the resected specimen was necrosis only in 25 (78%) and vital seminoma in 7 cases (22%). No biopsy revealed vital seminoma. Relapses occurred after a median of 3.7 (IQR 2.5 – 4.9) months in 16 pts (18%): 2/9 (22%) after biopsy, 12/46 (26%) on repeated imaging and 2/32 (6%) after resection (one necrosis, one < 10% vital seminoma). Site of relapse was the area of residual disease in 14 pts (88%) and additional distant relapse (one bone, one lung) in 2 pts (12%). All relapsed pts received successful salvage chemo apart from one who died from treatment and two pts who are alive with ongoing treatment. **Conclusions:** PET positive post chemo residual lesions in seminoma pts are false positive in about 75%. Relapses in PET positive pts occur early and can be salvaged with chemo. Further analysis is needed to identify risk factors for relapse.

4522 Poster Discussion Session; Displayed in Poster Session (Board #200), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Association of on-treatment plasma HGF levels with overall survival (OS) in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (INF) +/- bevacizumab (BEV): Results from CALGB 90206 (Alliance). *First Author: Daniel J. George, Duke Cancer Institute, Duke University Medical Center, Durham, NC*

Background: Elevated baseline HGF levels were associated with shorter OS in pts treated with BEV+INF. We evaluated on-treatment HGF levels to describe treatment-related changes and associations with outcome. **Methods:** We analyzed baseline EDTA plasma samples from 310 pts (148 INF; 162 BEV+INF) using an optimized multiplex ELISA platform for HGF at baseline and after 4-weeks (wks) on treatment. Primary endpoint of this analysis was OS. The Kaplan-Meier estimated the OS distribution and the proportional hazards model tested the prognostic importance of change at 4-wks from baseline in HGF levels in predicting OS, adjusting for treatment arm, bone metastases and stratification variables. **Results:** The median baseline HGF level in 310 pts was 161.4 pg/ml. Elevated HGF at 4-wks (>median) was associated with a worse OS (median OS = 14 vs 27 months; adjusted hazard ratio (HR)= 1.75, p< 0.0001). Only 9/155 pts (5.8%) with baseline HGF levels ≤ median developed elevated HGF (>median) at 4-wks; 66/155 pts (43%) with baseline HGF levels >median lowered HGF (<median) at 4-wks from baseline. Compared to pts with persistently elevated HGF levels, a decline in HGF levels at 4-wks (< median) was associated with improved OS (19 vs 13 months, adjusted HR=1.41, p=0.043). **Conclusions:** In RCC pts with low baseline HGF levels (< median), levels remain consistently low and are associated with improved OS. Conversely, in pts with high baseline HGF levels results are split; some patients continue to have high levels on treatment and are associated with a worse OS, suggesting that, HGF predicts for therapeutic benefit and represents a potential mechanism of resistance. Support: U10CA180821, U10CA180882. Clinical trial information: NCT00072046.

4523 Poster Discussion Session; Displayed in Poster Session (Board #201), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Integrated biomarker analysis for 412 renal cell cancer (RCC) patients (pts) treated on the phase 3 COMPARZ trial: Correlating common mutation events in *PBRM1* and *BAP1* with angiogenesis expression signatures and outcomes on tyrosine kinase inhibitor (TKI) therapy. *First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In RCC biology mutations in *PBRM1* and *BAP1*are largely non-overlapping and collectively affect >50% of pts. How and through which mechanism they influence disease kinetics is poorly understood. Sunitinib and pazopanib inhibit angiogenesis, a key driver in RCC. We analyzed mutation status and gene expression signatures in a large cohort of pts receiving first-line sunitinib or pazopanib on the COMPARZ trial. **Methods:** RNA and DNA were extracted from archival tissue. *PBRM1* and *BAP1*mutation status was determined via a custom exon-targeted platform. Transcriptome analysis was done using Affymetrix GeneChip HTA 2.0. We computed a 43 gene angiogenesis expression score with previously reported dynamic response to VEGF-directed therapy in xenograft models (Masiero, Cancer Cell 2013). DNA and RNA findings were correlated with clinical outcomes using parametric and non-parametric tests. **Results:** 412 pts contributed tumor RNA, 377 pts DNA; 362 pts both. PBRM1 and BAP1 were mutated (MT) in 44% and 15% of pts, respectively. Presence of *PBRM1*mutations correlated with superior PFS (p=0.008) and OS (p=0.004) on log-rank test, and PBRM1 mutation rate was higher in pts with objective response than those with progression (Fisher's Exact, p=0.012). In contrast, pts with MT BAP1 had inferior OS compared to those whose were wild type (WT) (log-rank, p=0.012). Across all 412 pts angiogenesis score associated favorably with outcome on uni and multivariate analyses (Cox proportional hazard regression, OS p<0.001 and PFS p<0.005); scores were higher in 123 pts with objective response than 81 pts with progression as best response (Mann-Whitney, p=0.009). Angiogenesis scores were higher in PBRM1 MT vs WT patients (Mann-Whitney, p<0.001), but lower in BAP1 MT vs WT patients (p<0.001). **Conclusions:** PBRM1 and BAP1 mutations appear to have opposite effects in advanced RCC. Loss of PBRM1 enhances the pro-angiogenic microenvironment of RCC with favorable effects on response to TKI; BAP1 loss associates with decreased angiogenic signaling and adverse outcome to TKI. Clinical trial information: NCT00720941.

4524 Poster Discussion Session; Displayed in Poster Session (Board #202), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Discovery and prevalence of cancer-susceptibility germline mutations (Mts) in patients (Pts) with advanced renal cell carcinoma (aRCC). *First Author: Maria Isabel Carlo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: About 5% of RCC is thought to be familial, but recent studies suggest this may be an underestimate (Int. J. Cancer;100:476). We studied the prevalence of germline cancer-susceptibility mts in pts with aRCC. **Methods:** Pts with aRCC (stage III or IV), unselected for suspicion of an inherited cancer syndrome, were offered germline testing for 76 cancer-associated genes between 10/2015 and 12/2016. Germline sequencing was done as part of MSK-IMPACT, a matched tumor-normal next-generation sequencing platform. **Results:** 203/213 pts accepted testing (median age 55, range 13-55) of whom 73% had clear cell RCC (ccRCC), 92% had metastases, 20% were early onset (≤46 yrs at diagnosis), 9% had a family history of RCC, 6% multifocal RCC at diagnosis, and 15% ≥2 primary malignancies. Pathogenic/likely pathogenic mts were found in 35 pts (17%): 12 (6%) with mts in genes associated with familial RCC; 10 (5%) mts in high/moderate penetrance genes not linked to RCC (Table).13 (6%) had mts in genes of low/uncertain penetrance or for autosomal recessive disease. Mts were present in 15% of ccRCC and 19% of non-ccRCC. Mts were not more common in pts with early onset, family history, multifocal RCC, or ≥2 malignancies ($p>0.1$ for each by Fisher's exact test). Notably, 4/12 pts with mts in familial RCC genes did not meet the American College of Medical Genetics (ACMG) criteria for testing (1 each *VHL*, *BAP1*, *SDHA*, *FH*). Prevalence of *CHEK2* mts was compared to population databases (ExAC); *CHEK2* conferred a relative risk of 10.9 ($p< 0.002$; CI=3.9-24.7) for RCC. **Conclusions:** 17% of aRCC pts had a germline mutation in a cancer-associated gene of which 33% of the high penetrance RCC germline mts were not identified using standard clinical criteria, providing rationale for broad testing. Once the increased risk is confirmed, *CHEK2* should be included in RCC genetic testing.

Selected Genes	Frequency (%)	# of ccRCC cases	# of nccRCC cases	Age at Dx
CHEK2	6 (3.0)	5**	2**	(52-69)
FH	5 (2.5)	0	5	(25-53)
BAP1	3 (1.5)	3*	2*	(44-64)
MET	1 (0.5)	0	1	67
SDHA/SDHB	2 (1.0)	1	1	35-55
VHL	1 (0.5)	1	0	57
MSH6	1 (0.5)	1	0	60
BRCA2	1 (0.5)	1	0	60
PALB2	1 (0.5)	0	1	28
RAD51C	1 (0.5)	1	0	57

*2 pts with *BAP1* had both ccRCC and nccRCC; **1 pt with *CHEK2* had both ccRCC and nccRCC

4525 Poster Session (Board #203), Sun, 8:00 AM-11:30 AM

Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma (UC). *First Author: Noah M. Hahn, Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: Anti-PD-L1 immunotherapy shows promising clinical activity in UC. We report a planned update of the safety and efficacy of durvalumab in patients (pts) with locally advanced/metastatic UC from a multicenter, phase 1/2 open-label study. **Methods:** Pts received durvalumab 10 mg/kg every 2 weeks (Q2W) up to 12 months (mo) or until unacceptable toxicity, progression, or starting another anticancer therapy. Primary endpoints were safety and confirmed objective response rate (ORR) by blinded independent central review (RECIST v1.1). Duration of response (DoR), progression-free survival (PFS) and overall survival (OS) were key secondary endpoints. Tumor PD-L1 expression was assessed by Ventana SP263 assay (PD-L1 high = ≥25% PD-L1 expression on tumor or immune cells). **Results:** As of Oct 24, 2016 (data cutoff [DCO]), 191 pts had received treatment. Median follow-up was 5.78 mo (range, 0.4–25.9). All pts had Stage 4 disease and 99.5% had prior anticancer therapy (95.3% post-platinum). As of DCO, ORR was 17.8% (34/191), including 7 CRs, with responses observed regardless of PD-L1 status (Table). Responses occurred early (median time to response, 1.41 mo) and were durable (median DoR not reached [NR]). Median PFS and OS were 1.5 mo (95% CI, 1.4, 1.9) and 18.2 mo (95% CI, 8.1, not estimable [NE]), respectively; the 1-year OS rate was 55.0% (95% CI, 43.9%, 64.7%). Grade 3/4 treatment-related AEs occurred in 6.8% of pts; grade 3/4 immune-mediated (im)AEs occurred in 4 pts; 2 pts discontinued due to imAEs (acute kidney injury and autoimmune hepatitis). **Conclusions:** Durvalumab 10 mg/kg Q2W shows favorable clinical activity and an excellent safety profile in locally advanced/metastatic UC pts. Table. Antitumor activity in UC pts, including second-line or greater (≥2L) post-platinum pts Clinical trial information: NCT01693562.

All UC	Total N = 191	PD-L1 high n = 98	PD-L1 low/negative n = 79	PD-L1 unknown n = 14
Confirmed ORR, % (95% CI)	17.8 (12.7, 24.0)	27.6 (19.0, 37.5)	5.1 (1.4, 12.5)	21.4 (4.7, 50.8)
CR, %	3.7	4.1	2.5	7.1
PR, %	14.1	23.5	2.5	14.3
Median DoR, mo (min, max)	NR (0.9+, 19.9+)	NR (0.9+, 19.9+)	12.25 (1.9+, 12.3+)	NR (2.3+, 2.6+)
≥2L post-platinum UC	n = 182	n = 95	n = 73	n = 14
Confirmed ORR, % (95% CI)	17.6 (12.3, 23.9)	27.4 (18.7, 37.5)	4.1 (0.9, 11.5)	21.4 (4.7, 50.8)

4526 Poster Session (Board #204), Sun, 8:00 AM-11:30 AM

Health-related quality of life as a marker of treatment benefit with nivolumab in platinum-refractory patients with metastatic or unresectable urothelial carcinoma from CheckMate 275. *First Author: Andrea Necchi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: CheckMate 275 (NCT02387996), a phase II, single-arm study of nivolumab (3 mg/kg every 2 weeks) treatment in platinum-refractory patients (pts) with metastatic urothelial carcinoma, showed an objective response rate of 19.6% (95% CI, 15.0%–24.9%) with manageable toxicity. The objective of this analysis was to examine the impact of nivolumab on health-related quality of life (HRQoL) in the study. **Methods:** HRQoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and three-level EQ-5D (EQ-5D-3L) and visual analog scale (VAS). Questionnaires were completed at baseline and every 8 weeks thereafter for the first 48 weeks. The analysis cohort included pts with scores recorded at baseline and ≥1 postbaseline assessments while on treatment. Data were analyzed using mixed models, adjusting for baseline score. **Results:** Of the 270 patients treated with nivolumab, 168 (62%) had an assessment at baseline and ≥1 postbaseline assessment and were included in HRQoL analyses. Completion rates at baseline were 97% for both questionnaires. Statistically significant ($P< 0.05$) improvements in mean scores for the EORTC QLQ-C30 subscales measuring role, emotional, and social functioning; global health status/quality of life; nausea/vomiting; pain; dyspnea; insomnia; appetite loss; constipation; and diarrhea were observed at ≥1 time points. With the exception of cognitive functioning, no significant worsening in subscale scores was observed in the EORTC QLQ-C30. Statistically significant and clinically meaningful improvement (based on a minimally important difference of 7) in EQ-5D VAS was noted between weeks 17 and 41. EQ-5D-3L utility index scores based on the UK tariff remained stable during treatment. **Conclusions:** Results of CheckMate 275 indicate that pts with metastatic or unresectable urothelial carcinoma whose disease progressed or recurred after treatment with a platinum agent exhibited stable, or in some cases statistically significantly improved, HRQoL while being treated with nivolumab, as measured by EORTC QLQ-C30 and EQ-5D-3L. Clinical trial information: NCT02387996.

4527 Poster Session (Board #205), Sun, 8:00 AM-11:30 AM

Phase I/II trial of cetuximab with 5-fluorouracil and mitomycin C concurrent with radiotherapy in patients with muscle invasive bladder cancer. *First Author: Syed A. Hussain, University of Liverpool, Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, United Kingdom*

Background: This phase I/II trial assessed the safety, feasibility and efficacy of cetuximab (Cet) in combination with 5-fluorouracil (5FU) and mitomycin C (MMC) with concurrent radiotherapy (RT) for the treatment of muscle invasive bladder cancer (MIBC). BC2001 trial has previously reported significant improvement in locoregional control in patients (pts) with MIBC who were randomised to synchronous chemo-RT compared to RT alone (James, Hussain, Hall et al NEJM 2012). Results for phase I have been reported previously. This abstract reports the combined results of phases I/II. **Methods:** From September 2012 to October 2016, 33 pts were recruited (7 pts to phase I from 2 UK centres and 26 patients to phase II from 5 UK centres). Pts received loading dose of Cet 400 mg/m^2 followed by weekly Cet 250 mg/m^2 for 7 weeks, continuous infusion 5FU 500mg/m^2/day during fractions 1-5 and 16-20 of RT and MMC 12mg/m^{2}on day 1 in combination with radical RT 64 Gy in 32 fractions. Neoadjuvant chemotherapy was mandatory in phase I but optional in phase II. Primary outcomes in phase I were feasibility and toxicity. Primary outcome in phase II was 3 month pathological complete response (CR) rate, secondary outcomes included toxicity, progression free survival (PFS) and overall survival (OS). **Results:** Median age of pts was 70 (range 46.9-85.6). Treatment completion rates in phase I were RT 100%, 5FU 100 %, MMC 100%, Cet 96%. Of the 28 analysable pts, phase II primary outcome data was available for 25 pts at the time of analysis with a 3 month pathological CR rate of 88%. 5 local progressions and 4 deaths were reported. 12 pts suffered at least one SAE. Grade 4 toxicities observed were dyspnoea, atrial fibrillation, interstitial pneumonitis, sepsis, thromboembolism, neutropenia and palpitations. The commonest grade 3 toxicities were skin rash, diarrhoea, low platelet count, low white blood cell count, fever and haematuria. The most common grade 1 and 2 toxicities were diarrhoea and skin rash. Data on PFS and OS will be presented. **Conclusions:** It was feasible and safe to add cetuximab to full dose chemo-RT with 5FU/MMC. The CR rate is encouraging and further randomised studies with this combination are warranted. Clinical trial information: ISRCTN80733590.

4528 Poster Session (Board #206), Sun, 8:00 AM-11:30 AM

Updated efficacy and safety of avelumab in metastatic urothelial carcinoma (mUC): Pooled analysis from 2 cohorts of the phase 1b Javelin solid tumor study. *First Author: Andrea B. Apolo, Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Avelumab, a fully human anti–PD-L1 IgG1 antibody, has shown promising efficacy and safety in 2 cohorts of patients (pts) with mUC. We now report updated data from a pooled analysis of these pts with mUC from JAVELIN Solid Tumor (NCT01772004) and further characterize the clinical activity of avelumab in this disease. **Methods:** Pts with mUC progressed after platinum-based therapy or cisplatin ineligible received avelumab 10 mg/kg 1-hour IV Q2W. Tumors were assessed every 6 weeks by independent review (RECIST v1.1). Endpoints included objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety (NCI CTCAE v4.0), and tumor PD-L1 expression. **Results:** As of Jun 9, 2016, 249 pts had received avelumab for a median of 12 weeks (range 2-92) and were followed up for a minimum of 6 weeks. Primary tumor site was upper tract (renal pelvis/ureter) in 23.3% and lower tract (bladder/urethra) in 76.7%. 242 pts (97.2%) had progressed on prior platinum therapy and 7 pts (2.8%) were platinum naive. In 161 post-platinum pts with ≥6 months of follow-up, confirmed ORR was 17.4% (95% CI 11.9-24.1; complete response in 6.2%) with a disease control rate of 39.8%. Response was ongoing in 23/28 responders at data cut (82.1%; median DOR not reached), and the 24-week durable response rate was 92.3% (95% CI 72.6-98.0). Responses occurred across PD-L1 expression levels tested (≥5% and < 5% tumor cell–staining [25.4% and 13.2%]). In all post-platinum pts (n = 242), median PFS was 6.6 weeks (95% CI 6.1-11.6), median OS was 7.4 months (95% CI 5.7-10.3) and 6-month OS rate was 54.9 (95% CI 47.7-61.7). Treatment-related adverse events (TRAE) of any grade occurred in 166/249 pts (66.7%); most common (≥10%) were infusion-related reaction (22.9%, all grade ≤2) and fatigue (16.1%). 21 pts (8.4%) had a grade ≥3 TRAE (fatigue [1.6%] and asthenia [0.8%] in > 1 pt). 34 pts (13.7%) had an immune-related AE (grade ≥3 in 2.4%). There was 1 treatment-related death (pneumonitis). **Conclusions:** Avelumab was well tolerated and showed durable responses in heavily pretreated pts with mUC, irrespective of tumor PD-L1 expression status. Clinical trial information: NCT01772004.

4529 Poster Session (Board #207), Sun, 8:00 AM-11:30 AM

Molecular profiling of small cell bladder cancer (SCBC) to reveal gene expression determinants of an aggressive phenotype. *First Author: Vadim S. Koshkin, Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH*

Background: SCBC is rare and its underlying biology poorly understood. Molecular profiling can shed light on the biology and identify treatment targets and biomarkers. **Methods:** A retrospective review of 63 patients (pts) with biopsy-confirmed SCBC at Cleveland Clinic (1994-2015) was performed. Percentage of small cell component (SC%) was defined by independent pathology review. DLL3 and PD-L1 protein expression were measured by IHC in 53 pts. Gene expression analysis was done in 38 primary SCBC tumor samples, 1 metastatic sample, and 5 normal bladder tissue samples (44 total) from the same cohort using HTG EdgeSeq OBP Assay with probes for 2568 genes. Analysis was performed via the RNAseq workflow (Partek Genomics Suite). **Results:** Among 63 identified pts, median age was 71 (39-90), 83% were men, median SC% was 100% (range 5-100%), median follow-up was 16.6 months and estimated median overall survival (OS) was 22.8 months. Unsupervised hierarchical clustering of gene expression patterns from 44 samples produced 4 distinct clusters. Pts with tumors in cluster 1 (that also included normal samples) did not have metastasis at diagnosis or distant recurrence, both of which were over-represented in the other 3 clusters. Kaplan-Meier analysis revealed a trend towards longer OS in cluster 1 patients (log rank p = 0.065). Higher gene expression of PRC1, NCAM1 (CD56) and DLL3 correlated with higher SC%, as did lower gene expression of ERBB2, PD-L1 and HPGD (p < 0.01). PD-L1 protein expression (≥1% cells) was noted in 30% of pts but did not correlate with outcome, SC%, DLL3 protein expression, or PD-L1 gene expression. DLL3 protein expression (≥1% cells) was noted in 68% of pts and DLL3 > 10% correlated with decreased OS (p = .03). Higher DLL3 protein expression correlated with DLL3 gene expression (Spearman r = 0.70, p < .01) and with SC% (r = .33, p = .01). **Conclusions:** This is the first study to reveal distinct gene expression patterns that define aggressive behavior, metastatic potential and outcomes in SCBC. The prognostic value of differential gene expression networks and the presence of underlying genomic and epigenetic alterations is the subject of ongoing prospective validation in a larger cohort.

4530 Poster Session (Board #208), Sun, 8:00 AM-11:30 AM

Health-related quality of life (HRQoL) of pembrolizumab (pembro) vs chemotherapy (chemo) for previously treated advanced urothelial cancer (UC) in KEYNOTE-045. *First Author: Ronald De Wit, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: In KEYNOTE-045 (NCT02256436) (N = 542), pembro 200 mg Q3W significantly improved OS over investigator's choice of paclitaxel, docetaxel, or vinflunine as second-line therapy for advanced UC following platinum-based chemo (HR 0.73; $P = 0.0022$). Fewer treatment-related AEs were reported with pembro. We present results of the prespecified HRQoL analysis of KEYNOTE-045. **Methods:** The EORTC QLQ-C30 HRQoL instrument was administered electronically at cycles 1–4, then every 2 cycles for up to 1 y and 30 d after discontinuation. The key HRQoL end points were 1) change from baseline to wk 15 and 2) time to deterioration (TTD) (defined as ≥10-point decrease from baseline) in the QLQ-C30 global health status/QoL score. HRQoL was assessed in patients (pts) who received ≥1 dose of assigned study treatment and completed ≥1 HRQoL instrument (N = 520). Score change from baseline was compared using a constrained longitudinal data analysis model. TTD was compared using a stratified log-rank test and Cox proportional hazards model. **Results:** Baseline global health status/QoL scores were similar between arms. HRQoL compliance at wk 15 was 88% for both arms. From baseline to wk 15, scores were stable for pembro (n = 266) (least squares [LS] mean +0.75 [95% CI −2.34 to +3.83]) but worsened for chemo (n = 254) (LS mean −8.30 [95% CI −11.76 to −4.83]); the difference in LS means between arms was 9.05 (95% CI 4.61-13.48; nominal 2-sided $P < 0.001$). At wk 15, pts without PD had improved scores with pembro but worsened scores with chemo (LS mean +5.97 vs −4.31), while pts with PD had less worsening with pembro (LS mean −3.54 vs −13.95). TTD was prolonged with pembro (HR 0.70; 95% CI 0.55-0.90; nominal 1-sided $P = 0.002$; median 3.5 mo vs 2.2 mo). Rates of improvement (defined as ≥10-point increase from baseline) at wk 15 were 31.2% with pembro and 22.0% with chemo; rates of deterioration were 28.9% and 40.6%, respectively. **Conclusions:** Pembro was associated with substantially better HRQoL for a longer duration than investigator-choice chemo in pts with previously treated advanced UC. Along with superior OS, these data support pembro as a new standard-of-care in this population. Clinical trial information: NCT02256436.

4531 Poster Session (Board #209), Sun, 8:00 AM-11:30 AM

Immune response results from vesigenurtacel-l (HS-410) in combination with BCG from a randomized phase 2 trial in patients with non-muscle invasive bladder cancer (NMIBC). *First Author: Gary D. Steinberg, Section of Urology, Department of Surgery, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: Vesigenurtacel-L (HS-410) is a vaccine comprised of an allogeneic cell line, selected for high expression from a series of bladder tumor antigens, and transfected with gp96-Ig. Cell-secreted gp96-Ig delivers these cell-derived antigens to a recipient's own antigen presenting cells, activating CD8+ cytotoxic T cells. Here we present the secondary immune outcomes from a randomized Phase 2 trial with HS-410 in combination with BCG in NMIBC. Trial ID NCT02010203. **Methods:** 78 patients with intermediate- (n = 5) or high-risk (n = 73) NMIBC who are either BCG-naïve or recurrent, with or without carcinoma in situ (CIS), were enrolled 1:1:1 to one of two doses of HS-410 (either 10^6 or 10^7cells/dose) or placebo in combination with 6 weeks of induction BCG, followed by 6 more weeks of HS-410 in the induction phase. Maintenance treatment consisted of 3-weekly treatments at the following timepoints: 3 mo., 6 mo., 12 mo. Concurrently, 16 patients (1 int. risk, 15 high-risk) were enrolled in an open-label monotherapy HS-410 arm for patients who did not receive BCG. The primary endpoint was 1-year RFS. Secondary immune evaluations include ELISPOT, tumor IHC, tumor antigen profiling, flow cytometry, urine cytokine analysis, and T cell receptor sequencing. **Results:** HS-410 treatment was well tolerated; AE profiles were similar across the treatment arms. HS-410 antigen expression showed prominent overlap with patient tumors. IFNγ ELISPOT assay demonstrated a high baseline response to HS-410; responses to overlapping peptide pools of HS-410 derived antigens defined immune responders (doubling of IFNγ-secreting cells). IHC demonstrated that ~60% of NMIBC patient tumor biopsies were TIL negative at baseline (n = 84), but that only ~15% of tumor biopsies were TIL negative post treatment (n = 40). Thus, TIL status may be used to define a responder and non-responder population to HS-410. **Conclusions:** Vesigenurtacel-L is well-tolerated, and immunologic responses consistent with vaccine mechanism of action may correlate with efficacy and suggest future biomarkers. Vesigenurtacel-L warrants further investigation as a potential treatment for NMIBC. Clinical trial information: NCT02010203.

4532 Poster Session (Board #210), Sun, 8:00 AM-11:30 AM

Atezolizumab (atezo) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC): Safety analysis from an expanded access study. *First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute, Boston, MA*

Background: A majority of mUC pts progress on standard platinum-based chemo regimens. Atezo (anti–PD-L1) was approved in the US for mUC in the post-platinum setting. Here we report the preliminary safety results from an expanded access program conducted to grant access to atezo, prior to commercial availability, to a broader range of mUC pts than are typically eligible for Phase I-III studies. **Methods:** From Nov 2015-Aug 2016, this study (NCT02589717) enrolled mUC pts who progressed during or following platinum. Atezo was given 1200 mg IV q3w, and pts could be treated post RECIST v1.1 PD until lack of clinical benefit (per investigator). Safety and clinical activity were key endpoints. PD-L1 expression on immune cells (IC) was assessed with the VENTANA SP142 IHC assay on the first 73 pts prior to protocol amendment omitting this requirement. This study was ended early following FDA approval of atezo. **Results:** 218 pts were enrolled at 36 sites in the US, with 214 treated pts comprising the safety/efficacy population (Table). Median treatment duration was 9 wks (range 3-26), corresponding to a median of 3 doses of atezo (range 1-8). Overall, 89% of pts had an AE. Treatment-related AEs (TRAEs) occurred in 46% (any Gr) and 7% (Gr3-4) of pts; 2 treatment-related Gr 5 AEs were seen (ileus; acute respiratory failure). TRAEs ≥ 5% were fatigue, decreased appetite and anemia. TRAEs leading to dose interruption or discontinuation occurred in 11% and 6% of pts, respectively. Investigator-assessed RECIST v1.1 ORR was 15% (95% CI: 9, 23), and disease control rate (ORR + SD) was 49% (95% CI: 40, 59). Additional clinical data will be reported. **Conclusions:** In this expanded access study, atezo was administered to > 200 mUC pts. Overall, atezo was safe and tolerable, supporting its use in a wider platinum-based population. Clinical trial information: NCT02589717.

Baseline characteristics.

Median age (range)	69 y (42-92)
Male	76%
Primary tumor[a]	
Bladder | Urethra	78% | 2%
Renal pelvis | Ureter	9% | 8%
Visceral mets[b] **(liver)**	66% (25%)
ECOG PS	
0 | 1	43% | 48%
2 | 3	8% | 1%
Hb < 10 g/dL	19%
CrCl < 60 mL/min	48%
PD-L1 IC2/3 | 0/1[c]	51% | 47%
Median prior agents for mUC (range)[d]	2 (1-8)
Prior cis | carbo[d]	45% | 55%

[a] Other: 4%; [b] n = 202 evaluable; [c] n = 71/73 pts evaluable; [d] n = 218

4533 Poster Session (Board #211), Sun, 8:00 AM-11:30 AM

Comparison of somatic mutation profiles from cell free DNA (cfDNA) versus tissue in metastatic urothelial carcinoma (mUC). *First Author: Michael L. Cheng, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Next-generation sequencing (NGS) of cfDNA is an emerging non-invasive strategy to define tumor mutation profiles that counters spatial and temporal limitations of sequencing single tissue specimens. We examined the feasibility of NGS of cfDNA in mUC and compared mutation profiles from cfDNA to results of tissue NGS previously performed in the clinical setting. **Methods:** Plasma cfDNA was collected in mUC pts and analyzed using a capture-based NGS assay (MSK-IMPACT) targeting 341-468 genes. NGS profiles from cfDNA and archival tumor tissue (using the same assay) were analyzed in parallel with an established bioinformatics pipeline to identify somatic variants. **Results:** In 26 pts, NGS analysis of cfDNA detected ≥1 somatic mutations (range 1-21) in 69% (18/26). For 15 pts, NGS data was available from archival tissue (11 primary tumors, 3 metastases, and matched primary/metastatic tissue in 1 case). The interval between cfDNA and tissue collection ranged from 35 days to > 4 yrs. 73% (11/15) of pts received intervening treatment, including 47% (7/15) with chemotherapy, 67% (10/15) with immunotherapy, and 40% (6/15) with both. In 40% (6/15), cfDNA harbored alterations not found in archival tumor tissue. In 73% (11/15), some mutations within archival tissue were not detected in cfDNA, including hotspot HER2 S310F and FGFR3 S249C mutations. Tumor and cfDNA mutation profiles were identical in 20% (3/15), with the tumor/cfDNA interval in this group ranging from 35 days to < 1.5 yrs. Somatic alterations including hotspot ERCC2 P463A and PIK3CA E545K mutations were detected in cfDNA from 3 pts where archival tumor tissue NGS failed. Thus, cfDNA identified new mutations in 50% (9/18) of pts for whom cfDNA identified somatic mutations and tissue NGS was previously attempted. **Conclusions:** NGS of cfDNA from mUC pts is feasible and successfully detected actionable alterations when archival tumor sequencing failed. The differences between tumor and cfDNA mutation profiles in many pts may reflect tumor evolution or intratumor heterogeneity. Mutation profiles in mUC may be incompletely assessed with NGS of archival tissue, and further investigation of plasma cfDNA for genomic profiling is warranted.

4534 Poster Session (Board #212), Sun, 8:00 AM-11:30 AM

Circulating tumor (ct)-DNA alterations in urothelial/bladder cancer (UC/BC): Updates on a dynamic genomic landscape. *First Author: Petros Grivas, Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH*

Background: Cell-free ctDNA may be potentially actionable, may have prognostic/predictive role and evolve after therapy. We updated our analysis of our retrospective study to shed light on UC/BC biology. **Methods:** Patients (pts) with UC/BC with ctDNA analysis for potentially actionable alterations using Guardant360 were identified. A 70-gene ctDNA next generation sequencing panel from a CLIA-licensed, CAP-accredited laboratory (Guardant Health, Inc.) offers complete exon sequencing for 29 cancer genes, critical exons in 39 genes and amplifications (16 genes), fusions (6 genes) and indels (3 genes) harvested from 10 mL of peripheral blood. Descriptive statistics were used. **Results:** There were 246 pts with 276 samples. At least 1 alteration was detected in 249 (90%) samples. Median age at time of ctDNA collection was 67 years (39-85), 78% men, median number of alterations per sample was 3.5 (1-35) most pts had MIBC. In MIBC pts, the most common alterations at the 1st ctDNA sample were in *TP53* (52%), *PI3KCA* (18%) *ARID1A* (17%), *FGFR2* (15%), *MET* & *NF1* (14%), EGFR (13%), BRAF (12%), FGFR3 (11%), RAF1 (10%), BRCA1 & CCNE1 (9%). In MIBC pts, the most common genes with increased copy number were *RAF1* & *CCNE1* (8%), *ERBB2* & *PI3KCA* (7%), *EGFR, BRAF, FGFR1, MYC* (each 5%), *MET* (4%), *KRAS* (3%). Most common altered pathways included TP53 signaling (56%), RAS/RAF/MEK/ERK (51%), RTK (48%), cell cycle (38%), FGFR family (34%), DNA damage response (25%), PI3KCA/AKT/mTOR (23%) and chromatin remodeling (17%). Interestingly, FGFR3 and RAS alterations were mutually exclusive in most cases, but each may co-occur with *TP53*alterations. 54 serial ctDNA samples from 24 pts (18 pts with 2 samples; 6 pts with 3 samples) revealed persistent, lost and new gene alterations. **Conclusions:** ctDNA was detected in 90% of pts and alterations were similar to those previously seen in UC tumor tissue. Tumor heterogeneity, interim therapy, genomic instability and clonal evolution can explain differences in serial samples. Correlation assessment with prior therapies and outcomes is being pursued to inform trial designs. Prospective validation, assessment of ctDNA concordance with tumor tissue DNA, and evaluation of clinical utility is warranted.

4535 Poster Session (Board #213), Sun, 8:00 AM-11:30 AM

Spectrum of tumor mutational load (TML) in genitourinary cancers (GU CA). *First Author: Muhammad Azam Hussain, Penn State College of Medicine, Hershey, PA*

Background: Immunotherapy (IO) is now standard of care for bladder and kidney cancer (CA) and is investigational in other GU CA such as prostate and germ cell CA. Tumor mutational load (TML) has correlated with response to IO in several tumor types. Herein, we explore TML across different histological subtypes in GU CA. In addition, we also assess the correlation between TML and PD-L1 status. **Methods:** 544 GU specimens were identified: bladder, 145; kidney, 164; prostate, 221; penile, 2; testicular, 12. TML was calculated using somatic non-synonymous missense mutations from a 592-gene panel (Illumina NextSeq). A high TML was > 17 mutations/MB. PD-L1 (SP142) was done depending tumor availability. **Results:** High TML was more prevalent in bladder CA (14.5%, 21/145) compared to other GU CA. Urothelial carcinomas had a noticeably high TML while squamous histology had a pronounced PD-L1 expression (Figure 1). A comparison of TML-high (n=15) versus TML-low (n=76) urothelial bladder CA showed the following differences (Figure 2). TML was rare in kidney CA (1.8%, 1/57); PD-L1 was high in sarcomatoid (33.3%, 5/15), CDC/RMC (28.6%, 2/7). Prostate adenocarcinoma had few TML-high (2.3%, 5/219) or PD-L1 expressing tumors (1.4%, 3/208). Tumors of penile or testicular origin lacked high TML and PD-L1 expression. No correlation was found between a high TML and PD-L1 expression. **Conclusions:** TML varied considerably amongst GU CA. As in other CA, TML-high scores did not predict PD-L1 expression and vice versa. Comprehension of the underlying biology may assist in determining which CA may respond better to IO.

Table 1: TML, PD-L1 in bladder CA subtypes.

Histology	TML	PD-L1
Adenocarcinoma	0% (0/11)	0% (0/11)
Neuroendocrine/Small Cell	0% (0/2)	0% (0/2)
Squamous Cell	12.5% (1/8)	37.5% (3/8)
Urothelial	16.5% (15/91)	20.5% (18/88)
Urothelial + Squamous	6.7% (1/15)	46.7% (7/15)
Not Otherwise Specified	22.2% (4/18)	27.8% (5/18)

Table 2: Gene mutation frequency in bladder CA.

Biomarker	Mutated Rate in TML-High Cohort	Mutated Rate in TML-Low Cohort	p-value
ARID1A*	22.2% (2/9)	0.0% (0/35)	0.004
ATM	13.3% (2/15)	2.6% (2/76)	0.065
BRCA2	20.0% (3/15)	1.3% (1/76)	0.001
PIK3CA	26.7% (4/15)	9.2% (7/76)	0.058
TSC1	13.3% (2/15)	1.3% (1/75)	0.018

* Lower # of interpretable *ARID1A*.

4536 Poster Session (Board #214), Sun, 8:00 AM-11:30 AM

Randomized study of intravesical chemotherapy using pirarubicin in patients with non-muscle-invasive bladder cancer in Japan: Comparing one immediate postoperative intravesical chemotherapy with short-term adjuvant intravesical chemotherapy after TURBT: Subanalysis in patients with intermediate risk. *First Author: Yoshio Naya, Meiji University of Integrative Medicine, Nantan, Japan*

Background: The objective is to evaluate the efficacy defining of 2-year tumor recurrence free rate of intravesical chemotherapy using pirarubicin (THP) for patients with intermediate risk. **Methods:** Between October 2010 and January 2015, 206 patients were enrolled in this study and finally 113 were randomized to one immediate postoperative intravesical instillation of THP 30mg (Group A), or additional intravesical instillation of THP 30mg weekly for 8 weeks after single postoperative instillation (Group B). The recurrent risk was stratified using EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2009 update. Of 113, 100 with intermediate risk were analyzed in this study. The patients were examined by cystoscopy and urine cytology every 3 months after trans urethral resection to determine bladder tumor recurrence. The primary endpoint was 2 year-recurrence-free survival rates. A statistical analysis was performed by SAS (SAS Institute Inc., Cary, USA). **Results:** The 2-year recurrence free survival rates were 66.2% in Group A and 86.1% in Group B, respectively (log rank test, p = 0.0043). In patients with recurrence score between 5 and 9, the 2-year recurrence free survival was 92.3% in Group B and 22.2% in Group A (log rank test, p = 0.0013). Cox regression analysis revealed that only additional instillation of THP was significant independent factor for recurrence free rate in patients with intermediate risk. There was no patient with progression during this period. Frequent adverse effects were frequent urination and micturition pain without severe adverse effect (Grade 3 or more). Limitation of this study is a failure to enroll sufficient number for statistical analysis. **Conclusions:** Additional instillation of THP 30mg weekly for 8 weeks reduced the risk of tumor recurrence without severe toxicity in NMIBC patients with intermediate recurrent risk.

4537 Poster Session (Board #215), Sun, 8:00 AM-11:30 AM

Intra-patient heterogeneity in urothelial cancer (UC) circulating tumor cells (CTC) and PDL1 expression to identify biomarkers of response and new therapeutic targets: A pilot study. *First Author: Waddah Arafat, University of Wisconsin, Madison, WI*

Background: Recent use of immune checkpoint inhibitors (CI) has improved overall survival (OS) in a subset of patients (pts) with metastatic UC. Intra-patient tumoral heterogeneity and epithelial-to-mesenchymal transition has been hypothesized as a driver of treatment resistance to both chemotherapy and CI in UC. There is a critical need to evaluate heterogeneity in UC for biomarkers of treatment response and new therapeutic targets. Trop2 is hypothesized to play a role in UC progression and is the target of a new antibody-drug conjugate, IMMU-132 that is being tested in UC trials. We report the phenotypic comparison of PDL1 expression among CTC sub-populations in UC pts. **Methods:** Peripheral blood samples were collected from pts with UC treated at Cleveland Clinic and U. of Wisconsin. Immunomagnetic capture and CTC enumeration using both EpCAM and Trop2 from matched blood samples was performed in the VERSA platform. Protein expression for PDL1 in these CTC populations was quantified. Longitudinal analysis of UC pts treated with chemotherapy or CI is ongoing. **Results:** CTC were captured using EpCAM and Trop2 in all 10 pts in our initial cohort. The frequency of Trop2 CTC was higher than EpCAM CTC with a mean of 248 Trop2 CTC (range 2-1885) compared to 76 EpCAM CTC (range 1-632). PDL1 expression was more frequent in Trop2 CTC than EpCAM CTC. In two pts progressing on Atezolizumab, Trop2 CTC had a higher frequency of PDL1 expression compared to EpCAM CTC (85% vs 2% in pt 1 and 2% vs 0% in pt 2). In pts followed longitudinally, Trop2 CTC dropped from 1885 to 1 in a pt with response to Atezolizumab and PDL1+ CTC declined from 4 to 0. After 1 cycle of Carbo/Gem in another pt, EpCAM CTC declined from 46 to 3 while Trop2 CTC from 116 to 47. **Conclusions:** This is the first report of CTC heterogeneity in pts with UC identifying high frequency of Trop2 CTCs with variable expression of PDL1 across different pts. Early results from longitudinal analysis suggest CTC as potential predictive / pharmacodynamic biomarkers of treatment response. Prospective data validation in larger cohort is ongoing, while IMMU-132 clinical trials in UC may provide context for future validation.

4538 Poster Session (Board #216), Sun, 8:00 AM-11:30 AM

Survival outcomes in elderly patients with muscle invasive bladder cancer: An analysis of the National Cancer Database. *First Author: Benjamin Walker Fischer-Valuck, Washington University School of Medicine in St. Louis, Department of Radiation Oncology, St. Louis, MO*

Background: Many elderly patients are precluded from radical cystectomy (RC) due to existing comorbidities or morbidities associated with RC. Chemoradiation therapy (CRT) is an alternative treatment in this population, but remains widely under-utilized with many receiving chemotherapy (CT) or radiation therapy (RT) alone. This population-based analysis sought to determine if CMT has similar overall survival (OS) to RC, and if CRT is associated with improved OS compared to monotherapy in these patients. **Methods:** We queried the National Cancer Database (NCDB) for all newly diagnosed MIBC (cT2-T4a N0 M0) cases in patients aged 80 years or older from 2004 to 2013. All included patients underwent TURBT followed by RC, RT alone, CT alone, CRT, or no further treatment. Only patients with radiation doses ($>=$ 50Gy) were included as receiving RT. Kaplan-Meier, log-rank, and multivariate Cox proportional hazards regression was performed with OS as the primary outcome. **Results:** 10,055 patients aged $>=$ 80 years were identified. 1,588 underwent RC, 839 received RT, 1,013 received CT, 1,035 had CRT, and 5580 had no further treatment. Mean age was 85.1 years (range, 80-90). 82.1% of patients had Stage II disease. Mean follow-up was 27.6 months (range, 0-137.8). Mean survival of the entire cohort was 28.0 months (95% CI, 27.2-28.8). Mean survival was 43.8 months (95% CI, 41.2-46.3) for patients with RC and 40.8 months (95% CI, 38.2-43.3) for CRT (P = 0.85). Mean survival was 29.1 months (95% CI, 26.8-31.4) and 30.7 months (95% CI, 28.2-33.2) for RT alone vs. CT alone, respectively ($P < 0.0001$ for both RC and CRT comparisons). 5-year OS for CT alone, RT alone, CRT, and RC was 15.7%, 15.1%, 24.0% and 29.6%, respectively. Multivariate analysis adjusting for age, year of diagnosis, gender, race, treatment location, treatment facility, insurance status, Charlson/Deyo Score, grade, and stage demonstrated an OS benefit in favor of CRT (HR 0.70; 95% CI, 0.63-0.77; $P < 0.0001$) and RC (HR 0.69; 95% CI, 0.63-0.76; $P < 0.0001$). **Conclusions:** For elderly patients with MIBC, both RC and CRT were associated with improved OS compared to CT or RT alone. CRT has similar OS compared to RC, and could be considered standard treatment in this population.

4539 Poster Session (Board #217), Sun, 8:00 AM-11:30 AM

Effectiveness of the Moreau strain of Bacillus Calmette-Guerin (BCG) for nonmuscle invasive bladder cancer. *First Author: Daher Cezar Chade, São Paulo Cancer Institute, University of Sao Paulo, São Paulo, Brazil*

Background: Intravesical instillation therapy of Bacillus Calmette-Guerin (BCG) for intermediate and high-risk non-muscle invasive bladder cancer (NMIBC) after complete transurethral resection has been widely shown to be more effective than any other adjuvant treatment. However, there are several different BCG strains not appropriately evaluated in clinical setting, but in current use. BCG Moreau is by far the most utilized strain in Brazil and has been recently introduced to the European market to cover the issue of BCG shortage, but there is insufficient data regarding its oncologic efficacy. **Methods:** We retrospectively analyzed 336 consecutive patients, who received adjuvant intravesical instillation therapy with BCG Moreau for intermediate- and high-risk NMIBC between January 2005 and February 2015 at a single institution. The end points of this study were time to first recurrence and progression to muscle-invasive disease. **Results:** Median age was 62 years (interquartile range 54-76, mean 64.3 years). In addition to induction BCG therapy, 228 (67.9%) patients received maintenance BCG. However, 35 (15.4%) patients interrupted maintenance BCG due to toxicity. Overall, after at least a complete induction BCG therapy, 87 (25.9%) patients presented with disease recurrence and 33 (9.8%) patients had disease progression. When analyzing on patients who received BCG maintenance in addition to induction therapy, 31 (13.6%) patients had disease recurrence and 10 (4.4%) had disease progression. The 5-year recurrence-free survival and progression-free survival rate was 69.8% (95% CI 52.8-77.2) and 86.2% (95% CI 69.9-93.2), respectively. **Conclusions:** BCG Moreau has shown to be safe and effective as adjuvant intravesical treatment in intermediate and high-risk NMIBC patients. Since results are comparable to other strains, wider use of BCG Moreau may be encouraged and prospective clinical trials stimulated for higher level of evidence.

4540 Poster Session (Board #218), Sun, 8:00 AM-11:30 AM

Safety and efficacy of docetaxel + b-701, a selective inhibitor of FGFR3, in subjects with advanced or metastatic urothelial carcinoma. *First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute, Boston, MA*

Background: Patients w/ locally advanced or metastatic urothelial carcinoma (UCC) have a poor prognosis. Prior to atezolizumab's approval, there were no approved treatments (txs) for pts who progressed after chemotherapy. Even w/ immune checkpoint inhibitors, most pts require additional txs. FGFR3 is frequently overexpressed in UCC and 15-20% of pts w/ advanced disease have tumors w/ FGFR3 gene mutations or fusions. B-701 (formerly R3Mab) is a fully human monoclonal antibody against FGFR3 that blocks activation of the wildtype and genetically activated receptor. NCT02401542 is a phase (ph) 1b/2 study designed to evaluate the safety and efficacy of B-701 plus docetaxel (D) in advanced UCC pts. **Methods:** The study has a lead-in (n=20 pts) and a randomized ph (n=201). Eligible pts: Stage IV UCC, relapsed/refractory to 1 or 2 prior chemotherapy regimens not including taxanes with ECOG 0-1. Txs: B-701 at 25 mg/kg q3w (+ loading dose on C1D8) and D at 75 mg/m^2 q3w. Efficacy assessed by RECIST 1.1. Primary obj: PFS and safety. Secondary obj: overall response rate (ORR); duration of response (DOR); disease control rate (DCR); overall survival (OS). Exploratory obj: association of FGFR3 status w/ efficacy and AEs. **Results:** As of 20 Jan 2017, 19 pts enrolled to lead-in ph w/median age 66 yrs, ECOG 1 58%, Hgb $<$10 gm/dL 5%, liver mets 26% and $\geq$ 2 prior regimens 63%. 17 evaluable for PFS/ORR. 5 pts w/ FGFR3 mut or TACC3-fus. Gr $\geq$3 AEs occurring in $\geq$2 pts: decreased neutrophils (26.3%), neutropenia (10.5%), decreased WBCs (10.5%). 2 pts had D dose reductions and 1 pt discontinued tx due to AE (disseminated intravascular coagulation). **Conclusions:** Preliminary results show that B-701 combines safely and effectively with D in UCC, with the combination being well tolerated and showing promising ORR and PFS in pts w/ FGFR3 mut/fus. The protocol has been amended to add Cohorts 2 (B-701+D) and 3 (B-701) (n=20 pts/cohort) for pts w/ FGFR3 mut/fus+ tumors only. Clinical trial information: NCT02401542.

	All (N=17)	FGFR3 mut/fus (N=5)
Best Response	1CR;2PRs	1CR;1PR
DOR	NR	NR
PFS (wks)	13.0+ (95% CI: 6-47.6+)	NR
Median OS (wks)	28.7 (95% CI:13.4 -37.6+)	NR

4541 Poster Session (Board #219), Sun, 8:00 AM-11:30 AM

Neoadjuvant chemotherapy followed by concomitant chemoradiation with gemcitabine in muscle invasive bladder cancer. *First Author: Abdul Mateen, Department of Radiotherapy and Oncology, MINAR Cancer Hospital, Multan, Pakistan*

Background: Urinary bladder cancer is one of the most prevelent genitourinay cancer in Pakistan. It is especially common in population that consumes smokeless tobacco. Advanced stage at diagnosis is usual presentaion due to illiteracy, poverty and lack of primary health facilities. The study was aimed to optimize treatment of muscle invasive bladder cancer in poor resource country. **Methods:** A total of 65 patients were enrolled for the study. All patients had muscle invasive disease on transurethral resection. Patients were to in stage range from T2-3, N0 and M0 to be selected. The patients were planned for gemcitabine and cisplatinum (GC) every three weeks in a dose of 1000 mg/m^2 and 40 mg/m^2 on D1 and D8 of each cycle respectively. Ultrasonography was performed to assess for any bladder mass at this point. The patients with no visible tumor were planned for whole bladder external radiotherapy (ERT) along with weekly gemcitabine 100 mg/m^2. A total of 63 Gray (Gy) was planned with 1.8 Gy per fraction and five fractions a week. Gemcitabine was given on 1st day of every week during whole course of ERT. Treatment interruptions were allowed depending upon chemotherapy and ERT related toxicity. Primary end point was to assess disease free survival (DFS) while overall survival was also assessed as a secondary end point. **Results:** 54 patients (83%) were available for assessment to treatment and to assess DFS and OS. Rest of the patients 11/65 (17%) were excluded from the analysis due to inability to complete the treatment. Five patients (8%) showed disease recurrence during treatment and were switched to other treatment. 11 patients (20%) showed bowel, 15 patients (28%) showed bladder and 8 patients (15%) showed hematological related grade 1-2 toxicity. Four year DFS and OS were 43% and 52% respectively. Mean and median DFS (year) were 3.16$\pm$0.36 (95% confidence interval [CI] 2.91 to 3.42) and 2.68$\pm$0.54 (95% CI 2.41 to 2.93) respectively. Mean and median OS (year) were 3.95$\pm$0.43 (95% CI 3.67 to 4.21) and 3.55$\pm$0.31 (95% CI 3.37 to 3.76) respectively. **Conclusions:** Neoadjuvant chemotherapy with GC followed by concomitant CRT using gemcitabine is an excellent choice for bladder preservation in poor resource countries.

4542 Poster Session (Board #220), Sun, 8:00 AM-11:30 AM

Cabazitaxel in patients with locally advanced or metastatic transitional cell carcinoma who developed disease progression within 12 months of platinum based chemotherapy: Results of a phase II trial—CAB-B1. *First Author: Anjali Zarkar, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom*

Background: There is a paucity of chemotherapy options for the treatment of patients who have relapsed following platinum based chemotherapy (CT). Cabazitaxel is a new taxane that showed in-vivo antiproliferative activity on resistant cell lines. **Methods:** CAB-B1 was a single centre phase II randomised controlled trial of Cabazitaxel (CAB; 25mg/m^2 q3 week for 6 cycles) versus best supportive care (BSC) in patients (pts) with histologically proven transitional cell carcinoma (TCC), locally advanced or metastatic, who had received platinum based treatment and recurred within 12 months of the last cycle of CT. Primary outcome was overall response rate (ORR) using RESIST. Secondary outcomes were Progression Free Survival (PFS), Overall Survival (OS), Quality of Life assessment, safety and tolerability. A total of 96 pts required to detect differences in ORR from 5% to 30%; 80% power; 5% alpha level; 10% dropouts. Stopping rules, using Simon's two stage optimal design to assess the individual effectiveness of CAB, required at least 1 ORR from 10 pts on CAB during 1st stage (i.e. total of 20 pts randomised) and 4 from 29 CAB pts in 2nd stage (assuming lower ORR limit of 0.05, target ORR of 0.20, 80% power, 5% alpha level). The trial was supported by grant from Sanofi. **Results:** Between January 2013 and October 2016, 20 pts were randomised (10 on each arm). 75% males; median age 68 years; 65% had recurred within 6 months of previous CT. BSC included paclitaxel CT for 9 pts and radiotherapy for 1 pt. 8 pts completed 6 cycles of CT (3 on CAB; 5 on BSC). 6 pts on each arm were evaluated for response after having 2/3 cycles; 2 pts had an ORR on CAB and 1 pt on BSC. 14 pts have died of disease (8 on CAB; 6 on BSC).Median OS was 5.6 months (95% confidence interval (CI) 0.7-15.2) for CAB pts and 8.2 months (95% CI 1.0-8.8) for BSC pts. Median PFS was 4.4 months (95% CI 0.7-9.4) for CAB pts and 4.1 months (95% CI 1.0-6.8) for BSC pts. **Conclusions:** It has been hard to recruit these poorly patients within a single centre, but CAB-B1 successfully reached the efficacy target for the 1st stage, showing that there could be a role for CAB in these pts. Clinical trial information: NCT01668459.

4543 Poster Session (Board #221), Sun, 8:00 AM-11:30 AM

Predictors of urinary diversion choice in patients with bladder cancer in integrated care settings. *First Author: Marilyn L. Kwan, Division of Research, Kaiser Permanente Northern California, Oakland, CA*

Background: Annually over 10,000 people with bladder cancer in the US have cystectomy surgery with urinary diversion (UD). While ileal conduit (IC) is most common, neobladder (NB) and continent pouch (CP) are options to retain urinary continence. Few studies in community settings have examined patient and clinician factors associated with UD choice. **Methods:** Eligible patients were age $\geq$21 with a cystectomy and UD for bladder cancer from 1/2010 to 6/2015 in 3 West coast Kaiser Permanente regions. Data were obtained from the EHR and chart review.We useda mixed effects logistic regression model with surgeon as a random effect, and region as a fixed effect, to identify patient factors associated with UD choice (IC vs NB/CP). We also examined whether surgeon factors were associated with UD choice above and beyond patient factors. **Results:** Among 1063 patients, 80% had an IC. IC patients were older (mean age 72 vs. 62), more likely female (24% vs. 16%), more likely diagnosed with AJCC stage III/IV (41% vs. 28%), and had higher Charlson comorbidity score (median 4 vs. 3) than NB/CP patients. Surgeons accounted for a sizable portion of the variability in UD choice (ICC = .26). The model with patient factors showed good fit (AUC = .93, Hosmer-Lemeshow test p = .22). Including surgeon factors (annual cystectomy volume, specialty training, clinical tenure) did not improve model fit (p = .32). Female sex, eGFR $<$ 45, 4+ comorbidities, and stage III/IV tumors were associated with higher odds of receiving an IC vs. NB/CP (Table). **Conclusions:** Patient factors predict much of the variability in UD choice. The high ICC indicates that surgeons also contribute to this process, but surgeon factors we examined were not uniquely associated with IC. Future studies should explore more nuanced surgeon factors, such as how UD choice is shaped by personal beliefs about UD and likely outcomes.

Patient factors that predict IC vs NB/CP in bladder cancer patients.

	OR	95% CI
Age (10 year units)	4.5	3.3, 6.2
Female vs Male (Ref)	2.4	1.3, 4.3
Kidney Function (eGFR)		
< 45	4.0	1.3, 12.5
45-60	0.8	0.4, 1.9
61-89	0.8	0.4, 1.8
> 90	Ref	
Charlson Comorbidity		
2	Ref	
3	1.2	0.7, 2.3
4+	2.5	1.5, 4.4
AJCC Stage		
0a	0.7	0.3, 1.6
0is	0.8	0.3, 2.4
I	0.9	0.5, 1.7
II	Ref	
III	2.1	1.0, 4.5
IV	3.9	1.9, 7.9

4544 Poster Session (Board #222), Sun, 8:00 AM-11:30 AM

Activity of RX-3117, an oral antimetabolite nucleoside, in subjects with metastatic bladder cancer resistant to gemcitabine: Preliminary results of a phase Ia/IIb study. *First Author: Jun Gong, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: RX-3117 is an oral small molecule antimetabolite, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117 has shown efficacy in xenograft models of gemcitabine resistant pancreatic, bladder and colorectal cancer. Preliminary data from an analysis of a phase 1b/2a clinical study of RX3117 in metastatic bladder cancer is described. **Methods:** This phase 1b/2a study (NCT02030067) was designed to evaluate safety, tolerability and efficacy following treatment with 700 mg administered orally once-daily for 5 consecutive days with 2 days off per week for 3 weeks with 1 week off in each 4 week cycle in a 2-stage design. Eligible subjects (aged $\geq$ 18 years) were those with relapsed/refractory metastatic bladder cancer with any number of prior therapies. Prior therapy with platinum-based chemotherapy was required. The primary endpoint was to assess the efficacy and safety of RX-3117 in metastatic bladder cancer, with secondary aims of evaluating PFS and CBR. **Results:** With 9 subjects enrolled, median age was 66 years, ECOG PS was 0-1. All subjects had received gemcitabine/cisplatin in the perioperative or metastatic setting, and 4 subjects had received 3 or more prior therapies. The most frequent related adverse events were anemia, mild-moderate fatigue, vomiting and diarrhea. No dose limiting toxicities were observed. PFS and CBR will be presented at the meeting, as 5 subjects continue to receive therapy at the time of this submission. One subject continues on treatment at 139 days with persistent stable disease. Molecular profiling of his bladder tumor showed alterations in *ARID1A*, *FBXW7*, *FGFR3*, *NF1*, and *TERT*. The patient previously responded to an FGFR3 inhibitor but progressed after 9 months, with ctDNA assessments showing incurrence of *TP53* alteration. Clinical benefit with RX-3117 was achieved in spite of incurrence of this alteration. **Conclusions:** RX-3117 demonstrated an excellent safety profile, and prolonged stable disease was seen in 1 subject who failed prior cisplatin/gemcitabine and FGFR3 inhibition. Activity persisted despite development a putative resistance alteration detected by ctDNA. Clinical trial information: NCT02030067.

4545 Poster Session (Board #223), Sun, 8:00 AM-11:30 AM

The clinical role of purified protein derivative skin test reaction in patients with non-muscle invasive bladder cancer treated with bacillus-Calmette Guerin. *First Author: Eiji Kikuchi, Department of Urology, Keio University School of Medicine, Tokyo, Japan*

Background: We investigated the association between purified protein derivative (PPD) skin test reaction prior to BCG therapy and clinical outcomes, both oncological outcomes and occurrence of side effects, in BCG-naïve non-muscle invasive bladder cancer (NMIBC) patients. **Methods:** A total of 288 NMIBC patients who received PPD skin test prior to BCG therapy were included. The PPD skin test reaction was categorized into three groups: positive, slightly positive, and negative. The presence of an induration was positive. If an induration was absent, an erythema 10 mm or more and less than 10 mm corresponds to slightly positive and negative, respectively. **Results:** Sixty-six (22.9%), 149 (51.7%), and 73 (25.3%) patients had positive, slightly positive, and negative PPD skin test results, respectively. The 5-year recurrence-free survival rate of patients with a positive PPD skin test was 89.4$\pm$4.1%, which was significantly higher than that of patients with slightly positive (65.5$\pm$4.2%, $p = 0.001$) and negative (56.4$\pm$6.6%, $p < 0.001$) results. Multivariate Cox regression analysis demonstrated that a positive PPD skin test was independently associated with tumor recurrence (Hazard ratio of 0.213, $p < 0.001$) but not with stage progression. The occurrence rate of major side effects in patients with a positive BCG skin test (33.3%) was significantly higher than that in patients with slightly positive (26.8%) and negative PPD skin tests (13.7%). The incidence rate of fever persisting beyond 2 days or fever of $\geq$38°C in patients with a positive PPD skin test (18.2%) was significantly higher than that in patients with slightly positive (8.7%) and negative PPD skin tests (4.1%). **Conclusions:** NMIBC patients with a positive PPD skin test and who were treated with BCG therapy had a significantly lower tumor recurrence rate and higher incidence of major side effects such as fever persisting beyond 2 days or fever of $\geq$38°C. Our findings suggest that PPD skin test prior to BCG therapy can predict clinical outcomes following BCG therapy and provide useful information regarding who would experience a strong therapeutic effect for BCG therapy and BCG-related major side effects.

4546 Poster Session (Board #224), Sun, 8:00 AM-11:30 AM

Oncological outcomes of intravesical gemcitabine and docetaxel for select patients with high grade recurrent NMIBC. *First Author: Niv Milbar, The James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD*

Background: Bacillus Calmette-Guerin (BCG) unresponsive patients with Non-Muscle Invasive Bladder Cancer (NMIBC) who prefer bladder preservation over Radical Cystectomy (RC) or are poor surgical candidates may be offered intravesical therapies. 2nd line intravesical Gemcitabine (GEM) combined with Docetaxel (DOCE) has been offered at Johns Hopkins Hospital (JHH). Our objective was to evaluate JHH experience with GEM/DOCE, and specifically to address appropriate endpoints for 2nd-line therapies in NMIBC. **Methods:** 33 patients who received full induction courses of GEM/DOCE since 2011, per the protocol adapted from Michael O'Donnell at U. Iowa, were identified in the IRB-approved JHH NMIBC database. Multivariable logistic regression determined factors associated with LG and HG recurrence. Cox proportional hazard models evaluated risk factors for disease free survival (DFS) and HG recurrence-free survival (HG-RFS). **Results:** Median DFS was 6.5 months with 42% 1-year and 24% 2-year DFS. Median HG-RFS was 17.1 months with 56% 1-year and 42% 2- year HG-RFS. Median HG-RFS among patients who initiated GEM/DOCE with HG pathology was 15.7 months, with 51% 1-year HG-RFS and 34% 2-year HG-RFS. Within initial HG-NMIBC presentation, 46% (13/28) had HG recurrence. 80% (4/5) of patients with initial LgTa had LG recurrence and 20% (1/5) had HG recurrence. There were no significant predictors for HG-RFS or DFS. There were 5 LG recurrences, and 16 HG recurrences, with 6 progressions among these. 7 patients underwent RC at a median of 14.9 months. **Conclusions:** GEM/DOCE is a well-tolerated alternative to immediate RC for highly selected patients with HG-NMIBC. As anticipated, including LG recurrence as an endpoint made GEM/DOCE appear less efficacious. However, since standard of care for LG recurrence is further intravesical therapy and recurrence does not result in worse cancer outcomes, it may not be an appropriate endpoint. Future studies of 2nd line therapies for NMIBC should identify endpoints based on clinically meaningful outcomes of interest.

4547 Poster Session (Board #225), Sun, 8:00 AM-11:30 AM

ATM/RB1 mutations to predict shorter overall survival (OS) in bladder cancer. *First Author: Monika Joshi, Penn State Milton S. Hershey Medical Center, Hershey, PA*

Background: DNA repair defect plays an important role in tumorigenesis, progression and treatment outcomes of urothelial cancer. Somatic mutations of ATM/RB1 genes are frequently found in urothelial cancer and have been associated with a better response to cisplatin-based neoadjuvant chemotherapy. However, their prognostic value overall in urothelial cancer have not been determined. **Methods:** Exome sequencing data of 130 urothelial bladder cancer patients (pts) from The Cancer Genome Atlas (TCGA) dataset were analyzed as a discovery cohort to determine the prognostic value of ATM and RB1 mutations. Results from discovery dataset were further validated by an independent cohort of 79 advanced urothelial cancer pts who received comprehensive genomic sequencing for urothelial cancer with FoundationOne. OS was measured from time of initial diagnosis and Cox proportional hazard regression analysis was performed to calculate the hazard ratio (HR) and 95% confidence interval (CI). **Results:** In the discovery dataset, somatic mutations of ATM/RB1 genes were present in 24% of pts and were associated with significantly shorter OS [all stages: adjusted HR = 2.67, 95% CI, 1.45–4.92, P = 0.002; stage II-III only: adjHR = 2.76, 95% CI, 1.23–6.20, P = 0.014]. There was high mutation load in pts carrying ATM/RB1 mutations (median mutation count: 196 versus 160, P = 0.09). In the validation (stage IV) dataset, ATM/RB1 mutations were present in 31.7% of pts and tended to associate with shorter OS (adjHR = 1.97, 95% CI, 0.89–4.40, P = 0.094) and higher mutation load (median mutation load: 8.1 versus 7.2 per Mb, P = 0.136), although statistical significance was not reached. **Conclusions:** These results suggest that ATM/RB1 mutations may be considered as a poor prognostic biomarker in unselected urothelial cancer pts and may correlate with higher mutational load. Further studies are required to determine patient characteristics that can further stratify prognosis based on ATM/RB1 mutation status, and evaluate the potential predictive role of ATM/RB1 mutation status in response to immunotherapy.

4548 Poster Session (Board #226), Sun, 8:00 AM-11:30 AM

Myeloid derived suppressor cells (MDSC) and inflammatory biomarkers in metastatic urothelial carcinoma (mUC). *First Author: Moshe Chaim Ornstein, Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH*

Background: MDSC are potent immunosuppressive cells with prognostic implications in many solid tumors. We previously reported significant correlations between MDSC and clinicopathologic features in localized UC. We hypothesized that different MDSC populations may correlate with inflammatory biomarkers and clinicopathologic features in mUC. **Methods:** Peripheral blood samples were collected from 46 mUC pts. MDSCs were measured in fresh unfractionated whole blood (WB) and in peripheral blood mononuclear cells (PBMC). MDSCs were identified by flow cytometry in WB and defined as LinloCD33+/HLADR- [(T)otal MDSC]. MDSC subsets were defined as (G)ranulocytic (CD15+CD14-), (M)onocytic (CD15-CD14+), (I)mmature (CD15-CD14-), or CD11b+. MDSC populations were presented as % of live nucleated blood cells and as absolute numbers from WB. Spearman correlations (r) and Wilcoxon rank sum test were used to assess correlations between MDSC populations & clinicopathologic factors. **Results:** Of 46 pts:78% men, median age at diagnosis 69 (31-83), 33% never smokers, 76% pure UC, 76% bladder primary, 28% prior intravesical therapy, 35% prior neoadjuvant chemotherapy, 56% prior cystectomy, 83% overweight/obese. G-MDSC was the predominant subset in WB (43%) and PBMC (39%), although M-MDSC were almost equally predominant in PBMC (35%). There was a correlation between the WB and PBMC values of T-, I-, and M- MDSC ($p \leq 0.05$). Higher % WB I-MDSC correlated with lower blood neutrophil/lymphocyte ratio (NLR) ($p = 0.009$), while higher WB G-MDSC and %PBMC G-MDSC were associated with higher NLR ($p = 0.03$ and $p = 0.02$, respectively). Higher I-MDSC / G-MDSC ratio was associated with lower NLR ($r = -0.35$, $p = .02$) and with various clinicopathologic parameters. **Conclusions:** HigherI-MDSC / G-MDSC ratio correlates inversely with NLR, which is considered an inflammatory biomarker and had prognostic value in other studies. The mechanism of MDSC interaction with inflammatory response in mUC pts merits evaluation and is being investigated in a larger cohort of UC pts on chemotherapy or immunotherapy (with longer follow up).

4549 Poster Session (Board #227), Sun, 8:00 AM-11:30 AM

Incidence of secondary malignancies (SM) in patients (pts) with germ cell tumors (GCT) who received high-dose chemotherapy (HDCT): A retrospective study from the European Society for Blood and Marrow Transplantation (EBMT) database. *First Author: Simona Secondino, Medical Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

Background: Little is still known about the incidence of SM in young adult pts with GCT after HDCT, owing to the rarity of the disease, and the need for registries with long term follow-up (FUP) data. In Europe, the EBMT may provide a suitable platform for such retrospective analyses. **Methods:** Criteria for patient selection included diagnosis of GCT, adult male gender, ≥2yr of FUP after the administration of HDCT. Summary statistics were used to describe pt characteristics and outcomes. χ^2 tests were used to compare groups according to the length of FUP. Kaplan-Meier estimates were used to estimate overall survival (OS). Univariable Cox regression analyses examined clinical factors potentially associated with OS. Survival times were calculated from the HDCT administration date. To estimate the probability of developing SM, the cumulative incidence of SM was calculated for all pts. **Results:** From 1981 to 2014, 9,153 autografts, accounting for 5,100 pts, have been registered. Of them, 1,855 had ≥2yr of FUP. Among the latter, a total of 56 cases of SM were identified (3.0%). 28 (50%) had solid SM, 22 (39.3%) hematologic (hem) SM (5 had uncoded SM). Median age at first HDCT was 34 years (IQR: 30-42), median age at development of SM was 42 (37-51). 26 pts (46.4%) received single HDCT cycle, 22 (39.3%) multiple HDCT cycles (8 unknown). 31 pts had ≥5 yr FUP, 25 pts 2-5 yr FUP. The median latency of SM was 3.3yrs (IQR: 1.8-6.1) for hem SM and 5.6yrs (IQR: 1.2-10.8) for solid SM. Median FUP was 6.4yrs. Univariably, the type of SM (solid vs. hem) was significantly associated with OS. Hem vs solid SM: HR: 2.17 (95%CI: 1.19-4.97, $p = 0.020$). Median OS of pts who developed solid SM was 13.3yrs compared to 4.1yrs of those with hem SM. The retrospective nature of the data is the major limitation. **Conclusions:** In the largest European database of SM in GCT pts, we observed different trends for SM development according to the SM type. This information may be important for FUP guidelines of these pts. Dataset implementation is ongoing and we will compare the SM incidence from EBMT database with SM rates in the general EU population.

4550 Poster Session (Board #228), Sun, 8:00 AM-11:30 AM

Life expectancy 20 years after cisplatin-based treatment for testicular cancer (TC). *First Author: Sjoukje Lubberts, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands*

Background: Four decades have passed since the introduction of cisplatin-based chemotherapy for metastatic TC, providing the opportunity to evaluate very long-term survival. Although 80-90% of the patients are cured, the effect of treatment on residual life span is unknown. Aim of the study was to investigate life expectancy after TC treatment: from prolonging survival after cancer diagnosis, focus shifts to regaining a normal residual life span. **Methods:** Patients with metastatic TC treated with cisplatin-based chemotherapy > 20 years ago (1977 - 1996) at the University Medical Center Groningen were included. Survival status and cause of death were obtained from medical records, Netherlands Cancer Registry and general practitioners. Events were defined as death due to any cause (overall mortality) and death due to TC or TC treatment complications (TC specific mortality). Standardized mortality ratios (SMR) were calculated as ratio between observed and expected deaths, derived from the age-matched nationwide male population (Dutch Central Office of Statistics). SMRs were calculated for overall mortality, non TC specific mortality (censoring death from TC or treatment-related complications), mortality from cardiovascular disease (censoring death from other causes than cardiovascular disease (ICD-10 I0-I99)) and mortality from secondary malignancies (censoring death from other causes than secondary malignancies (ICD-10 C0-C99 excluding C62: TC)). **Results:** We included 321 metastatic TC patients with a median age of 28 years (range 16 - 64) at start of chemotherapy. After a median follow-up of 25 years (range 0 - 38) 106 patients died (33%). SMR for overall mortality was 4.0 (95% CI 3.6 - 4.4) and for non TC specific mortality 1.5 (95% CI 1.1 - 1.9). SMR for secondary malignancies was 1.7 (95% CI 1.0 - 2.2) and for cardiovascular diseases 1.5 (95% CI 0.7 - 2.2). Median age at death was 5-10 years lower in TC patients than expected. **Conclusions:** Twenty years after cisplatin-based chemotherapy, TC patients have a 50% increased risk of dying from non TC causes compared to the general population. These findings suggest that cisplatin-based treatment for TC comes at the expense of about 7.5 life years and induces early aging.

4551 Poster Session (Board #229), Sun, 8:00 AM-11:30 AM

Thromboembolic events after high-intensity training during cisplatin-based chemotherapy for testicular cancer. *First Author: Lene Thorsen, Oslo University Hospital, Oslo, Norway*

Background: Physical activity (PA) is believed to reduce acute side-effects as deconditioning, fatigue and nausea during chemotherapy and enhance post-treatment physical and psychosocial recovery. The national multicenter randomized TAST-trial (clinicaltrial.gov: NCT02577172) aimed to determine the effect of high-intensity training (HIT) during chemotherapy for testicular cancer (TC) on acute and post-treatment physical- and psychosocial outcomes. **Methods:** Patients aged 18 – 60 years with newly diagnosed metastatic TC, planned for 3 or 4 cisplatin-based chemotherapy cycles in combination with etoposide (EP) or etoposide plus bleomycin (BEP), were randomized to HIT during 9 or 12 weeks of chemotherapy or to one lifestyle counseling session (LCS) during first cycle. The HIT included two supervised endurance interval sessions per week, of which 10-15 minutes per session at 85 – 95 % of peak heart rate. The intensity, duration and number of the intervals were predetermined, but adjusted in accordance to the patients' daily condition. Thromboembolic (TE) complications were registered consecutively. **Results:** Among the first 9 patients randomized to HIT, 33% (3 patients aged 22, 30 and 44 years) developed severe TE complications; 2 cases of pulmonary embolism (respectively at day 9 and 7 of BEP cycle 2) and 1 myocardial infarction (at day 7 of BEP cycle 3). Common for these patients were non-seminoma TC, clinical stage IIA, good prognosis group and no known risk factors for TE events. TE complications were not observed among the 10 patients randomized to the LCS. **Conclusions:** Since TC patients within good prognosis group are expected to have about 5 % risk of TE complications during or shortly after cisplatin-based chemotherapy, we cannot exclude that the HIT may have contributed to the unexpected high number of TE events. Until possible mechanisms explaining our observations have been explored, we discourage high-intensity endurance training during cisplatin-based chemotherapy for TC. These observations led to closure of the TAST-trial after inclusion of 19 of 94 planned patients. Clinical trial information: NCT02577172.

4552 Poster Session (Board #230), Sun, 8:00 AM-11:30 AM

Phase II-study of sequential high-dose-chemotherapy with paclitaxel, ifosfamide, carboplatin, etoposide(P-ICE) in patients with relapsed or refractory germ cell tumors (GCT). *First Author: Thomas Kegel, University of Halle, Halle, Germany*

Background: High-dose chemotherapy (HD-CTx) is an active option for salvage chemotherapy in patients (pts) with refractory or relapsed GCT. All previous trials with HD-CTx used one or two cycles of high dose chemotherapy (CTx) including 2 or a maximum of 3 drugs. Another potentially more active option is the application of four sequential HD-CTx cycles (Schmoll et al, JCO 2003). **Methods:** We conducted a phase II trial of 1(-2) cycle(s) induction CTx with standard dose P-ICE (Paclitaxel 135mg/m² d1, Ifosfamide 1500mg/m² d1-3, Carboplatin 150mg/m² d1-3, Etoposide 150mg/m² d1-3), followed by 4 sequential cycles of HD-P-ICE (Paclitaxel 200mg/m² d1, Ifosfamide 3300mg/m² d1-3, Carboplatin 330mg/m² d1-3, Etoposide 330mg/m² d1-3). Eligibility criteria: relapse or progression under one or more induction CTx, ECOG PS (0-1), Creatinine-clearance > 30ml/min, adaequate liver function, measurable tumor or at least marker-elevation. **Results:** 37 pts entered the trial and 33 are evaluable (4 pts never received HD-CTx due to lack of stem cells (3) or medical reasons (1)). Prior CTx:1 (N = 26), 2 (N = 4), 3 (N = 3); primary extragonadal: 6; seminoma/ non-seminoma 5/28; ECOG-PS: 0 (19), 1 (14). Response rate: CR/NED 17 (51.5%), CR/NED/PR-/SD- with marker normalization 21 (63.6%), PD 12 (36.4%). DFS of CR/NED: median 59 (8-105) months; RFS of all favourable responders 60 (8-105) months, PFS total 46 (2-105) months. OS for all pts. 51 (6-105) months, OS Favourable Responders: 65 (23 – 105), Non-favourable Responders: 11 (6-27) months,. Toxicity was tolerable without treatment related death, with mainly grade 4 bone-marrow toxicity and grade 2 mucositis and/or diarrhea. **Conclusions:** Sequential HD-CTx with one cycle of SD-P-ICE and four cycles HD-CTx is feasible with acceptable toxicity and favourable efficacy. Sequential HD-CTx using the four most active drugs might be a potentially option for this pts-population due to good tolerability, applicability and interesting long-term outcome. Comparison of the standard approach with 1 to 3 sequential high dose cycles of Carboplatin/ Etoposide is ongoing (TIGER-Trial). Clinical trial information: EUDRA-CT: 2006-006004-11.

4553 Poster Session (Board #231), Sun, 8:00 AM-11:30 AM

Long-term causes of relative excess mortality after diagnosis of testicular germ cell tumor. *First Author: Oivind Kvammen, Helse Midt-Norge, Trondheim, Norway*

Background: Despite today's excellent cure rates among testicular germ cell tumor (TGCT) patients, reduced long-term relative survival (RS) is an increasing concern. We recently reported a continuing decline in RS among TGCT patients diagnosed in Norway, even beyond 30 years of follow-up. Late effects of treatment is the main culprit. Although several reports describe increased mortality from second cancer (SC), cardiovascular disease (CVD), and other causes (OC) among TGCT survivors, data beyond 20 years of follow-up are scarce. The study aim was to analyze long-term relative risks (RR) and causes of death (CD) among TGCT patients diagnosed in Norway, 1953-2014. **Methods:** Data sources were the Cancer Registry of Norway and the Norwegian Cause of Death Registry. All men diagnosed with TGCT in Norway during 1953-2014 were included, except spermatocytic seminomas. End of follow-up was December 31st, 2014. Patients were classified by CD, histology, disease extent and age at diagnosis, as well as by decade of diagnosis and follow-up time. Standardized mortality ratios (SMR), compared with the general Norwegian male population, were computed. **Results:** At end of follow-up, 2359 of 9390 patients were deceased. CD was obtained for 2320 patients; 37.6 % TGCT, 24.5 % SC, 19.1 % CVD and 18.8 % OC. SMR for all SC were significant particularly after 20 years of follow-up (1.8 – 3.1), with similar findings in localized disease at diagnosis. SMR were most consistently elevated beyond 20-30 years for SC of the pancreas, large intestine and bladder. By contrast, SMR for CVD were significant among patients diagnosed 2000-14, both before and after one year of follow-up (2.6). There were no significant SMR for CVD beyond 20 years of follow-up. Several OC SMR were elevated, such as for digestive and genitourinary diseases beyond 20-30 years (2.2 – 5.1). **Conclusions:** TGCT patients have increased RR of SC and OC death even beyond 20-30 years of follow-up, while the increased RR of CVD death is mostly confined to the first decade. CVD deaths in patients diagnosed 2000-14 are a particular concern. Continuing optimization of TGCT treatment and follow-up schemes is required, including further research on toxicity mechanisms.

4554 Poster Session (Board #232), Sun, 8:00 AM-11:30 AM

Individualization of high dose carboplatin based on therapeutic drug monitoring (TDM) for the treatment of testicular germ cell tumors (TICE protocol): Results of a multicenter phase II study. *First Author: Fabienne Thomas, Institut Claudius Regaud, IUCT-Oncopole, CRCT, Inserm, Toulouse, France*

Background: We conducted a national phase II multicenter trial that aimed at evaluating the efficacy and tolerance of Paclitaxel plus Ifosfamide followed by high-dose carboplatin plus etoposide treatment (TICE) in previously treated germ cell tumors. The particularity of our study (in comparison with the standard protocol [Motzer RJ, et al. J Clin Oncol 2000 Mar; 18(6): 1173-1180.]) is that the carboplatin dose was individualized for each patient according to therapeutic drug monitoring (TDM) in order to reach the target AUC of 24 mg.min/ml over 3 days. **Methods:** In total, 89 patients were evaluable for pharmacokinetic study. Blood samples were taken on day 1 to determine the carboplatin clearance using a Bayesian approach (NONMEM 7.2) and to adjust the dose on day 3 to reach the target AUC of 24 mg.min/ml over 3 days. On days 2 and 3, samples were taken for retrospective assessment of the actual AUC and the intra- and inter-cycle clearance variability. Secondly, a population pharmacokinetic analysis was also performed on 59 patients using NONMEM to develop a covariate equation for carboplatin clearance prediction adapted for future patients treated with the TICE protocol. The performance of this new equation was then prospectively evaluated on the other 30 patients along with different methods of carboplatin clearance prediction. **Results:** TDM allowed us to control the carboplatin exposure with a mean actual AUC of 24.5 mg.min/ml (22.2 and 28.0 for 5th and 95thpercentile respectively) per cycle. We observed a modest but significant decrease of carboplatin clearance over cycles (median value of change of -11.8% from cycle 1 to cycle 3, maximum value of -36%). The new covariate equation allows unbiased and more accurate prediction of carboplatin clearance in the prospective validation cohort compared to other equations. **Conclusions:** Carboplatin TDM allowed the target AUC to be accurately reached and thereby avoid over- or under-exposure. We propose a new equation to predict carboplatin clearance more adapted to these particular patients (young males) that could be used as an alternative if the TDM cannot be organized. Clinical trial information: 2008-005068-14.

4555 Poster Session (Board #233), Sun, 8:00 AM-11:30 AM

Histologic determinants of long-term overall survival in patients (pts) with germ cell tumors (GCT). *First Author: Samuel Funt, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: GCT display totipotential differentiation ranging from pluripotent embryonal carcinoma to extraembryonic (choriocarcinoma, yolk sac) to somatic cell types (teratoma [T]). We hypothesized that long-term survival after platinum-based chemotherapy (PC) is dependent upon histology. **Methods:** Advanced GCT pts who received PC from 4/1975 to 5/1996 and had a pre-PC primary tumor specimen available were included. Each pre-PC cell type was reviewed and confirmed. Residual tumor size post-PC was recorded when available. Differences in cumulative incidence (CUI) of death due to disease (DOD) between histologic cell types and other baseline characteristics were evaluated using a competing risks approach and the Fine & Gray test. **Results:** Pre-PC primary tumor specimens (96% testis, 3% mediastinum) were available from 231 pts. Median age was 29 years (y) and median followup 17 y (range 0.3-35 y). 41 pts had pure seminoma; of the remaining 190 with nonseminomatous GCT (NSGCT), 81 had an element of T (n=29 mature T, n=42 immature T, n=10 both). At PC start, 60% of pts were IGCCCG good risk, 26% intermediate, and 13% poor with no difference for NSGCT based on presence vs. absence of T (p=0.53). Of 72 deaths, 50 were DOD, 20 from other causes, and 2 from unknown causes. The 5, 10, and 15 y CUI of death from any cause was 20%, 23%, and 26%, respectively. CUI of DOD at 5, 10 and 15 y was 18%, 20%, 22%, respectively. CUI of DOD at 2, 5, 10 and 15 y by histologic group is provided in the Table. Presence of T was associated with greater CUI of DOD vs. NSGCT without T (p=0.04) and mature T with a greater CUI of DOD vs. immature T (p=0.03). NSGCT pts with T were also more likely to have residual retroperitoneal disease >1cm after PC vs. those without T (50 vs. 4.2%; p=0.01). **Conclusions:** With long-term followup, the presence of an element of T, particularly mature T, in mixed NSGCT was associated with a higher risk of DOD than tumors without T, which have the same risk of DOD as pure seminoma. These data suggest that the presence of T in the primary tumor may be an important clinical predictor of long-term outcome in men with GCT.

Cumulative incidence (%) of DOD by histology.

	2 y	5 y	10 y	15 y
NSGCT with T	17	25	29	31
NSGCT without T	12	15	17	17
Seminoma	10	15	15	18

4556 Poster Session (Board #234), Sun, 8:00 AM-11:30 AM

Genomic comparison of matched primary and metastatic germ cell tumors (GCT). *First Author: Francois Audenet, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tumor genomic analysis may be useful in patients with GCT as a means of identifying potentially actionable genomic alterations or mutations such as *TP53* that confer resistance to chemotherapy. As GCTs often exhibit significant morphologic heterogeneity, we evaluated the level of concordance between genomic alterations in matched primary and metastatic GCT samples. **Methods:** GCT patients enrolled on an institutional prospective sequencing protocol with available primary and metastatic tumor tissue were eligible. Each tumor was subjected to MSK-IMPACT, an exon capture sequencing assay, which detects copy number alterations (CNAs) and mutations in 410 cancer-related genes. For each primary-metastasis pair, concordance and clonality was assessed using the FACETS algorithm. **Results:** Matched primary-metastasis tumor pairs were available for 36 patients (78% nonseminoma, 22% seminoma, median age 33.5 years). All patients received chemotherapy, with 25 (69%) receiving treatment prior to analysis of the metastatic samples. The frequency of genetic alterations was low with a median of 3 mutations (1-7), 7 amplifications (1-26) and 1 deletion (1-9) detected per sample, with no significant difference in mutational/CNA burden between primaries and metastases. Of 109 unique mutations across patients, only 44 (40%) were concordant between the primary and matched metastasis, including 5 of 9 hotspot mutations. For CNAs, 184 (81%) of 226 were concordant. Only 24 of 109 (22%) mutations were clonal (defined as predicted to be present in all cancer cells) in either the primary or metastatic matched samples; of these, only 4 were clonal in both the primary and metastatic samples, including 2 hotspots. However, 4 of 5 alterations in *TP53/MDM2* were shared by both the primary and metastasis pairs. In a separate exploratory cohort, 4 *TP53* mutations were identified in 3 primary tumors and 1 metastasis, and all 4 mutations were also detected by cell-free DNA profiling. **Conclusions:** Genomic concordance, particularly for mutations, is poor between primary and metastatic GCT samples. Cell-free DNA analysis may help overcome this limitation by identifying alterations in progressive tumors without need for a new biopsy.

4557 Poster Session (Board #235), Sun, 8:00 AM-11:30 AM

Efficacy of epirubicin-paclitaxel (EPI-TAX) prior to high-dose chemotherapy (HDCT) in germ cell tumors (GCTs): A 17-year experience. *First Author: Jean-Pierre Lotz, Medical Oncology Department, Hospital Tenon (AP-HP), Paris, France*

Background: GCTs patients (pts) relapsing after conventional-dose salvage chemotherapy (CDCT) are candidates to receive HDCT with hematopoietic stem cell (SC) support. We have previously reported (Ann Oncol 2014; 25: 1775-82) that non-refractory pts can benefit from HDCT. We here analyzed the efficacy of the induction regimen EPI-TAX. **Methods:** All male GCTs pts treated by EPI-TAX between 1998 and 2015 were identified from clinical records at Tenon Hospital. Primary aim was response rate after EPI-TAX. Secondary aims were efficacy of SC harvest, Beyer score, toxicities and overall survival (OS) after HDCT. Kaplan-Meier methods were used for analysis. **Results:** Of the 170 pts treated (EPI 100 mg/m2, TAX 250 mg/m2, days 1-15), 142 (83.5%) had received $>$ 2 previous lines of CDCT. 79 (46.5%) had disease progression at the time of treatment and 44 were absolutely refractory to cisplatin. The other pts were in remission (65) or had stable disease (SD, 26). Most of pts (75.3%) had Beyer score $>$ 1. Following EPI-TAX, favorable responses were achieved in 140 pts (82.4%,CI95% 79.8-85.0; 21 complete responses, 68 partial responses and 51 SD). EPI-TAX was able to control disease in 56 (70.9%, CI95% 61.0-80.8) out of 79 pts who were in progression. Beyer score after EPI-TAX resulted 0 in 70.6% of pts. Successful harvested of SC was achieved in 146 (85.8%, CI95% 80.5-91.1) pts. EPI-TAX was well tolerated with peripheral neuropathy as the main non-hematopoietic toxicity. Treatment discontinuation was needed in 3 (1.8%) pts and 2 (1.2%) related deaths were observed. Following EPI-TAX, 155 (91.2%) pts received HDCT. HDCT was given in consolidation, once progressive disease was controlled by EPI-TAX or for progressive pts. With a median follow-up of 31 months (0.5-223) the 2- and 10-years OS for the subgroup consolidation were 78.2% (95%CI 69.1-87.4) and 66.9% (95%CI 55.4-78.6). Disease control by EPI-TAX resulted in 55.8% (95%CI 42.4-69.2) and 38.2% (95%CI 24.9-51.4) 2- and 10-y OS compared to 14.6% (95%CI 0-33.2, logrank p = 0.006) 2-y OS for progressive pts. **Conclusions:** EPI-TAX is effective to collect SC and to control disease of pts who were in progression after CDCT allowing them to receive HDCT.

4558 Poster Session (Board #236), Sun, 8:00 AM-11:30 AM

High-dose chemotherapy (HDCT) plus peripheral-blood stem-cell transplant (PBSCT) for patients (pts) with relapsed germ-cell tumors (GCT) and active brain metastases (mets). *First Author: Maitri Kalra, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: The optimal management of progressive brain mets in pts with GCT remains unsettled. Treatment options include chemotherapy, stereotactic or whole brain radiation (XRT), surgery, or a combination thereof. Global germ cell cancer group analysis suggested multimodality therapy improves survival probabilities in pts with brain mets at relapse (JCO.2016;1;34(4): 345-51). We report our experience on managing 25 consecutive pts with relapsed GCT and progressive brain mets undergoing HDCT with PBSCT at Indiana University from 2006-2016. **Methods:** All pts received HDCT consisting of carboplatin 700 mg/m2 days 1-3 and etoposide 750 mg/m2 i.v. days 1-3 followed by PBSCT on day 5 for upto 2 cycles. Pts were treated with craniotomy, XRT, chemotherapy alone, or a combination of modalities. Patient and disease characteristics, management of brain mets, and outcomes were measured. Platelet transfusions were given to maintain platelet counts $>$ 30,000 and goal of $>$ 50,000 in those with signs of hemorrhage. **Results:** Patient characteristics and outcomes are summarized in Table 1. Median age was 27.7 years (range, 16-48). All pts had progressive brain mets at time of starting HDCT. AFP ranged 1.6 to 1130, hCG 0.5 to 25601. At median follow-up of 24.8 months (range 2.5 to 118.5 months), 11 pts (44%) were alive with NED, 2 pts were alive with relapsed disease, and 12 pts died of disease progression. 17/18 patients developed progressive CNS mets despite radiation and/or craniotomy and of those, 8 are alive with NED. Toxicity was as previously published with this regimen (N Engl J Med 2007;357:340-8). **Conclusions:** Patients with relapsed GCT with progressing brain mets, including those with prior locoregional therapy, are curable with HDCT.

Characteristic (N)	Alive with NED (11)	Dead of disease (12)	Alive with relapsed disease (2)
CNS as primary presentation (7)	4 (36.37%)	3 (25%)	-
Predominant histology of craniotomy specimen (13)			
Embryonal carcinoma (5)	4	1	-
Yolk Sac (6)	3	3	-
Teratoma (1)	1	0	-
Negative for malignancy (1)	1	-	-
Craniotomy and XRT before HDCT (10)	6	4	-
Craniotomy alone before HDCT (2)	2	-	-
XRT alone before HDCT (6)	1	4	1
HDCT alone (7)	2	4	1

4559 Poster Session (Board #237), Sun, 8:00 AM-11:30 AM

Applying radiomics to predict pathology of post chemotherapy retroperitoneal nodal masses in germ cell tumors (GCT). *First Author: Jeremy Howard Lewin, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: After chemotherapy, $>$ 50% of patients (pts) with metastatic testicular GCT who undergo retroperitoneal lymph node dissection (RPNLD) for residual masses are found to have fibrosis (F) alone on pathological examination. To minimize overtreatment, better prediction algorithms are needed to identify pts with F who can avoid RPLND. Radiomics uses image processing techniques to extract quantitative textures/features from tumor regions of interest (ROI) to train a classifier that predicts pathological findings. We hypothesized that radiomics may identify pts with a high predicted likelihood of F who may avoid RPLND. **Methods:** Pts with GCT who had an RPLND for nodal masses $>$ 1cm after first line platinum chemotherapy were included. Preoperative contrast enhanced axial CT images of retroperitoneal ROI were manually contoured. 153 radiomics features trained a radial basis function support vector machine classifier to discriminate between viable GCT /Mature Teratoma (T) vs F. Nested ten-fold cross-validation protocol was employed to determine classifier accuracy. Clinical variables and restricted size criteria were used to optimize the classifier. **Results:** A total of 82 pts with 102 ROI were analyzed (GCT: 21; T: 41; F: 40). The discriminative accuracy of radiomics to identify GCT/T vs F was 72%($\pm$2.2)(AUC: 0.74 ($\pm$0.028); positive predictive value: 67% (48-92%); negative predictive value: 74% (62-84%)(p = 0.001)). No major predictive differences were identified when data was restricted by varying maximal axial diameters (AUC range: 0.58($\pm$0.05) - 0.74($\pm$0.03)). Prediction algorithm using clinical variables alone identified an AUC of 0.71 ($\pm$0.15). When these variables were added to the radiomic signature, the best performing classifier was identified when axial tumors were limited to diameter $<$ 2cm (accuracy: 88.2 ($\pm$4.4); AUC: 0.80 ($\pm$0.05)(p = 0.02)). **Conclusions:** A predictive radiomics algorithm had an overall discriminative accuracy of 72% that improved to 88% when combined with clinical details. Further independent validation is required to assess whether radiomics, in conjunction with standard clinical predictors, may allow pts with a high predicted likelihood of F to avoid RPLND.

4560 Poster Session (Board #238), Sun, 8:00 AM-11:30 AM

Intermediate prognosis in metastatic germ cell tumors (IPGCT): Outcome and prognostic factors. *First Author: Christoph Alexander Seidel, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: The IGCCCG classification published in 1997 is based on data from the 1970-80s. Approximately 25% of metastatic GCT patients belong to the intermediate prognosis category, that was associated with a 5-year overall survival (OS) rate of 79%. However, more recent data suggest significant changes. We have thus performed an international registry of IPGCT patients to analyze current treatment, outcome, and potential prognostic factors. **Methods:** Data of IPGCT patients, diagnosed between 1979-2012, were retrospectively collected from 14 centers. Treatment and outcome before and after implementation of IGCCCG were analyzed. For patients diagnosed since 1997 prognostic factors were investigated by uni- and multivariate analysis to test whether current patients or subgroups may require less intensive treatment. **Results:** This registry includes 637 patients: group 1 diagnosed prior 1997 (n = 237), and group 2 since 1997 (n = 400). Mean follow-up duration was 128.4 months (IQR: 168.9). Patients in group 1 and 2 received first-line treatment with BEP (median 4 cycles; range 1 - 6) in 98% and 97%, respectively. Response to chemotherapy (CR and marker negative PR) was similar: 91% group 1; 94% group 2; (p = 0.233), but survival curves were significantly superior in group 2 associated with a 5-year OS rate of 87% (group 2) and 81% (group 1), respectively (p = 0.011; 95%CI 294-317). Recurrence rates were higher in group 1 (36% versus 24%; p = 0.001). Patients treated with 3 cycles BEP (n = 58) in both groups had a similar outcome concerning OS compared to patients treated with 4 cycles (n = 489) (p = 0.415). Uni- and multivariate analysis revealed LDH levels $<$ 2.0 UNL prior chemotherapy (p = 0.018; HR 0.35) and an adequate tumor marker decline at days 18-21 (half-life) of first cycle (p = 0.025; HR 2.58) as independent prognosticators, both associated with 5-year OS rates of 94%, respectively. **Conclusions:** Outcome of intermediate patients seems improved after implementation of the IGCCCG classification and less intensive regimes may also be sufficient. Here, patients treated with 3xBEP had a non-inferior outcome. A baseline LDH $<$ 2.0 UNL and an adequate tumor marker decline after first treatment cycle can be used for further stratification.

4561 Poster Session (Board #239), Sun, 8:00 AM-11:30 AM

Safety and usefulness of patient-centered shared survivorship care after chemotherapy for testicular cancer. *First Author: Hink Boer, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands*

Background: Testicular cancer (TC) survivors are at risk to develop early cardiovascular morbidity. Close collaboration between oncologists and primary care physicians (PCPs) is mandatory for optimal cardiovascular risk management. We designed a simple shared survivorship care program in which TC patients regularly visit their PCP instead of their oncologist. The primary aim of this study was to test safety and feasibility of shared-care follow-up after chemotherapy for metastatic TC. **Methods:** TC patients with complete remission after chemotherapy and age $\geq$18 years were eligible. Participants received a personalized survivorship care plan with scheduled visits to the oncologist and PCP, which was available both on paper and as a mobile application. During PCP visits, signals indicating cancer recurrence, cardiovascular risk and psychosocial issues were assessed. Safety boundaries were defined for the occurrence of failed response to signals indicating cancer recurrence. Patient data were monitored real-time to check if the shared-care follow-up was carried out within these boundaries. Secondary outcomes were satisfaction among TC patients and PCPs, measured with an evaluation questionnaire, and anxiety levels, measured with the Hospital Anxiety and Depression Scale. **Results:** 64% of eligible TC patients and 99% of the approached PCPs were willing to participate; 162 patients were enrolled in the shared-care program and 241 primary care visits took place. No failures occurred in the detection of relapsed TC. Therefore, the safety boundary was crossed, indicating that shared-care follow-up is a safe alternative to hospital-only follow-up. Four primary care visits were deemed as failed visits because of logistic issues.Anxiety levels did not increase during shared-care follow-up (3.6 *vs* 3.3 (p = 0.38). Patients were satisfied with the knowledge of PCPs and appreciated this regular contact. 78% of the PCPs would like to extend their role in shared-care follow-up. **Conclusions:** This easy to use shared survivorship care program is safe and feasible in the follow-up of TC patients. Communication within this patient-centered follow-up program may be further supported with e-health tools. Clinical trial information: NCT01783145.

4562 Poster Session (Board #240), Sun, 8:00 AM-11:30 AM

A phase I study of cabozantinib plus nivolumab (CaboNivo) and cabonivo plus ipilimumab (CaboNivoIpi) in patients (pts) with refractory metastatic (m) urothelial carcinoma (UC) and other genitourinary (GU) tumors. *First Author: Andrea B. Apolo, Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: We report the safety and clinical activity of the combination of CaboNivo and CaboNivoIpi in pts with mUC and other mGU tumors (NCT02496208). **Methods:** In this phase I trial 30 pts were treated in 4 dose levels (DL) for part 1 (CaboNivo) and 18 pts were treated in 3 DL for part 2 (CaboNivoIpi). Pts received Cabo PO daily and Nivo IV (part 1) with Ipi 1mg/kg x 4 doses q3wks (part 2). A mUC and a renal cell carcinoma (RCC) expansion cohort of CaboNivo has initiated enrollment. Tumors were assessed for overall response rate (ORR) q8wks (RECIST 1.1). Adverse events (AEs) were graded (G) by NCI-CTCAE v4.0. **Results:** From 7/22/15 to 12/31/2016, 48pts (CaboNivo N = 30; CaboNivoIpi N = 18) (mUC N = 19; bladder urachal N = 4; bladder squamous cell carcinoma (bSCC) N = 2; germ cell tumor (GCT) N = 4; castrate-resistant prostate cancer (CRPC) N = 9; RCC N = 2, sarcomatoid RCC N = 2, Sertoli cell N = 1, and trophoblastic tumor N = 1 were treated. Median age was 58 (range 35-77), 41 (85%) were male. Common treatment-related G1/2 AEs for CaboNivo: ALT increase (67%), fatigue (63%), diarrhea (60%), hypothyroidism (57%); CaboNivoIpi: fatigue (72%), diarrhea (61%), anorexia (61%); Grade 3 AEs for CaboNivo: hypertension (23%), neutropenia (17%), hypophosphatemia (13%), lipase increase (10%), fatigue (7%), aseptic meningitis (3%); CaboNivoIpi: hypophosphatemia (19%), hypertension (19%), fatigue (13%), hyponatremia (13%), nausea (13%), lipase increase (11%), colitis (6%); G4 CaboNivo: lipase increase (7%) thrombocytopenia (3%); CaboNivoIpi lipase increase (6%) There were no G5 toxicities, no DLTs. 43 pts were evaluable for response: ORR was 30% 13/43 [3 CR (2 mUC, 1 bSCC); 10 PRs (4 mUC, 2 penile, 1 sarcomatoid RCC, 1 urachal, 1 CRPC, 1 bSCC)]. ORR for CaboNivo 39% (mUC 44%); CaboNivoIpi 18% (mUC 29%). 11/13 (85%) of responses were ongoing at cutoff. **Conclusions:** CaboNivo and CaboNivoIpi combinations were well tolerated with no DLTs and have durable efficacy in mGU tumors particularly mUC. Rare tumors such as bSCC, urachal, and penile cancers demonstrated response to the combination. Larger cohorts of mUC and rare GU tumors are ongoing. Clinical trial information: NCT02496208.

4563 Poster Session (Board #241), Sun, 8:00 AM-11:30 AM

Efficacy and safety of nivolumab in patients with metastatic renal cell carcinoma (mRCC) and brain metastases: Preliminary results from the GETUG-AFU 26 (Nivoren) study. *First Author: Bernard J. Escudier, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Nivolumab (N) has been shown active in patients (pts) with mRCC after failure of 1 or 2 TKIs. Efficacy and safety of N in pts with brain metastases (BM) from RCC is still unknown. The aim of this study is to report preliminary data of the Nivoren study in pts with BM. **Methods:** GETUG-AFU 26 (Nivoren) is a prospective phase 2 study assessing safety and efficacy of N in a broader mRCC patient population than those recruited in the pivotal phase 3, including pts with BM (previously treated or not, but not requiring steroids), with previous mTOR inhibitor, with PS 2 as well as in previously highly pretreated pts. N was given every 2 weeks at 3mg/kg, until disease progression or unacceptable toxicity. Treatment was allowed beyond progression in case of clinical benefit. All pts had brain CT scan or MRI at baseline. **Results:** Up to December 2016 , 588 pts have been enrolled including 55 pts with BM (35 (67%) ,6 (12%) and 11 (21%) with 1, 2 or $>$ 2 BM, respectively. Of those 55 pts, 10 pts (23%) were PS 2 and 25 (58%) PS 1, and 16 patients (29%) had received more that 2 lines of therapy. No previous treatment for BM was performed in 67% (n = 37), while 9% had previous brain surgery (n = 5 ;) or brain radiation (n = 17 (31%). 2/55 pts never received N. Median duration of therapy in BM pts was 2.4 months (varying from 0 to 9) with a 3-months PFS of 60% (IC95% = 45 – 73). Median OS is not reached at the time of this analysis. Among 44 pts with assessment of response on BM, 10 (23%) had objective response while 21 (48%) had local progressive disease. Neurologic deterioration requiring steroids was observed in 15 pts (32%) . Updated data will be presented at the meeting. **Conclusions:** This is the first large study to report preliminary safety and efficacy of N in RCC pts with BM. Safety of N in this pt population appears to be acceptable, although some pts do require steroids because of brain progressive disease. Objective response in the brain was observed in 23% of pts. Further follow up is required to determine the real benefit of N in this group of mRCC pts. Clinical trial information: NCT03013335.

4564 Poster Session (Board #242), Sun, 8:00 AM-11:30 AM

Pazopanib exposure-response assessment as adjuvant therapy for patients with localized or locally advanced renal cell carcinoma (RCC) following nephrectomy. *First Author: Cora N. Sternberg, San Camillo Forlanini Hospital, Rome, Italy*

Background: PROTECT was a Phase 3 randomized placebo-controlled study to evaluate pazopanib efficacy and safety as adjuvant RCC treatment. The starting dose was 800 mg daily, which was reduced to 600 mg in an attempt to improve tolerability. Pazopanib trough concentrations (Ctrough) were collected from 358 patients at the 600-mg starting dose at two timepoints (Week 3/ 5 and Week 16/20). This analysis characterized the relationship between Ctrough and efficacy and safety endpoints. **Methods:** The relationship between pazopanib Ctrough and disease-free survival (DFS) was explored by Cox regression analysis. DFS of pazopanib Ctrough quartiles was explored using Kaplan-Meier plots. Exposure-safety relationship was explored via summaries of all grade adverse events (AEs), grade 3/4 (G3/4) AEs, and AE-related treatment discontinuation by Ctrough quartiles. **Results:** The geometric mean (geo-CV%) of Ctrough at 600-mg dose was 31.4 (57%) μg/mL and 25.3 (70%) μg/mL for Week 3/5 and Week 16/20, respectively. At Week 16/20, Ctrough values overlapped among patients receiving 400-, 600-, and 800-mg doses. Cox regression analysis showed pazopanib Ctrough at Week 3/5 as a significant covariate for DFS after adjusting for TNM staging and Fuhrman Nuclear grading (HR: 0.58, 95% CI, 0.42, 0.82; p = 0.002). Longer DFS was observed in higher Week 3/5 Ctrough quartiles (median DFS by quartile—Q1: 41.89 months, Q2-Q4: median DFS not reached). Incidence of all-grade AEs, as well as G3/4 hypertension, increased as Ctrough increased. Treatment discontinuation due to hypertension among pazopanib-treated subjects was low (3.1% vs < 1% in the placebo group). Ctrough was not correlated to G3/4 ALT increase. Incidence of other G3/4 AEs plateaued at higher Ctrough. No relationship was observed between Ctrough and treatment discontinuation due to AEs. **Conclusions:** Pazopanib Ctrough levels in PROTECT were consistent with levels associated with efficacy in the advanced setting. Higher pazopanib Ctrough correlated with longer DFS. Higher pazopanib exposure did not increase the incidence of G3/4 AEs, with the exception of hypertension, which was adequately controlled and managed. Clinical trial information: NCT01235962.

4565 Poster Session (Board #243), Sun, 8:00 AM-11:30 AM

Microvessel density as a prognostic marker in high-risk renal cell carcinoma. *First Author: Sarah A. Weiss, Yale School of Medicine, New Haven, CT*

Background: Increased vascularity is a hallmark of renal cell carcinomas (RCC), particularly clear cell RCC. The vascular endothelial growth factor (VEGF) pathway, implicated in tumor angiogenesis, is dysregulated in RCC. The phase 3 trial ECOG-ACRIN E2805 enrolled 1,943 patients (pts) with resected high-risk RCC (pT1b high grade to pT4 any grade or N any). Pts were randomized to adjuvant sunitinib, sorafenib, or placebo. Our aim was to determine the prognostic and predictive role of microvessel density (MVD), VEGF receptors, and ligands in nephrectomy specimens. **Methods:** We obtainedpre-treatment primary RCC tissue from 822 pts and built tissue microarrays using 3 cores from each sample. Using quantitative immunofluorescence we measured tumor MVD (area of CD34-expressing cells) and intensity of the VEGF/VEGF-R family (VEGF-R1, R2, R3 and VEGF-A, B, C, D) in tumor cells. We tested for association with disease-free survival (DFS) and overall survival (OS) by the stratified log-rank test. Associations with treatment arm and clinicopathologic variables were determined. **Results:** High MVD (above the median) was associated with prolonged OS for the entire cohort (p = 0.021, HR 0.63) and for pts treated in the placebo group (p = 0.014). The association between high MVD and OS was weaker in patients treated with sunitinib or sorafenib (p = 0.060). High VEGFD expression overall was associated with shorter OS (p = 0.027) but not for placebo (p = 0.16). Yet high MVD was not associated with improved DFS (p = 1.00). High MVD correlated with above-median age (> 56) (p = 0.032), Fuhrman grade I/II (p < 0.001), clear cell histology (p < 0.001), and absence of necrosis (p < 0.001) but not with gender, sarcomatoid features, lymphovascular invasion, or tumor size. In multivariable analysis, MVD remained independently associated with improved OS for the entire cohort (p = 0.013). **Conclusions:** High MVD in nephrectomy specimens of high-risk RCC pts is associated with improved OS, regardless of treatment arm. MVD is thus an independent prognostic, rather than predictive, biomarker. Further studies should assess whether incorporating MVD into clinical models will predict outcome in resected high-risk RCC pts and if MVD can be used for pt selection for adjuvant therapy.

4566 Poster Session (Board #244), Sun, 8:00 AM-11:30 AM

Everolimus (EVE) exposure as a predictor of toxicity (Tox) in renal cell cancer (RCC) patients (Pts) in the adjuvant setting: Results of a pharmacokinetic analysis for SWOG S0931 (EVEREST), a phase III study (NCT01120249). *First Author: Timothy W. Synold, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: S0931 is assessing recurrence-free survival in RCC pts randomized to receive EVE versus placebo for one year following nephrectomy. To date, there has been a higher than expected dropout rate due to bothersome tox. Previous reports have shown an association between EVE trough levels and both tox and disease response in RCC pts. Therefore, we have assessed EVE trough levels to evaluate the relationship between measured exposure and probability of tox. This analysis has been approved by the DSMC. **Methods:** Patients received 10 mg daily EVE or placebo for nine 6-week cycles. Pre-dose whole blood samples collected pre-cycle 2 and pre-cycle 3 were analyzed for EVE. Pts with pre-cycle 2 and/or pre-cycle 3 EVE results were used in the analysis. When both trough levels were available, results were averaged. Pts were segregated into quartiles (Q) based on EVE levels and logistic regression was used to model the following adverse event outcomes using EVE trough as a predictor; any grade 3+ tox, grade 2+ triglycerides, grade 2+ hyperglycemia, grade 2+ oral mucositis, grade 2+ rash, and premature stopping of EVE. Hazard and odds ratios were adjusted for age, BMI and performance status. **Results:** This study reached its accrual goal and closed on 9/15/2016 with 1545 (775 EVE) randomized patients. A total of 386 pts are included in this preliminary analysis. Median EVE trough was 12.8 ng/mL (range 3.1, 75.6) per 10 mg dose. Event rates for tox were: any grade 3+ tox = 46%, grade 2+ triglycerides = 33%, grade 2+ hyperglycemia = 15%, grade 2+ oral mucositis = 34%, grade 2+ rash = 15%, and premature stopping of EVE = 40%. The risk of grade 2+ triglycerides was increased in Q2 and Q3 vs Q1 (OR = 2.95; p = 0.001 and OR = 3.48; p < 0.001). The risk of grade 2+ rash was increased in Q2 and Q4 vs Q1 (OR = 2.95; p = 0.02 and OR = 3.20; p = 0.01). There was also a trend towards an increased risk of any grade 3+ tox in Q3 vs Q1 (OR = 1.72; p = 0.07). **Conclusions:** This analysis has identified significant associations between EVE exposure and the probability of tox. EVE analysis is ongoing and the final results will be presented. Clinical trial information: NCT01120249.

4567 Poster Session (Board #245), Sun, 8:00 AM-11:30 AM

Efficacy and safety of pegylated human IL-10 (AM0010) in combination with an anti-PD-1 in renal cell cancer. *First Author: Aung Naing, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: IL-10 has anti-inflammatory activity and stimulates the cytotoxicity and proliferation of CD8+ T cells at higher concentrations. IL-10 receptors and PD1 are expressed on activated CD8 T cells, providing a rationale for combining AM0010 and an anti-PD1. The efficacy and safety profile for AM0010 alone was established in poor to intermediate risk RCC pts treated in 3rdLOT. Objective responses were observed in 4 of 15 pts with RCC. In the dose escalation of AM0010 plus pembrolizumab, 4 of 8 patients had an objective response. The mPFS was 16.7 months and the mOS has not been reached, median follow up (mFU) is 19.3 mo. **Methods:** In this Phase 1b, 29 pts. with metastatic RCC were enrolled until Nov. 18 2016 on AM0010 (10 ug/kg daily SC) and nivolumab (3mg/kg, q2wk IV). 2 had favorable, 20 had intermediate and 4 had poor IMDC risk (3 were not available). Pts. had a median of 1 prior therapy (range 1-3). All pts. had received a VEGFR-TKI. Tumor responses were assessed with irRC. Immune responses were evaluated by serum cytokines, activation of blood derived T cells and peripheral T cell clonality. **Results:** AM0010 plus nivolumab was well tolerated. TrAEs were reversible. There were no autoimmune colitis, pneumonitis, or endocrine disorders. 14 patients had at least 1 G3/4 TrAE, including anemia (9), thrombocytopenia (5), hypertriglyceridaemia (4). 2 pts had a reversible cytokine release syndrome with splenomegaly and increased immune mediated red blood cell phagocytosis most likely precipitated by T-cell activation, as both pts had tumor responses. As of Jan 31 2017, partial responses (PR) were observed in 8 of 26 evaluable pts (31%). An additional 13 of 26 pts had stable disease (41%), 7 pts had tumor reductions of more than 30%. The mPFS and mOS has not been reached with a mFU of 5.2 mo. (range 0.3-10.3). AM0010 + anti-PD1 increased Th1 cytokines in the serum while decreasing TGFb, an expansion of proliferating PD1+ Lag3+ activated CD8 T cells and de-novo oligoclonal expansion of T cell clones in the blood. **Conclusions:** AM0010 in combination with nivolumab is well-tolerated in RCC pts. The efficacy and the observed CD8 T cell activation is promising and encourages the continued study of AM0010 in combination with nivolumab. Clinical trial information: NCT02009449.

4568 Poster Session (Board #246), Sun, 8:00 AM-11:30 AM

Prognostic role of circulating tumor cells-CTCs in metastatic renal cell carcinoma. *First Author: Umberto Basso, Medical Oncology Unit, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy*

Background: CTCs can be isolated in peripheral blood of cancer pts and have demonstrated to have prognostic role in several metastatic tumors such as breast, colorectal and prostate cancer. Few data are available for Renal Cell Carcinoma-RCC. **Methods:** We designed a multicenter prospective observational trial aiming to assess the association between CTC counts and PFS of RCC pts treated with an antiangiogenic tyrosine-kinase inhibitors as a first-line regimen for metastatic disease. OS and response rate were secondary objectives. Both basal and sequential counts were enumerated by Cellsearch system at 4 time points: day 0 of treatment, +1 mo, +3 mo, at progression or 12 mo in the absence of progression. Ethics Committee approval was obtained. **Results:** Among 246 pts, 195 are eligible for the present analysis, 71.4% males, median age 69 yrs (range, 27 to 91), 81% with previous partial/total nephrectomy. Treatment was sunitinib (77.5%), pazopanib (21%) or sorafenib (1.5%). According to Heng criteria there were 24.6% good, 62.6% intermediate and 24.6% poor prognosis pts. After a median follow-up of 31.5 mo, median PFS is 13.6 mo (23% censored), 49.2% of pts are still alive. Investigator-assessed best response was 3.8% complete, 37.3% partial response, 33% stable, 25.9% progression. At baseline 91 pts had 1 or more CTCs, median 2, range 1 to 263. Pts with at least 1 CTC had a significantly shorter PFS compared to negative pts (8.8 vs 16.6 mo, p = 0.03), HR = 1.41 (95%CI 1.02-1.9). Thirty pts had $>=3$ CTCs, with a median PFS of 5.8 vs 15 mo in the remaining pts (p = 0.002), HR = 1.99 (CI 1.28-3.03). Percentage of pts with $>=3$ CTCs increased from 6.6% of good, 18.4% intermediate and 38.9% poor Heng score pts (p = 0.042). Pts with $>=3$ CTCs had a shorter estimated OS of 13.8 mo vs 52.8 mo (p = 0.003), HR = 1.99 (CI 1,17-3.2). Correlation between CTC positivity and response rate was not significant. **Conclusions:** In this robust multicenter prospective cohort of first-line metastatic RCC pts, the presence of 3 or more CTCs predicts a significantly shorter PFS and OS. Further analyses are ongoing on apoptotic markers of CTCs and concomitant counts of endothelial cells collected in the same cohort.

4569 Poster Session (Board #247), Sun, 8:00 AM-11:30 AM

Inter and intra-tumor heterogeneity of PD-L1 and MET expression in metastatic renal cell carcinoma (mRCC). *First Author: Lisa Derosa, Department of Cancer Medicine, Gustave Roussy Cancer Campus, Paris-Sud University, Villejuif, France*

Background: Although inhibition of PD-1/PD-L1 and MET receptors have clinical efficacy in mRCC, their expression is not a predictive biomarker. Heterogeneity between the sites of disease might be one explanation. The aim of our study was to evaluate PD-L1 and MET expression in primary and metastases (brain (BM)/pancreas (PM)) RCC lesions and their correlation with clinicopathologic characteristics. **Methods:** RCC specimen from different institutions were collected. Clinicopathologic characteristics were assessed by revision of samples. PD-L1 and MET expression in tumor cells (TC) and immune cells (IC) ($>$ 1%) were assessed by immunohistochemistry. **Results:** 180resected RCC specimen were successful collected (42 primary tumors and 138 metastases (87 BM/51 PM)). Overall, 22%, 51% and 23% of patients had at least one specimen expressing PD-L1 TC, IC and MET, respectively. In primary tumours, the proportion was 12%, 50% and 0%, respectively. In metastasis, the proportion of PD-L1 TC was 22% (23% in BM vs 19% in PM, p = 0.631), PD-L1 IC was 48% (47% in BM vs 49% in PM, p = 0.821) and MET was 24% (35% in BM vs 2% in PM, $p < 0.001$). Comparing paired samples (primary tumour and metastasis) there was discordances of PD-L1 in TC or IC and of MET expression in 30%, 27% and 24% of samples, respectively. These two first disagreements seem varied over time. The discordance in PD-L1 TC or IC and MET between primary tumor and PM (BM) was 15% (40%), 33% (22%) and 0% (67%), respectively. Some correlations were observed between MET and PD-L1 and clinicopathologic characteristics. **Conclusions:** In this largest analysis, evaluating heterogeneity between primary tumor and metastases (brain/pancreatic lesions) in mRCC, PD-L1 and MET expression suggests that the assessment as predictive biomarkers may require analysis of metastatic lesions.

		Metastases				
Biomarker expression	**Primary RCC**	**All**	**PM**	**BM**	**P value**	**All specimens**
All patients (N = 180)						
PD-L1 TC	12%	22%	19%	23%	< 0.631	22%
PD-L1 IC	50%	48%	49%	47%	< 0.821	51%
MET	0%	24%	2%	35%	< 0.001	23%

4570 Poster Session (Board #248), Sun, 8:00 AM-11:30 AM

Clinical outcomes by nephrectomy status in METEOR, a randomized phase 3 trial of cabozantinib (cabo) vs everolimus (eve) in patients (pts) with advanced renal cell carcinoma (RCC). *First Author: Nizar M. Tannir, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Most pts with advanced RCC undergo nephrectomy (Nx) as curative or palliative therapy. In a retrospective analysis of pts treated with targeted therapy, pts who were older and had more comorbidities and higher tumor grade were less likely to have had Nx. Pts without Nx had shorter overall survival (OS) than pts with Nx (Hanna, J Clin Oncol 2016). Here we report outcomes for cabo vs eve in pts with advanced RCC with or without prior Nx in the phase 3 METEOR trial (NCT01865747). **Methods:** 658 pts with clear cell RCC and $\geq$1 prior VEGFR TKI were randomized 1:1 to receive cabo at 60 mg qd or eve at 10 mg qd. Stratification was by MSKCC risk group and number of prior VEGFR TKIs. Endpoints included progression-free survival (PFS), OS, and objective response rate (ORR). **Results:** 85% of enrolled pts had prior Nx of which 7% were partial; 15% had no prior nephrectomy (NoNx). Baseline characteristics, including Karnofsky performance status (KPS), MSKCC risk group, time from diagnosis to randomization, and median sum of diameters (SoD) for tumor target lesions, were less favorable for the NoNx subgroup (Table). Improved PFS and OS with cabo vs eve were observed regardless of Nx status. For the Nx subgroup, the hazard ratio (HR) was 0.51 (95% CI 0.41-0.64) for PFS and 0.66 (95% CI 0.52-0.84) for OS; for the NoNx subgroup, the HR was 0.51 (95% CI 0.30-0.86) for PFS and 0.75 (95% CI 0.44-1.27) for OS. Median OS was longer in the Nx subgroup for both treatment arms (Table). ORR per independent radiology committee (IRC) for cabo vs eve was 17% vs 4% for Nx and 21% vs 2% for NoNx. Grade 3 or 4 adverse events for both subgroups were generally consistent with the safety profiles of cabo and eve in the overall population. **Conclusions:** Cabo improved PFS, ORR, and OS compared with eve in pts with advanced RCC irrespective of nephrectomy status. Clinical trial information: NCT01865747.

	Prior Nephrectomy		No Nephrectomy	
	Cabo (N=283)	**Eve (N=279)**	**Cabo (N=47)**	**Eve (N=49)**
KPS <80, %	8	6	13	12
MSKCC poor risk, %	11	11	21	27
Diagnosis to randomization < 1 yr, %	14	18	43	51
Target lesion SoD per IRC, mm	61	63	94	104
Median PFS per IRC, mo	7.4	3.9	6.6	4.4
Median OS, mo	22.0	17.2	16.3	12.5

4571 Poster Session (Board #249), Sun, 8:00 AM-11:30 AM

Integrative analysis of sarcomatoid clear-cell renal cell carcinomas reveals an immune subgroup. *First Author: Gabriel G. Malouf, Pitié-Salpêtrière Hospital, Paris, France*

Background: Integrative analysis of clear-cell renal cell carcinomas (ccRCC) has revealed four transcriptomic subgroups associated with distinct patients outcomes. Integrative analysis of sarcomatoid ccRCC which represent the most agressive forms of ccRCC remains unknown. **Methods:** We performed integrative analysis of sarcomatoid (n = 28) and Fuhrman grade IV ccRCC (n = 9) using whole-exome sequencing (n = 37), RNA-sequencing (n = 32), and DNA methylation profiling by Infinium 450K arrays (n = 31). Correlation with clinico-pathlogical tumor features and patients outcomes were performed. **Results:** The most frequent somatic mutations in sarcomatoid ccRCC were *VHL* (71%), *PBRM1* (50%), *SETD2* (21%), *BAP1* (11%), and *TP53* (11%). Hierarchical unsupervised clustering of gene expression revealed two transcriptomic subgroups C1 and C2 which do not differ in term of clinical features, presence of sarcomatoid dedifferentiation and patients outcomes. Furthermore, these clusters do not differ according to their genomic features (*VHL, PBRM1* and *SETD2* mutations) or their mutational loads. Strikingly, C1 cluster was highly enriched for genes related to T cell receptor signaling pathway ($p = 2.6x10^{-6}$) and adapative immunity ($p = 8.5x10^{-5}$); in addition, the C1 « immune » subgroup was characterized by up-regulation of genes related to cell cycle. Conversely, C2 cluster revealed down-regulation of metabolic pathways ($p = 7.\ 5x10^{-5}$). At the epigenetic level, methylome clustering revealed two distinct epi-clusters, epi-C1 (n = 10) and epi-C2 (n = 21); patients with tumors belonging to C2 epi-cluster displayed 9p loss and harbored inferior progression-free survival as compared to those in C1 epi-cluster (11 months versus NR ; P = 0.02); of note, this was independent of clinico-pathological tumor features and transcriptomic classification. **Conclusions:** Our data suggest that genetic and epigenetic landscapes of sarcomatoid ccRCC might not differ from grade IV ccRCC. In addition, we discovered an immune sarcomatoid ccRCC cluster. This finding provides a rationale for use of immune checkpoint inhibitors in sarcomatoid ccRCC.

4572 Poster Session (Board #250), Sun, 8:00 AM-11:30 AM

Long-term response and time to response to pazopanib (PAZ) and sunitinib (SUN) in metastatic renal cell carcinoma (mRCC): COMPARZ subanalysis. *First Author: Nizar M. Tannir, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: COMPARZ (NCT00720941) was a phase 3, randomized, controlled, open-label trial that demonstrated comparable efficacy of first-line PAZ and SUN, but favorable safety and quality of life profiles for PAZ in 1110 patients with mRCC (NEJM 2013;369:722). The objectives of this study were to identify patients from COMPARZ who exhibited a long-term response (LTR) to PAZ and SUN, determine time to response, and describe the clinical characteristics of patients who achieved LTR. **Methods:** Patients in the intention-to-treat population of COMPARZ were analyzed for differences in LTR (≥10 months [mos]) as measured by responder rate with either complete response or partial response (CR/PR) and PFS rate, and time to response. We also compared the clinical characteristics between long-term and shorter-term responders within and between each treatment arm. **Results:** The overall percentage of long-term responders with CR/PR (PAZ = 14%, SUN = 13%) and PFS (PAZ = 31.4%, SUN = 33.6%) in the PAZ and SUN groups were similar. This similarity was observed regardless of the cut-off for long-term duration of response. However, a shorter time to achieve CR/PR was observed in the overall population with PAZ (11.9 weeks [95% CI, 11.3–12.1] vs 17.4 weeks; [95% CI, 12.7–18.0]). Analysis conducted to identify baseline clinical characteristics that may be related to LTR will be reported. **Conclusions:** These exploratory subanalyses in long-term responders support the overall efficacy results with PAZ and SUN, which were reported in the COMPARZ trial. However, the results here demonstrate that the time to response was shorter with PAZ versus SUN. Clinical trial information: NCT00720941.

4573 Poster Session (Board #251), Sun, 8:00 AM-11:30 AM

Differential expression of c-Met between primary and metastatic sites in clear-cell renal cell carcinoma (ccRCC) and its association with PD-L1 expression. *First Author: Aly-Khan A. Lalani, Dana-Farber Cancer Institute, Boston, MA*

Background: Preclinical models show that c-Met promotes survival of renal cancer cells through the regulation of programmed death-ligand 1 (PD-L1). The relationship between c-Met and PD-L1 in human ccRCC is not well characterized. We compared c-Met expression between primary and metastatic sites in ccRCC tissues and evaluated the association with PD-L1 expression. **Methods:** Pairedprimary and metastatic samples from 45 ccRCC patients were included. Areas with predominant and highest Fuhrman nuclear grade (FNG) were selected. c-Met expression was evaluated by IHC using an anti-Met monoclonal antibody (MET4 Ab, VARI) and calculated by a combined score (CS, 0-300) as: intensity of c-Met staining (0-3) x % of positive cells (0-100). PD-L1 expression was previously assessed by IHC (PMID: 26014095). c-Met expression (average c-Met CS) between paired primary and metastatic samples were compared using Wilcoxon signed-rank test. Associations of c-Met expression with PD-L1 expression (+/-) and other clinical features were assessed with Wilcoxon rank-sum tests. **Results:** Our cohort included 45 primary ccRCCs and 54 corresponding metastases. c-Met expression was higher in metastatic sites compared to primary (c-Met CS: 55 vs. 28, p=0.0003) and was numerically-greater in PD-L1+ vs. PD-L1- tumors. Higher c-Met expression was associated with higher FNG and T-stage in both primary and metastatic sites (Table). **Conclusions:** Higher c-Met expression in metastases compared to paired primary tumors in our cohort of ccRCC suggests that testing for biomarkers of response to c-Met inhibitors should be conducted in metastases. Although the observation of higher c-Met expression in PD-L1+ tumors requires further investigation, it supports exploring these targets in combination trials.

		c-MET expression - primary			c-MET expression - metastases		
Marker		**N**	**Median (IQR)**	**p**	**N**	**Median (IQR)**	**p**
PD-L1	(-), ≤ 0 %	32	24 (9,46)	0.34	36	51 (26,81)	0.45
	(+), > 0 %	13	30 (12,64)		9	60 (35,130)	
FNG	3	32	20 (6,43)	0.04	32	53 (14,81)	0.42
	4	13	52 (20,75)		13	60 (35,130)	
T-stage	Tx-T2	20	24 (9,38)	0.13	20	48 (26,81)	0.72
	T3-T4	25	30 (12,70)		25	55 (30,83)	

4574 Poster Session (Board #252), Sun, 8:00 AM-11:30 AM

Effects of pazopanib (PAZ) and sunitinib (SUN) dose modification on safety and efficacy in patients with metastatic renal cell carcinoma (mRCC) from COMPARZ. *First Author: Georg A. Bjarnason, Sunnybrook Research Institute, Toronto, ON, Canada*

Background: COMPARZ was a randomized, controlled, open-label, phase 3 trial that demonstrated comparable efficacy of first-line PAZ and SUN, but favorable safety and quality of life profiles for PAZ in patients (pts) with mRCC (NEJM 2013;369:722). We evaluated the relationship between dosing, safety, and efficacy in PAZ- and SUN-treated pts who did or did not undergo dose reduction or interruption resulting from adverse events (AEs) and other reasons. **Methods:** The AEs and median progression-free survival (mPFS) of PAZ and SUN were evaluated for pts with no, any, 1, and ≥2 dose reductions or dose interruptions lasting ≥7 days. **Results:** Similar percentages of pts in the PAZ and SUN groups had a dose interruption (44% vs 49%, respectively) or reduction (44% and 51%, respectively). The incidence of AEs in pts from the PAZ and SUN groups with dose modifications was higher compared to those with no dose modifications. Longer mPFS was observed in pts with dose modification (Table). Pts treated with PAZ or SUN with no dose reductions had mPFS of 7.3 months (mos) and 5.5 mos, respectively, whereas pts with any dose reduction had mPFS of 12.5 mos and 13.8 mos, respectively. Similarly, pts treated with PAZ or SUN with no dose interruptions lasting ≥7 days had mPFS of 8.2 mos and 5.6 mos, respectively, whereas those with any dose interruption lasting ≥7 days had mPFS of 12.6 mos and 13.8 mos, respectively. Pts with 2 or more dose interruptions or reductions had mPFS > 16 mos with both SUN and PAZ. **Conclusions:** Consistent with previous data for SUN, the current analyses showed longer mPFS with PAZ and SUN when dose modification is required to manage toxicity, suggesting that pts are not disadvantaged by such dose reductions or interruptions. Pts not requiring dose modification may have sub-optimal therapeutic drug exposure. Clinical trial information: NCT00720941.

Dose reduction(s), mPFS, (95% CI)	**PAZ, mos**	**SUN, mos**
None	7.3 (5.3–8.3)	5.5 (4.3–8.1)
Any	12.5 (10.9–15.0)	13.8 (11.1–16.4)
1	11.1 (8.3–13.5)	11.1 (10.2–13.8)
≥2	16.4 (11.1–18.6)	16.5 (11.5–19.3)
Dose interruption(s) ≥7 days, mPFS, (95% CI)		
None	8.2 (5.5–8.3)	5.6 (5.4–8.2)
Any	12.6 (9.9–16.4)	13.8 (11.1–16.6)
1	8.3 (6.0–11.0)	11.0 (8.2–14.0)
≥2	16.7 (13.7–19.4)	16.6 (13.6–19.6)

4575 Poster Session (Board #253), Sun, 8:00 AM-11:30 AM

A phase I clinical trial of CM082 (X-82) in combination with everolimus for treatment of metastatic renal cell carcinoma. *First Author: Xinan Sheng, Peking University Cancer Hospital and Institute, Beijing, China*

Background: CM082 is an oral multikinase inhibitor targeting VEGFR, PDGFR and CSF1R with a shorter half-life and limited tissue accumulation, designed to lower toxicity and enable combination with other therapies. This is a phase I study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of CM082 in combination with everolimus in patients with metastatic renal cell carcinoma. **Methods:** A 3+3 dose escalation design with expansion cohort was utilized to determine the dose-limiting toxicities (DLT) and the maximum tolerated dose (MTD) of CM082 plus everolimus at 5 mg PO daily for patients with metastatic clear cell renal cell carcinoma. Eligibility include PS 0-1, age ≥18 y, measurable disease, adequate organ function. **Results:** 22 patients (M/F: 16/6; median age: 55 y [range 32-69]; 21/22 pts [95.5%] had received prior anti-VEGF treatment (tx); 2/22 pts [9.1%] had also received prior mTOR-targeted tx) were treated at 3 dose levels of CM082 (100 mg [n = 4]; 150 mg [n = 3]; 200 mg [n = 15]) in combination with everolimus 5 mg. One patient in cohort 1 was not evaluable for DLT due to consent withdrawal. DLT were observed in one patient: G4 thrombocytopenia at 200 mg. CM082 200 mg plus everolimus 5 mg did not exceed MTD, but was chosen as the optimal biological dose regimen. Median duration of tx was 24 wk (range 1-57, 7/22 [32%] pts ongoing. The most common tx-related adverse events (AEs), all grades, were proteinuria 96% (G3, 5%); leukopenia 77% (G3, 9%); neutropenia 59%, hypercholesterolemia 64%, anemia 50% (G3, 9%), hypertension 46% (G3, 14%), raised aspartate aminotransferase 41%, fatigue 45%, diarrhea 32%, hypertriglyceridemia 32% (G3, 5%) and thrombocytopenia 20% (G4, 5%). At 200mg, partial response (PR) was observed in 5/14 (36%) patients, durable stable disease (SD) (≥24 week) or PR were achieved in 10/14 (71%) patients. Median PFS was 170 days (5.7 months) at this cohort. **Conclusions:** CM082 200mg in combination with everolimus 5 mg appeared to be well tolerated when administered to pretreated patients with advanced RCC in this Ph1 study. The preliminary efficacy warrant further evaluationand and the follow-up Ph 2/3 study is underway. Clinical trial information: NCT02577458.

4576 Poster Session (Board #254), Sun, 8:00 AM-11:30 AM

The association of tumor infiltrating CD8$^+$ and Foxp3$^+$ cells with overall response rate (ORR) in metastatic renal cell carcinoma (mRCC) patients treated with high-dose aldesleukin (HD IL-2). *First Author: Jean-Christophe Pignon, Brigham and Women's Hospital, Boston, MA*

Background: In the prospective, biomarker validation HD IL-2 "Select" study, durable remissions and prolonged survival were seen in both proposed "good" and "poor-risk" patients, based on clear-cell histology sub-classification and carbonic anhydrase-9 (CA-9) IHC staining. Given the toxicity and limited efficacy of HD IL-2, efforts to improve its therapeutic index are warranted. Since the high-affinity receptor of IL2 is expressed on both T regulatory cells and activated effector T lymphocytes, we explored the association between HD IL-2 response and tumor infiltration of CD8$^+$ T and FoxP3$^+$cells. **Methods:** Archival tumor tissue was collected for pathologic analysis on 120 mRCC patients enrolled in the HD IL-2 "Select" trial. Density of tumor infiltrating CD8$^+$ T cells and Foxp3$^+$ cells (cell/mm^2) were evaluated in the invasive margin (IM) and the tumor center (TC) by IHC and automated image analysis using Aperio algorithms. The association between ORR and immune cell density was assessed using Fisher exact test. **Results:** Tumor specimens of 89 patients were available for analysis. 24 pts experienced response (R, including 2 CR and 22 PR) and 65 pts did not respond (NR, including 11 SD and 54 PD). Baseline patient characteristics were similar between R and NR groups. A very high density of CD8$^+$ cells in the IM, or a high density of Foxp3$^+$ cells in the TC were significantly associated with ORR. A stronger association with ORR was found for patients having both high density of CD8$^+$ cells in the IM and Foxp3$^+$ cells in the TC. **Conclusions:** In this prospective, biomarker validation study, response to HD IL-2 was associated with a high density of CD8$^+$ cells in the invasive margin, and a high density of Foxp3$^+$cells in the tumor center. Independent validation is ongoing. To improve the predictive value of Foxp3, characterization of Foxp3 expressing cells (Tregs vs activated effector T cells) in highly infiltrated tumors is underway.

Marker	Percentile Cutoff (cells/mm2)	R %	NR %	Total n	p-value
CD8 IM	≥ 75th (759)	41	18	77	0.039
Foxp3 TC	≥ 25th (3.7)	95	67	89	0.004
	≥ 50th (8.1)	75	41	89	0.005
CD8 IM + Foxp3 TC	≥ 75th and ≥ 25th	41	9	77	0.002

4577 Poster Session (Board #255), Sun, 8:00 AM-11:30 AM

Safety and efficacy of nivolumab for metastatic renal cell carcinoma (mRCC): Real world data from an Italian expanded access program (EAP). *First Author: Ugo De Giorgi, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*

Background: Nivolumab showed a survival benefit in a randomised phase III trial in pre-treated mRCC. The EAP provided the opportunity to treat patients (pts) in real world clinical practice before market availability of the drug clinical practice. The aim of this analysis was to evaluate the safety and activity of nivolumab in a real world setting. **Methods:** Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for mRCC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events using CTCAE v.4.0. **Results:** Totally, 389 pts were enrolled in the EAP across 95 Italian sites, median age was 65 years (range, 34-85) with 70 (18%) aged ≥ 75 yrs. Pts had a clear-cell RCC in 92% of cases, bone metastases in 50% and brain metastases in 8%, and received more than one previous line in 79% of cases. At the time of this analysis, median number of doses received was 10 (1-31) and 82 (21%) pts were treated beyond progression. Among 389 pts, 18 pts (5%) discontinued treatment due to AE. The best overall response rate was 17% including one complete and 66 partial responses, whereas 121 (31%) had stable disease. With a median follow-up of 7 months (range, 1 to 16), 6-month and 9-month survival rates were 83% and 77%, respectively. Response and survival rates were comparable among pts regardless age, presence of brain or bone metastases and number of prior therapies. **Conclusions:** This EAP represents the most extensive reported real-world experience with nivolumab in pre-treated RCC pts. These first data seem to confirm efficacy and safety data of the pivotal trial in a real world setting. Results in patient populations poorly (elderly or bone metastases) or not represented at all (brain metastases) in the pivotal trial encourage the use of nivolumab in these subgroups of RCC pts.

4578 Poster Session (Board #256), Sun, 8:00 AM-11:30 AM

Outcomes based on age in the phase 3 METEOR trial of cabozantinib (cabo) vs everolimus (eve) in patients with advanced renal cell carcinoma (RCC). *First Author: Frede Donskov, Aarhus University Hospital, Aarhus, Denmark*

Background: The incidence of RCC increases with age with the highest incidence at ~75 years of age (Znaor, Eur Urol 2015). The Phase 3 METEOR trial (NCT01865747) showed a significant improvement in progression-free survival (PFS; HR 0.58, 95% CI 0.45–0.74; P < 0.0001), overall survival (OS; HR 0.66, 95% CI 0.53–0.83, P = 0.0003), and objective response rate (ORR; 17% vs 3%; P < 0.0001) for cabo compared with eve in patients with advanced RCC previously treated with VEGFR TKIs (Choueiri, NEJM 2015, Lancet Oncol 2016). Here we present outcomes by 3 categories of age for the METEOR trial. **Methods:** 658 patients were randomized 1:1 to cabo (60 mg qd) or eve (10 mg qd). Stratification factors were MSKCC risk group and number of prior VEGFR TKIs. Endpoints included PFS, OS, and ORR. Subgroup analyses by age (< 65, 65 to 74, and ≥75 years) are presented. **Results:** At baseline, 60% of patients were < 65 years old, 31% were 65 to 74 years old, and 10% were ≥75 years old. Subgroups by age generally had similar baseline characteristics in both arms. The HRs for PFS favored cabo for all age groups (HR 0.53, 95% CI 0.41–0.68 for < 65 years old; 0.53, 95% CI 0.37–0.77 for 65 to 74 years old; and 0.38, 95% CI 0.18–0.79 for ≥75 years old). ORR per independent radiology committee for cabo vs eve was 15% vs 5% for < 65 years old, 21% vs 2% for 65 to 74 years old, and 19% vs 0% for ≥75 years old. HRs for OS also favored cabo (HR 0.72, 95% CI 0.54–0.95 for < 65 years old; 0.66, 95% CI 0.44–0.99 for 65 to 74 years old; and 0.57, 95% CI 0.28–1.14 for ≥75 years old). Median OS for cabo vs eve was 21.4 mo vs 17.1 mo for < 65 years old, not reached vs 18.0 mo for 65 to 74 years old, and 18.4 mo vs 14.0 mo for ≥75 years old. Older patients more frequently had dose reductions (60% with cabo and 22% with eve for < 65 years old vs 85% with cabo and 36% with eve for ≥75 years old). Grade 3 or 4 adverse events were generally consistent with the safety profiles in the overall population although some events such as fatigue and hypertension occurred at a higher rate in older patients. **Conclusions:** Treatment with cabo improved PFS, ORR, and OS compared with eve in patients with advanced RCC irrespective of age. Adverse events in older patients were more frequently managed with dose reductions. Clinical trial information: NCT01865747.

4579 Poster Session (Board #257), Sun, 8:00 AM-11:30 AM

Development and clinical validation of circulating tumor cell (CTC) biomarkers in clear cell renal cell carcinoma (ccRCC) for the OMNIVORE clinical trial. *First Author: Waddah Arafat, University of Wisconsin, Madison, WI*

Background: New therapeutic strategies and biomarkers of treatment resistance are needed for metastatic ccRCC patients (pts) progressing on Nivolumab (Nivo). The upcoming OMNIVORE phase II clinical trial will evaluate whether adding Ipilumimab improves rPFS for pts with SD or PD on Nivo alone. We report development and clinical validation of predictive CTC biomarkers that will be evaluated in the OMNIVORE trial. **Methods:** We tested blood samples from ccRCC pts collected on biomarker trials at Dana Farber and U. of Wisconsin. Carbonic Anhydrase (CA) IX was used to capture CTCs in the VERSA platform to compare protein and gene expression signatures of resistance to Nivo. HLA and PD-L1 expression on CTC was quantified with independent confirmation with multicolor flow cytometry (FC). **Results:** We identified CTCs in 26/27 pts using RCC-specific CA IX antibody. Staining with CAXII and PAX8 confirmed CTC were of renal origin. The range of captured CK+/CAXII+/CD45- CTCs was 3-279 (median 15) from 18 pts. Multicolor FC found 8/9 pts with triple positive events for renal specific markers CAIX/CAXII/PAX8 [0-14.9%, median 0.32]. PDL1 and HLA staining was validated in cell line and pts samples with high reproducibility. PDL1 was expressed in < 10% of CTCs while HLA expression had high intra- and interpatient heterogeneity. Three pts had CTCs positive for both HLA and PDL1 that correlated with a high frequency of CTCs that were positive for 3 RCC markers (1.3, 5.1 and 14.9% of events) for an R^2 value of 0.92 ($p < 0.0001$). In 3 pts with ongoing response to Nivo (9-13 moths) triple positive events were 0, 0.2 and 0.3% (median 0.25%) and absent expression of PDL1/HLA. In 3 pts with early progression on Nivo (< 5 mo), triple positive CTCs ranged 0.33-14.9% (median 5.05%) with CTCs from 2/3 pts positive for PDL1/HLA. **Conclusions:** We report the first identification of ccRCC CTCs using CAIX, CAXII and PAX8 as confirmatory markers. CTC frequency and PDL1/HLA expression is lower in Nivo responders versus pts with early progression. High but variable HLA expression suggests variant resistance mechanisms. The utility of theses predictive and pharmacodynamic biomarkers will be tested in the OMNIVORE trial.

4580 Poster Session (Board #258), Sun, 8:00 AM-11:30 AM

Checkpoint inhibitors in metastatic renal cell carcinoma patients including elderly subgroups: Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). *First Author: Steven Yip, University of Calgary, Calgary, AB, Canada*

Background: Immuno-oncology (IO) checkpoint inhibitor treatment outcomes are poorly characterized in the real world metastatic renal cell cancer (mRCC) patient population, including geriatric patients. **Methods:** Using the IMDC database, a retrospective analysis was performed on mRCC patients treated with IO, as listed below. Patients received one or more lines of IO therapy, with or without a targeted agent. Duration of treatment (DOT) and overall response rates (ORR) were calculated. Cox regression analysis was performed to examine the association between age as a continuous variable and DOT. **Results:** 312 mRCC patients treated with IO were included. In patients who were evaluable, ORR to IO therapy was 29% (32% first-, 22% second-, 33% third-, and 32% fourth-line treatment (Tx)). Patients treated with second-line IO therapy were divided into favorable, intermediate, and poor risk using IMDC criteria; the corresponding median DOT rates were not reached (NR), 8.6 mo, and 1.9 mo, respectively ($p<0.0001$). Based upon age, hazard ratios were calculated in the first- through fourth-line therapy setting, ranging from 1.03 to 0.97. **Conclusions:** The ORR to IO appears to remain consistent, regardless of line of therapy. In the second-line, IMDC criteria appear to appropriately stratify patients into favorable, intermediate, and poor risk groups for DOT. Premature OS data will be updated. In contrast to clinical trial data, longer DOT is observed in real world practice. Age may not be a factor influencing DOT.

	1st Line IO	2nd line IO	3rd line IO	4th line IO
Total N	63	116	82	51
Atezolizumab-Based (Atezo) Tx				
Nivolumab-Based (Nivo) Tx	17	2	1	1
Pembrolizumab-	40	111	81	49
Based (Pembro) Tx	3	2	0	1
Avelumab-Based Tx	3	1	0	0
Non-Clear Cell	9%	10%	9%	6%
Brain mets	3%	8%	7%	3%
KPS < 80	5%	18%	20%	35%
Age ≥ 70	10%	27%	21%	29%
IMDC Criteria				
Favorable	26%	16%	8%	3%
Intermediate	53%	68%	67%	76%
Poor	21%	15%	25%	21%
Best Response				
CR	4%	0%	0%	3%
PR	30%	22%	38%	28%
SD	55%	39%	33%	31%
PD	11%	39%	29%	38%
ORR < 70 YO	35% (17/49)	21% (13/61)	42% (16/38)	35% (8/23)
ORR ≥ 70 YO	25% (1/4)	25% (4/16)	14% (1/7)	22% (2/9)
DOT (mo) (95%CI)	11.8 (8.3-27.8)	9.2 (6.5-13.6)	8.5 (5.1-12.8)	7.8 (5.6-NR)

4581 Poster Session (Board #259), Sun, 8:00 AM-11:30 AM

Genomic instability and DNA damage repair in clear cell renal cell carcinoma. *First Author: Patrick Glen Pilie, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Kidney cancer accounts for 2-3% of all new cancers with clear cell renal cell carcinoma (ccRCC) the most common subtype. ccRCC is characterized by a high level of genomic instability, suggesting defective DNA damage repair (DDR). The most frequent genomic alteration in ccRCC involves loss of the 3p chromosomal arm which harbors the von Hippel Lindau gene (*VHL*), in addition to nearby genes *SETD2*, *BAP1*, and *PBRM.* We hypothesized that VHL loss leads to defective DDR as an early event in ccRCC carcinogenesis, giving way to a mutator phenotype. We posited that assessment of very early ccRCC tumors would inform us regarding the core mutations required to drive tumorigenesis in ccRCC, and that we could confirm these findings in appropriate model systems. **Methods:** We performed whole-exome (WES) DNA sequencing on 11 early-stage ccRCC tumors from 5 individuals, along with their matched normal DNA. We then analyzed ccRCC samples with and without somatic *VHL* mutations from the Cancer Genome Atlas (TCGA) for mutational load. Finally we assessed DDR signaling activity in renal proximal tubular cell lines (RPTEC) with *VHL/SETD2* knockdown and in murine embryo fibroblasts (MEFs) from *Vhl* and *Setd2*knockout mice treated with etoposide via γH2AX expression and direct repeat-green fluorescent protein reporter assay. **Results:** All 11 samples revealed loss of 3p with pathogenic germline or somatic mutation in remaining *VHL* allele. No mutations were found in genes frequently mutated in larger ccRCC, including *PBRM1*, *BAP1* or *SETD2*. WES revealed ~100 mutations/tumor, with no shared mutations across samples, even within the same individual. TCGA analysis showed similar mutational loads across ccRCC samples. MEFs with biallelic loss of *Vhl* and monoallelic loss of *Setd2* and RPTEC with *VHL* and *SETD2*knockdown displayed increased DNA damage with impaired homologous repair and increased non-homologous end joining (NHEJ). **Conclusions:** Early stage ccRCC tumors with loss of *VHL* and chr 3p demonstrate genomic instability and a mutator phenotype similar to more advanced ccRCC. Cell line models of early ccRCC show increased DNA damage with a greater reliance on error-prone NHEJ machinery. These defects could be targeted for synthetic lethal treatment strategies.

4582 Poster Session (Board #260), Sun, 8:00 AM-11:30 AM

Association of circulating tumor DNA (ctDNA) detection in metastatic renal cell carcinoma (mRCC) with tumor burden. *First Author: Manuel Caitano Maia, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil*

Background: In a series of 224 pts with advanced RCC, we have previously reported ctDNA detection in 79% of pts (Pal SK *et al* ASCO GU 2017). Clinical factors associated with detection are unknown. M**ethods:** Data was obtained from pts with radiographically confirmed stage IV RCC who received ctDNA profiling as a part of routine clinical care using a CLIAA-certified platform evaluating 73 genes. Detailed clinical annotation was performed, including assessment of Heng risk score, previous and current treatments and calculation of tumor burden using scan data most proximal to ctDNA assessment. Tumor burden was equated to the sum of longest diameter (SLD) of all measurable lesions. **Results:** 32 pts were assessed (M:F 19:13) with a median age of 62 (range, 34-84). 25 pts, 4 pts and 3 pts had clear cell, sarcomatoid and papillary histology, respectively. Heng risk was good, intermediate and poor in 13, 18 and 1 pt, respectively. Pts received a median of 2 lines of prior tx. Specifically, 4 pts were not on active therapy (tx), 16 pts were receiving VEGF-directed tx, 6 pts were receiving checkpoint inhibitors (CPIs) and 6 pts were receiving combined VEGF/CPI tx. ctDNA was detected in 16 pts (50%) with a median of 2 genomic alterations (GAs) per pt. No associations were found between Heng risk, histology or tx type and presence/absence of ctDNA. However, pts with detectable ctDNA had a higher SLD compared to pts with no detectable ctDNA (99.6 vs 50.0 mm; P = 0.041). Furthermore, when evaluated as a continuous variable, number of GAs was correlated with SLD (P = 0.023). *TP53* and *VHL* alterations were the most frequent GAs in this series, each occurring in 25% of the cohort. All 3 pts with brain metastases had ctDNA detected. **Conclusions:** With the caveat of a limited sample size, it appears that SLD (a surrogate for tumor burden) is higher in mRCC pts with detectable ctDNA, and increasing SLD may be associated with a higher number of GAs. Further validation of these findings may help identify appropriate pts for ctDNA assessment and maximize yield in clinical practice.

4583 Poster Session (Board #261), Sun, 8:00 AM-11:30 AM

Impact of geographic region on overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC): Results from a pooled clinical trials database. *First Author: Andre Poisl Fay, PUCRS School of Medicine, Porto Alegre, Brazil*

Background: Health determinants vary according to the geographic region and may impact the outcomes of mRCC patients treated on clinical trials of targeted therapy. We investigate the OS by geographic region of mRCC patients treated in the targeted therapy era. **Methods:** We conducted a pooled analysis of mRCC patients treated on phase II and III clinical trials. Clinical characteristics and survival data were collected. Statistical analyses were performed using the Kaplan-Meier method and log-rank test in univariate analysis. **Results:** Overall, 4736 patients were included in the analysis. Patient characteristics differed according to geographic region (table). No statistically significant differences in OS were observed when comparing US/Canada (USC, reference) to other regions: Latin America (LA), Asia/Oceania/Africa (AOA), and Eastern Europe (EE). OS differed among patients enrolled on trials in the USC compared to Western Europe (WE) (20.3 vs.17.4 months, respectively; HR: 1.15; 95%CI 1.03-1.3 $p = 0.015$). All grade treatment-related adverse events (AE) were reported more frequently in USC. There were no significant differences in grade 3-5 AEs between groups. **Conclusions:** We highlight that despite differing baseline characteristics, OS was similar among most geographic regions. Factors such as disease biology, access to care, AE reporting, and quality of care that may contribute to potential differences in outcomes among regions need to be further characterized.

	USC (n = 1544) n(%)	AOA (n = 1254) n(%)	WE (n = 897) n(%)	EE (n = 792) n(%)	LA (n = 250) n(%)
Mean Age(yrs)	60.5	57.8	60.6	58.8	57.4
ECOG PS 0	841(54.5)	653(52.1)	476(53)	358(45.2)	167(66.8)
Prior Nephrectomy	1235(80)	846(67.5)	654(72.9)	380(48)	125(50)
BMI > 25	1073(80.1)	557(44.4)	509(56.7)	506(63.9)	173(69.2)
Baseline HTN	871(56.4)	405(32.3)	407(45.4)	334(42.2)	106(42.4)
IMDC Poor Risk Disease	389(25.2)	247(19.7)	215(23.9)	252(31.8)	42(16.8)

4584 Poster Session (Board #262), Sun, 8:00 AM-11:30 AM

Sunitinib in patients with metastatic renal cell carcinoma: Clinical outcome according to IMDC risk group. *First Author: Brian I. Rini, Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH*

Background: In a phase III study (NCT00083889), treatment-naïve patients (pts) with metastatic renal cell carcinoma (mRCC) of all prognostic risk groups were treated with sunitinib or interferon-α (IFN-α). Since sunitinib has become the reference standard of care and serves as the comparator in multiple randomized trials sometimes restricted to prespecified risk groups, a retrospective analysis of outcome according to prognostic group from the phase III study was performed. **Methods:** Investigator-assessed efficacy data were analyzed for pts based on risk group (International mRCC Database Consortium [IMDC] criteria). The objective was to determine objective response rate (ORR), median progression-free survival (mPFS), and median overall survival (mOS) benchmarks by risk group. **Results:** Of sunitinib-treated pts, 134 were favorable, 205 were intermediate, and 34 were poor risk. The median sunitinib treatment duration/median number of cycles was 16.7 mo/12 cycles, 11.0 mo/8 cycles and 2.6 mo/2.0 cycles for favorable-, intermediate-, and poor-risk pts, respectively. ORR, PFS, and OS benchmarks for sunitinib-treated pts are shown in the Table. In sunitinib-treated intermediate-risk pts with 1 vs 2 risk factors, respectively: ORR was 43.3% vs 40.8%, mPFS (95% confidence interval [95% CI]) was 11.2 (9.7–13.6) vs 8.5 (5.6–10.7) mo, and mOS (95% CI) was 28.2 (23.0–not estimable) vs 16.3 (13.2–19.4) mo. **Conclusions:** This retrospective analysis provides ORR, PFS, and OS benchmarks for current and future clinical trial interpretation in mRCC pts with different prognostic risk treated with sunitinib.

Endpoint	Favorable risk (n=134)	Intermediate risk (n=205)	Poor risk (n=34)
ORR, %	58.2	42.4	17.6
(95% CI)	(49.4–66.7)	(35.8–49.7)	(6.8–34.5)
PFS, mo	16.0	10.7	2.5
(95% CI)	(13.6–17.3)	(8.6–12.5)	(2.3–6.5)
PFS HR, mo (vs IFN-α; 95% CI)	0.57 (0.42–0.78)	0.47 (0.37–0.59)	0.91 (0.54–1.54)
OS, mo (95% CI)	NE (NE–NE)	23.0 (19.8–27.8)	5.1 (4.3–9.9)
OS HR, mo (vs IFN-α; 95% CI)	1.05 (0.66–1.67)	0.79 (0.62–1.03)	1.01 (0.64–1.60)

HR=hazard ratio; NE=not estimable

4585 Poster Session (Board #263), Sun, 8:00 AM-11:30 AM

Evaluation of disease-free survival as an intermediate metric for overall survival in localized renal cell carcinoma: A trial-level meta-analysis. *First Author: Lauren Christine Harshman, Dana-Farber Cancer Institute, Boston, MA*

Background: Adjuvant trials aim to integrate systemic therapy earlier to increase cure rates over surgery alone. Overall survival (OS) is a critical endpoint for these studies but requires long durations to events and significant patient resources. We explored the potential use of disease-free survival (DFS) as an intermediate readout for OS in the adjuvant setting for localized renal cell carcinoma (RCC). **Methods:** We performed a systematic literature review following the PRISMA guidelines. Inclusion criteria required randomized controlled trials (RCT) for adjuvant systemic therapy in localized RCC, which reported on both DFS and OS. Data on hazard ratio (HR) and 5-year event-free rate from Kaplan-Meier estimates were extracted. We performed a trial level meta-analysis and correlated these estimates for OS and DFS, weighted by the number of DFS events. R-square > 0.7 would indicate a strong correlation and potential for surrogacy. **Results:** Thirteen RCTs encompassing 6,473 patients treated with various forms of systemic therapy were eligible for the analyses. Minimum follow-up was 40 months. There was a moderate correlation between 5-year DFS and 5-year OS rates (R-square = 0.49, 95% CI:0.15-0.68) and between treatment effects as measured by DFS and OS hazard ratios (R-square = 0.44, 95% CI:0.00-0.69). **Conclusions:** Across trials of adjuvant systemic therapy for localized RCC, we observed a moderate correlation between 5-year DFS and OS rates and between treatment effects (HRs) on these endpoints. Further granularity may be achieved using individual patient data to assess different and earlier time points for surrogacy than are commonly reported.

Summary of trial level correlations between DFS and overall survival.

Correlation	No of units	R-square	95% CI
Correlation between 5 yr OS and DFS	22*	0.49	0.15-0.68
Correlation between DFS and OS treatment effects (HR)**	11	0.44	0.00-0.69

*11 (trials) * 2 (arms) = 22 units **Natural log transformed

4586 Poster Session (Board #264), Sun, 8:00 AM-11:30 AM

Nivolumab treatment for patients with non-clear cell renal cell carcinoma: A multicenter retrospective analysis. *First Author: Vadim S. Koshkin, Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH*

Background: Nivolumab (Nivo) is approved for metastatic renal cell carcinoma (mRCC) refractory to prior antiangiogenic therapy. However, the clinical activity of Nivo in non-clear cell RCC subtypes remains unknown as these patients were not part of the trial population. **Methods:** Patients (pts) from 3 centers who received at least one dose of Nivo as monotherapy for mRCC between 12/2015 and 01/2017 were identified. All patients had histologically-confirmed non-clear cell histology. A retrospective analysis focusing on patient and treatment characteristics, objective response according to RECIST v1.1 and adverse events (AEs) was undertaken. **Results:** Twenty-three patients were identified. Median age was 59 years (33-82), 78% were male, 61% were white, 30% black and 9% Hispanic. MSKCC risk groups were 19% favorable, 67% intermediate, 14% poor. Most common histologies were Unclassified (48%) and Papillary (44%), followed by Collecting duct and Mucinous tubular and spindle cell carcinoma (MTSCC) (4% each). The majority of pts had ECOG PS 0 (57%) or 1 (33%). At diagnosis, 65% had metastatic disease; most common sites were lung (57%), retroperitoneal lymph nodes (35%), and liver or bone (26% each). Most pts (74%) had prior nephrectomy and had received one (74%) or > 1 (26%) prior systemic therapy, most commonly sunitinib (65%), pazopanib (30%) or axitinib (17%). No pts had prior IL-2, but one pt had atezolizumab on trial. After a median follow-up of 6.5 months (mos) and 8 Nivo doses, median PFS was 4.2 mos and median OS was not reached. Among 21 pts evaluable for best response, 6 (29%) had PR and 4 (19%) had SD. Median time to best response was 5.1 mos. At the time of analysis, 9 pts were still on Nivo, 2 were on treatment break, 8 pts had subsequent treatment after PD on Nivo, and 2 were lost to follow-up. Two of 23 pts died. Most common AEs ($> 10\%$, any grade) were fever (13%) and fatigue (13%). Nivo treatments were postponed in 6 pts due to intolerance and stopped in3 pts. There were no treatment-related deaths. **Conclusions:** Nivolumab monotherapy demonstrated a substantial objective response rate and was well tolerated in a heterogeneous population of treatment-refractory patients who had mRCC with non-clear cell histology.

4587 Poster Session (Board #265), Sun, 8:00 AM-11:30 AM

T cell infiltration (TCI) in matched renal biopsy (bx) and nephrectomy (nx) samples in renal cell carcinoma (RCC). *First Author: Haris Zahoor, Cleveland Clinic, Cleveland, OH*

Background: TCI in tumors has been investigated as a biomarker of response to checkpoint inhibitors. A neo-adjuvant trial of checkpoint inhibition in locally-advanced RCC is ongoing at Cleveland Clinic, where TCI in pre-treatment renal mass bx will be compared to post-treatment nx specimens. However, there are no data regarding the association of TCI in matched bx and nx samples without intervening treatment. Understanding this association will enable further study of this potential biomarker in future studies. **Methods:** Matched bx and nx samples (without intervening systemic therapy) were identified from patients with non-metastatic RCC. Selected tissue sections from bx and nx samples were reviewed, and marked for intra-tumoral lymphocytes by the Pathologist. Immunohistochemistry (IHC) was utilized to stain these selected tissue sections for T cell markers (CD3, CD4 and CD8), and additional immune markers including PD-1, PDL-1 and CD11b. Intra-tumoral staining was then quantified in the pre-marked tissue sections as counts per total tumor area surveyed. Spearman correlation (ρ) was used to measure the strength of association. **Results:** 30 matched pairs were investigated. The median interval between bx and nx was 2.8 (0.2-87.7) months. Clear cell was the most common histology (29/30; 97%). There was a positive correlation between the frequency of $CD8^+$T cells between matched bx and nx samples ($\rho = 0.39$; $p=0.03$). CD3, CD4 and CD11b did not show significant correlation. (Table) PD-1 (bx 4/29, nx 16/29) and PDL-1 (bx 5/28, nx 10/28) expression was positive in the minority of samples. **Conclusions:** Bx material can potentially be used to assess the degree of $CD8^+$ TCI in RCC nx samples. However the utility of bx evaluation for $CD4^+$TCI and expression of PD-1, PDL-1 and CD11b requires further study.

	Bx		Nx			
Marker	Median	Range	Median	Range	ρ	p-value
CD3	6.37×10^{-3}	$6.96 \times 10^{-4} - 5.13 \times 10^{-2}$	1.68×10^{-3}	$1.65 \times 10^{-4} - 1.06 \times 10^{-2}$	0.11	0.55
CD4	3.18×10^{-3}	$3.87 \times 10^{-5} - 3.28 \times 10^{-2}$	2.35×10^{-3}	$3.64 \times 10^{-5} - 3.03 \times 10^{-2}$	0.19	0.30
CD8	2.73×10^{-3}	$4.89 \times 10^{-5} - 2.01 \times 10^{-1}$	1.24×10^{-3}	$3.22 \times 10^{-5} - 3.80 \times 10^{-2}$	0.39	0.03
CD11b	9.33×10^{-4}	$1.53 \times 10^{-5} - 2.86 \times 10^{-2}$	7.82×10^{-4}	$1.84 \times 10^{-5} - 7.68 \times 10^{-3}$	0.23	0.22

4588 Poster Session (Board #266), Sun, 8:00 AM-11:30 AM

Incidence of T3a upstaging and survival after partial nephrectomy: Size-stratified rates and implications for prognosis. *First Author: Arnav Srivastava, Johns Hopkins, Baltimore, MD*

Background: The use of partial nephrectomy (PN) to treat renal cell carcinoma has grown in the past decade, with expansion to larger tumors. Performing PN for larger tumors may increase the number of patients up-staged to pT3a after surgery, who may have underwent radical nephrectomy (RN), if known preoperatively. We aimed to estimate the proportion of patients up-staged to T3a disease after PN, stratified by size. We also compared size-stratified survival of up-staged pT3a patients to those with T1a, T1b, or T2 disease. **Methods:** From 1998 – 2013, we identified patients undergoing PN or RN from the Surveillance Epidemiology and End Results registries. The proportion of patients receiving PN found to have pT3a disease was quantified by size. Cox proportional hazards models compared cancer-specific (CSS) and overall survival (OS) for PN patients with pT1a, pT1b, and pT2 disease to size-stratified pT3a patients. Also, we compared PN patients with pT3a disease to RN patients with pT3a disease. **Results:** From the 28,854 patients undergoing PN, the estimated proportion up-staged to pT3a increased along with tumor size: 4.2% for T1a, 9.5% for T1b, and 19.5% for T2. Among those receiving PN, survival analysis showed worse CSS for up-staged pT3a patients versus stratified pT1a (HR = 1.87, p = 0.02), pT1b (HR = 1.91, p = 0.01), and pT2 (HR = 2.33, p = 0.01) patients. When assessing OS, only in tumors $<$ 4cm did the pT3a cohort demonstrate worse OS (HR = 1.25, p = 0.04). Comparing PN and RN for pT3a disease, size-adjusted analysis revealed no difference in CSS or OS. Lastly, among pT3a patients undergoing PN, patients with larger tumors, measuring 4 – 7cm (OS: HR = 1.44, p = 0.04) or 7 – 16cm (OS: HR = 2.64, p $<$ 0.01), had worse survival than those with tumors $<$ 4cm. **Conclusions:** A greater proportion of patients experience T3a up-staging after PN with increasing initial T stage. Up-staged pT3a patients have worse CSS after PN compared to those with similarly sized localized tumors. Also, pT3a patients after PN showed similar survival to pT3a patients after RN. However, pT3a patients undergoing PN had worse survival with increasing tumor size, reinforcing the need for improvements in identifying patients at risk of up-staging.

4589 Poster Session (Board #267), Sun, 8:00 AM-11:30 AM

Impact of perioperative chemotherapy and radiation for locally advanced penile squamous cell carcinoma (PSCC). *First Author: Amanda Redden Hathaway, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

Background: While neoadjuvant chemotherapy preceding radical surgery (S) for PSCC appears to provide the most optimal outcomes, there are no randomized studies. The impact of triple-modality S plus perioperative chemotherapy (C) plus radiation (XRT) for PSCC is unclear. The differential outcomes provided by perioperative XRT vs. perioperative C are also unclear. Given the absence of prospective trials, we retrospectively analyzed the U.S. National Cancer Database (NCDB) to study this issue. **Methods:** Data from the NCDB was obtained for pts with locally advanced PSCC from 1998-2011. Patients who underwent S for PSCC pathologic stage $\geq$1 with data for receipt of perioperative C and/or XRT and follow-up were eligible for analysis. The following variables were evaluated: pathologic stage, age, Charlson Comorbidity Index (CCI), race, overall survival (OS), socioeconomic status based on median income of area of residence and therapy (S+C, S+XRT, S+C+XRT). Treatment patterns were described. Multivariate analyses (MVA) were conducted to determine the impact of factors on OS with P $<$ 0.05 considered significant. **Results:** A total of 418 pts were evaluable including 132 in the S+XRT group, 166 in the S+C group and 120 in the S+C+XRT group. The number of pts with stages 1, 2, 3, 4 and unknown were 26, 78, 146, 137 and 31, respectively. In the MVA, stage was independently significantly prognostic (p = 0.002), while age (p = 0.056) and CCI (p = 0.057) were trending significant. S+C+XRT was not statistically better than S+XRT (HR 1.37 [95% CI: 0.935 - 2.007]) or S+C (HR 0.834 [95% CI: 0.589 - 1.180]). Additionally, S+C was not associated with significantly different OS compared to S+XRT (HR 1.142 [95% CI: 0.790 - 1.652]). Limitations of a retrospective analysis apply. **Conclusions:** This is the largest retrospective study of perioperative therapy for locally advanced PSCC. Triple modality therapy (S+C+XRT) did not extend OS compared to dual modality therapy (S+C or S+XRT). Additionally, the analysis did not identify whether C or XRT should be preferred in pts receiving dual modality therapy. The phase II International Penile Cancer Adjuvant Trial (InPACT) will investigate these conundrums for this orphan malignancy.

TPS4590 Poster Session (Board #268a), Sun, 8:00 AM-11:30 AM

Phase 3 KEYNOTE-361 trial: Pembrolizumab (pembro) with or without chemotherapy versus chemotherapy alone in advanced urothelial cancer. *First Author: Thomas Powles, Barts Cancer Institute, London, United Kingdom*

Background: Only 5%-15% of patients (pts) with advanced bladder cancer attain long-term survival with standard first-line cisplatin-based chemotherapy. Programmed death 1 (PD-1)/PD-L1 inhibitors have proven effective in recurrent, advanced urothelial cancer. Emerging data suggest these agents may also be useful in the first-line setting. In KEYNOTE-052, first-line pembro, an anti–PD-1 antibody, demonstrated antitumor activity and acceptable safety in cisplatin-ineligible pts with advanced urothelial cancer. KEYNOTE-361 (NCT02853305) is a randomized, open-label, phase 3 study of pembro with or without chemotherapy versus chemotherapy alone in pts with advanced urothelial carcinoma. **Methods:** Key eligibility criteria include age $\geq$18 years; histologically or cytologically confirmed unresectable/metastatic urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra; measurable disease (RECIST v1.1, investigator review); no prior systemic chemotherapy ([neo] adjuvant platinum-based chemotherapy with recurrence $>$ 12 months after completion is allowed); ECOG PS 0-2; and provision of a tumor sample for biomarker analyses. Pts will be randomly assigned 1:1:1 to receive pembro 200 mg every 3 weeks (Q3W), pembro + investigator's choice of chemotherapy (gemcitabine [1000 mg/m^2 on day 1 and 8 Q3W] + cisplatin [70 mg/m^2 Q3W]), or chemotherapy alone. Cisplatin-ineligible pts randomly assigned to chemotherapy will receive gemcitabine + carboplatin [AUC 5 Q3W]. Chemotherapy choice must be selected before randomization. Treatment will continue until progressive disease, unacceptable adverse events (AEs), or 35 cycles of pembro (pembro arms only). Response will be assessed Q9W for the first year and Q12W thereafter. AEs will be evaluated throughout and graded per NCI CTCAE v4.0. Primary end points are progression-free survival (RECIST v1.1 per central review) and overall survival; secondary end points include objective response rate and safety and tolerability. Efficacy outcomes will be compared for pembro vs chemotherapy and pembro + chemotherapy vs chemotherapy. Enrollment is ongoing; ~990 pts will be enrolled. Clinical trial information: NCT02853305.

TPS4591 Poster Session (Board #268b), Sun, 8:00 AM-11:30 AM

S1605: Phase II trial of atezolizumab in BCG-unresponsive non-muscle invasive bladder cancer. *First Author: Parminder Singh, Mayo Clinic Arizona, Phoenix, AZ*

Background: Radical cystectomy is the standard of care for patients with BCG-unresponsive high risk non-muscle invasive bladder cancer (NMIBC). Based on the reported efficacy of atezolizumab in metastatic urothelial carcinoma and the known expression of PD-L1 expression in NMIBC after BCG therapy, this trial will evaluate the activity of atezolizumab in BCG-unresponsive high risk NMIBC. **Methods:** This is a single arm phase II trial testing systemic atezolizumab (1200 mg IV) every 3 weeks for one year in 135 patients with BCG-unresponsive high risk NMIBC. The study will enroll 70 patients with CIS (with or without concomitant Ta/T1) and 65 with Ta/T1 only. Patients with CIS at baseline will undergo mandatory repeat biopsy at 6 months, and all other patients only for suspected recurrence. Patients with persistent CIS, high grade Ta/T1 recurrence or progression to muscle invasive or metastatic disease will be taken off treatment. The co-primary endpoints are: (1) complete response (CR) at 6 months in the CIS subgroup, and (2) event-free survival (EFS) at 18 months in the overall population. A hierarchical approach will be used to test the two co-primary endpoints. Secondary endpoints include duration of CR as well as progression-free, cystectomy-free, bladder cancer-specific and overall survival in all patients. Response will be correlated to expression of PD-L1 and CD8 by IHC, and to molecular subtypes and immune signatures by RNA-sequencing. Results: If $\geq$28 (40%) CIS patients respond, the agent will be considered promising. This design has a significance level of 4.6%, and a power of 96%. If the lower bound of the 90% confidence interval of the 18-month EFS excludes 20%, the investigators will conclude the regimen significantly improves EFS relative to historical data (type I error rate 0.05 and statistical power 0.93). Conclusion:Successful completion of this trial could lead to a new treatment paradigm for patients with BCG-unresponsive high risk NMIBC. Funding: NIH/NCI grants: CA180888, CA180819, CA180820, CA180821, and CA180863. Clinical trial information: NCT02844816.

TPS4592 **Poster Session (Board #269a), Sun, 8:00 AM-11:30 AM**

P3BEP (ANZUP 1302): An international randomised phase 3 trial of accelerated versus standard BEP chemotherapy for adult and paediatric male and female patients with intermediate and poor-risk metastatic germ cell tumours (GCTs). *First Author: Peter S. Grimison, Chris O'Brien Lifehouse, Sydney, Australia*

Background: Bleomycin, etoposide, cisplatin (BEP) administered 3-weekly x 4 remains standard 1st line chemotherapy for metastatic GCTs. Accelerating regimens by giving them 2-weekly rather than 3-weekly has improved cure rates in other cancers. This is the first international randomised clinical trial for intermediate and poor-risk metastatic extra-cranial GCTs involving both adult and paediatric age groups open to both males and females. We aim to determine if accelerated BEP is superior to standard BEP. **Methods:** DESIGN: Open-label, randomised, stratified multicentre, 2 stage, phase 3 trial. Primary endpoint for stage I (n = 150) is complete response rate (RR), and for entire trial (n = 500) is progression free survival (PFS). SAMPLE SIZE: 150 and 500 patients gives > 80% power to detect a 20% improvement in RRs and 7% absolute improvement in 2yr PFS, respectively. POPULATION: Males and females aged 11-45 yrs with intermediate or poor-risk metastatic GCTs of the testis, ovary, retroperitoneum or mediastinum for 1st line chemotherapy. TREATMENT:Randomisation 1:1 to 4 cycles of "standard BEP" or "accelerated BEP": cisplatin 20mg/m2 IV days 1-5; etoposide 100mg/m2 IV days 1-5; bleomycin 30000 IU IV weekly; and pegylated G-CSF 6mg SC on Day 6; given every 3 weeks or every 2 weeks respectively. Accelerated BEP arm receives 4 additional weekly doses of bleomycin. ASSESSMENTS: Response assessments at 30-day safety assessment, and 6 months from randomisation or after all post-chemotherapy intervention is completed. Regular follow-up to 5 years, then annually. Archival tumour tissue and baseline blood collected for translational substudies. STATUS: 27 sites open in ANZ, 34 patients recruited by February 2017. International collaborations with UK (led by Cambridge Clinical Trials Unit) and US (led by Childrens Oncology Group) confirmed with sites expected to open by early 2017, and more sites sought for stage 2. Funded by Cancer Council Australia and Cancer Australia. ANZUP supported by Cancer Australia and previously CINSW. ANZCTR: ACTRN12613000496718. Clinical trial information: NCT02582697.

TPS4593 **Poster Session (Board #269b), Sun, 8:00 AM-11:30 AM**

The ABC-study: A randomized phase III study comparing one course of adjuvant bleomycin, etoposide, and cisplatin (BEP) and one course of carboplatin AUC7 in clinical stage I seminomatous testicular cancer. *First Author: Torgrim Tandstad, St. Olav's University Hospital, Trondheim, Norway*

Background: Clinical stage I seminomatous testicular cancer is by far the most frequent presentation of testicular cancer. Treatment options include surveillance or adjuvant treatment, internationally one course of adjuvant carboplatin (AUC7) is the preferred adjuvant treatment. Tumor size and stromal invasion in the rete testis can be used to identify patients with a higher risk of relapse. Recent data have showed only a modest effect of adjuvant carboplatin in preventing relapse, and more potent adjuvant therapies should be explored to this group of patients. **Methods:** The ABC-study is a investigator initiated randomized, open, phase III study comparing standard adjuvant chemotherapy in the form of one course carboplatin AUC7 to one course of BEP (Bleomycin, etoposide and cisplatin), in patients with one or two risk factors. Based on SWENOTECA data from one course of adjuvant carboplatin AUC7 we estimate the relapse rate in patients with one or two risk factors to be 9 %. We consider a reduction in relapse free survival of 7 % to be the minimum difference that will lead to routine use of one course of adjuvant BEP. To demonstrate an improvement in relapse rate from 9 to 2 % with an $\alpha = 0.05$ and $\beta = 0.80$, 332 evaluable patients are required. We expect a dropout rate of maximum 5 %, and therefore intend to randomize a total of 348 patients. Enrollment in the study started in 2015, and as of February 1. 2017 a total of 66 patients have been enrolled. Accrual have been slower than expected, but the current accrual rate is about 6-7 patients a month. We invite institutions and collaboratory groups to participate in this study. NCT02341989. EUDRACT 2014-004075-23. Clinical trial information: NCT02341989.

TPS4594 **Poster Session (Board #270a), Sun, 8:00 AM-11:30 AM**

Avelumab plus axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma: Phase 3 study (JAVELIN Renal 101). *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA*

Background: The combination of a checkpoint inhibitor with an anti-VEGF agent is a promising treatment strategy for advanced renal cell carcinoma (aRCC). Avelumab is a fully human IgG1 anti–PD-L1 antibody with clinical activity in aRCC and other tumor types (eg, Apolo et al. ASCO 2016; Gulley et al. ECC 2015). Axitinib is an anti-VEGF receptor tyrosine kinase inhibitor approved for second-line treatment of aRCC (Rini et al. Lancet 2011) that has also shown clinical activity as a first-line (1L) therapy (Hutson et al. Lancet Oncol 2013). In an ongoing phase 1b study in treatment-naïve patients (pts) with aRCC, avelumab + axitinib administered at standard monotherapy doses showed a tolerable safety profile and encouraging antitumor activity (Larkin et al. ESMO 2016). JAVELIN Renal 101 is a randomized, multicenter, phase 3 study (NCT02684006) comparing avelumab + axitinib vs sunitinib in pts with treatment-naïve aRCC. **Methods:** The primary objective is to demonstrate superiority of avelumab + axitinib vs sunitinib in prolonging progression-free survival (PFS) in the 1L treatment of pts with aRCC. Eligibility criteria include: aRCC with a clear cell component, ECOG PS $\leq$1, no prior systemic therapy for advanced disease, and measurable disease per RECIST v1.1. Approximately 583 pts will be randomized 1:1 and stratified based on ECOG PS (0 vs 1) and region (US vs Canada/Europe vs rest of the world). Pts receive either avelumab 10 mg/kg IV Q2W + axitinib 5 mg orally BID continuously (cycle length 6 weeks) or sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off. Treatment is discontinued for unacceptable toxicity or if any other criteria for withdrawal are met. Pts may continue treatment beyond progression (RECIST v1.1) if investigator-assessed clinical benefit is achieved and treatment is well tolerated. PFS is assessed by blinded central review. Secondary efficacy assessments include overall survival, objective response, disease control, duration of response, and time to response. Safety, PK, and biomarker analyses will also be performed. The trial is currently active at 103 sites across 12 countries and as of Feb 2017, more than 40% of patients have been enrolled. Clinical trial information: NCT02684006.

TPS4595 **Poster Session (Board #270b), Sun, 8:00 AM-11:30 AM**

A phase III trial to compare efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab vs sunitinib alone in first-line treatment of patients (Pts) with metastatic renal cell carcinoma (RCC). *First Author: Robert J. Motzer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptor 1–3, fibroblast growth factor receptor 1–4, platelet-derived growth factor receptor alpha, and RET and KIT. Based on a phase 2 study (Motzer et al. *Lancet Oncol* 2015), LEN was approved in combination with everolimus (EVE) for treatment of metastatic RCC following 1 prior VEGF-targeted therapy. A phase 1b/2 study of LEN in combination with pembrolizumab (PEM) in pts with RCC LEN is also underway. We report the design of a multicenter, open-label, phase 3 trial of LEN plus EVE or PEM vs sunitinib (SUN; a standard therapy for RCC) as first-line treatment for advanced RCC. **Methods:** Pts aged $\geq$ 18 years with confirmed advanced RCC diagnosis, $\geq$ 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, Karnofsky Performance Status $\geq$ 70, controlled blood pressure, and adequate blood coagulation, renal, hepatic, and bone marrow function are eligible. Pts will be randomized 1:1:1 to receive LEN 18 mg/day + EVE 5 mg/day, LEN 20 mg/day + PEM 200 mg every 3 weeks, or SUN 50 mg/day (on a schedule of 4 weeks on treatment followed by 2 weeks off) until disease progression, unacceptable toxicity, withdrawal of consent, or study end. The primary endpoint is to show superiority of LEN+EVE or LEN+PEM over single-agent SUN as first-line treatment for advanced RCC in improving progression-free survival (PFS). Secondary endpoints include comparison of objective response rate, overall survival, PFS on next-line therapy, health-related quality of life, and safety and tolerability in pts receiving LEN+EVE or LEN+PEM vs SUN. Exploratory endpoints include PFS in the LEN+PEM arm using immune-related RECIST, comparison of duration of response, disease control rate, and clinical benefit rate in pts treated with LEN+EVE or LEN+PEM vs SUN, and analysis of the relationship between blood biomarkers and outcome. No interim analysis is planned for efficacy or futility. Enrollment of 735 pts is planned to achieve 90% power at 2-sided $\alpha = 0.05$ to detect a difference in $\geq$ 1 of the primary comparisons. Clinical trial information: NCT02811861.

TPS4596 Poster Session (Board #271a), Sun, 8:00 AM-11:30 AM

A phase III randomized study comparing perioperative nivolumab vs. observation in patients with localized renal cell carcinoma undergoing nephrectomy (PROSPER RCC). *First Author: Lauren Christine Harshman, Dana-Farber Cancer Institute, Boston, MA*

Background: The anti-PD-1 antibody nivolumab (nivo) improves overall survival (OS) in metastatic treatment refractory RCC and is generally tolerable. In 2017, there is no standard adjuvant therapy proven to increase OS over surgery alone in non-metastatic (M0) disease. Mouse solid tumor models have revealed an OS benefit with a short course of neoadjuvant PD-1 blockade compared to adjuvant therapy. Two ongoing phase 2 studies of perioperative nivo in RCC patients (pts) have shown preliminary feasibility and safety with no surgical delays or complications. The PROSPER RCC trial will examine if the addition of perioperative nivo to radical or partial nephrectomy can improve clinical outcomes in pts with locally advanced RCC. With the goal of increasing cure and recurrence-free survival (RFS) rates in M0 RCC, we propose a three-pronged, multidisciplinary approach of presurgical priming with nivo followed by resection and adjuvant PD-1 blockade. **Methods:** Tumorbiopsy prior to randomization is mandatory to ensure the correct diagnosis and will permit unparalleled correlative science in this global, randomized, unblinded, phase 3 National Clinical Trials Network study. 766 pts with clinical stage ≥T2 or any node positive M0 RCC of any histology will be enrolled. The study arm will receive nivo 240mg IV for 2 doses prior to surgery followed by nivo adjuvantly for 9 months (q2 wks x 3 mo followed by q4 wks x 6 mo). The control arm will undergo the current standard of care: surgical resection followed by observation. Pts are stratified by clinical T stage, node positivity, and histology. There is 84.2% power to detect a 14.4% absolute increase in the primary endpoint of RFS from the ASSURE historical control of 55.8% to 70.2% at 5 yrs (HR 0.70). The study is also powered to detect a significant OS benefit (HR 0.67). Key safety, feasibility, and quality of life endpoints are incorporated. PROSPER RCC exemplifies team science with a host of planned correlative work to investigate the significance of the baseline immune milieu and changes after neoadjuvant priming and to identify predictive gene expression patterns. Additional collaborations are welcomed.

TPS4597 Poster Session (Board #271b), Sun, 8:00 AM-11:30 AM

Phase 3 KEYNOTE-426 trial: Pembrolizumab (pembro) plus axitinib versus sunitinib alone in treatment-naive advanced/metastatic renal cell carcinoma (mRCC). *First Author: Brian I. Rini, Cleveland Clinic, Cleveland, OH*

Background: Antiangiogenic agents, including sunitinib and axitinib, have shown clinically significant efficacy in patients (pts) with mRCC. Results from a phase 1b study in 52 pts suggest first-line pembro, an anti–programmed death 1 antibody, in combination with axitinib, has substantial antitumor activity in mRCC (objective response rate [ORR], 71%) and manageable toxicity. The phase 3, multicenter, open-label, randomized KEYNOTE-426 study (NCT02853331) is designed to evaluate the efficacy and safety of pembro plus axitinib versus sunitinib alone in pts with treatment-naive mRCC. **Methods:** Key eligibility criteria include age ≥18 years, histologically confirmed mRCC with clear cell component (with or without sarcomatoid features), measurable disease (RECIST v1.1, investigator review), no prior systemic therapy for advanced disease, Karnofsky performance status ≥70%, and provision of a tumor sample for biomarker analyses. Before randomization, pts will be stratified by International Metastatic RCC Database Consortium risk category and geographic region. 840 pts will be randomly assigned 1:1 to receive pembro 200 mg every 3 wk + axitinib 5 mg twice daily or sunitinib 50 mg once daily for 4 wk followed by 2 wk off. Treatment will continue until progressive disease, unacceptable adverse events (AEs), or withdrawal of consent. Pts in the pembro arm may receive up to 35 doses of pembro, after which axitinib-only treatment may continue. Imaging will be performed at wk 12, then every 6 wk for the first year, and every 12 wk thereafter. Bone scans will be performed at baseline, and if positive, repeated at wk 18, 30, 42, and 54, and every 24 wk thereafter. AEs will be monitored throughout and graded per National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0. Primary end points are to compare progression-free survival (RECIST v1.1, central review) and overall survival between treatment arms. Secondary end points include the comparison of ORR, duration of response, disease control rate, safety, and patient-reported outcomes between arms. Enrollment is ongoing. Clinical trial information: NCT02853331.

TPS4598 Poster Session (Board #272a), Sun, 8:00 AM-11:30 AM

A phase III study of atezolizumab (atezo) vs placebo as adjuvant therapy in renal cell carcinoma (RCC) patients (pts) at high risk of recurrence following resection (IMmotion010). *First Author: Robert Uzzo, Fox Chase Cancer Center, Philadelphia, PA*

Background: Nephrectomy is the SOC in early RCC; however, the 5-y relapse rate is 30-40% in stage II or III pts, with tumor stage and grade correlating with survival and recurrence after surgery. Currently, there is a limited role for adjuvant therapy after nephrectomy in pts who have had complete tumor resection; observation is standard. In a Ph II first-line metastatic RCC study, treatment with single-agent atezo (anti–PD-L1) resulted in an ORR of 25%. Thus, IMmotion010, a Ph III, multicenter, randomized, placebo-controlled, double-blinded trial, will evaluate the efficacy and safety of atezo as adjuvant therapy in RCC pts who are at high risk of recurrence after resection (NCT03024996). **Methods:** Eligible RCC pts (clear cell or sarcomatoid histologies) will have undergone nephrectomy (radical or partial) and be at high risk of recurrence (T2 Grade 4, T3a Grade 3-4, T3b/c any Grade, T4 any Grade or TxN+ any Grade) or have had complete resection of limited metachronous/synchronous metastasis. Pts must show no residual disease or evidence of metastases by CT scan at enrollment. ECOG PS ≤ 1 and tumor specimens evaluable for PD-L1 will also be required. Pts will be randomized 1:1 to receive atezo 1200 mg IV q3w or placebo IV q3w for 16 cycles or 1 y; stratification will be by disease stage (T2/T3a vs T3b/c/T4/N+ vs metastasectomy), region (North America [excluding Mexico] vs rest of world) and PD-L1 status on tumor-infiltrating immune cells (IC; PD-L1 IC expression < 1% vs ≥ 1%). The primary endpoint is independent review facility (IRF)-assessed disease-free survival (DFS), defined as the time from randomization to the first documented recurrence event (local recurrence, new primary RCC, distant metastasis) or death. Secondary endpoints include OS, investigator-assessed DFS, IRF-assessed and investigator-assessed DFS in pts with ≥ 1% PD-L1 IC, disease-specific survival, distant metastasis-free survival and the 3-y rates of IRF-assessed DFS and investigator-assessed DFS. Safety and biomarkers will be evaluated. The planned analysis will occur when at least ≈ 65% of pts in the 2 populations have died. 664 pts will be enrolled at 150-200 sites worldwide. Clinical trial information: NCT03024996.

TPS4599 Poster Session (Board #272b), Sun, 8:00 AM-11:30 AM

A randomized, phase II efficacy assessment of multiple MET kinase inhibitors in metastatic papillary renal carcinoma (PRCC): SWOG S1500. *First Author: Sumanta K. Pal, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: PRCC constitutes approximately 15% of RCC cases, and no standard of care exists for metastatic disease. Approved VEGF- and mTOR-directed therapies for clear cell RCC in metastatic PRCC (mPRCC) have generally been ineffective. Trials assessing sunitinib and everolimus in non-clear cell RCC show a numerical advantage in progression-free survival (PFS) with sunitinib therapy. Prospective studies evaluating sunitinib in mPRCC show a broad range of efficacy, with PFS ranging from 1.6-6.6 months. Another possible approach to treating mPRCC is to target the *MET* proto-oncogene, which is frequently altered across both type I and type II disease. SWOG 1500 is a randomized, phase II study which will compare sunitinib to three MET-directed therapies in pts with mPRCC. **Methods:** Eligible pts will have PRCC (type I, type II or NOS), Zubrod performance status 0-1, and measurable metastatic disease. Pts may have received up to 1 prior systemic therapy, with the exception of prior VEGF-directed treatments. Treated brain metastases are allowed. Tissue must be available for central pathologic review of papillary subtype. Pts will receive either oral sunitinib, cabozantinib, crizotinib or savolitinib in a 1:1:1:1 randomization, with stratification by (1) prior therapy (0 vs 1) and (2) PRCC subtype (type I vs type II vs NOS). The primary endpoint of the study is to compare PFS with sunitinib to PFS with MET-directed therapies. Secondary endpoints in the study include comparison of response rate, overall survival and safety profile. Translational aims of the study include correlation of clinical outcome with MET mutation, copy number and other markers of MET signaling. Radiographic assessment will be performed every 12 wks. Interim analyses are planned for each arm. A total of 275 pts will be enrolled, with 26 pts registered as of Jan 30, 2017. Clinical trial information: NCT02761057.

TPS4600 Poster Session (Board #273a), Sun, 8:00 AM-11:30 AM

Tivo-3: A phase 3, randomized, controlled, multi-center, open-label study to compare tivozanib hydrochloride to sorafenib in subjects with refractory advanced renal cell carcinoma (RCC). *First Author: Brian I. Rini, Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH*

Background: Tivozanib is a biochemically potent and selective VEGF tyrosine kinase inhibitor in clinical development in RCC. Other agents used for treatment of RCC inhibit multiple tyrosine kinases in addition to the VEGF receptor tyrosine kinase, leading to off-target toxicities such as fatigue, hand-foot syndrome, stomatitis, and neutropenia. The adverse event (AE) profile of tivozanib demonstrates minimal off-target toxicities. TIVO-1 (AV-951-09-301) was an open-label, randomized, controlled, multinational, multi-center, parallel-arm trial comparing tivozanib to sorafenib in patients with advanced RCC. The blinded independent radiological assessment showed the median progression free survival (mPFS) in the tivozanib arm to be 11.9 months (95% confidence interval (CI) [9.3, 14.7]), compared with 9.1 months (95% CI [7.3, 9.5]) in the sorafenib arm ($p = 0.042$, HR = 0.797). Overall survival had a negative trend, most likely due to a one-way crossover for patients randomized to sorafenib. This study is designed, in part, to demonstrate that the negative trend in OS was an artifact. **Methods:** Subjects with metastatic RCC who have failed 2 or 3 prior systemic regimens, one of which includes a VEGFR TKI other than sorafenib or tivozanib, will be randomized in a 1:1 ratio stratified by the IMDC risk category (favorable; intermediate; poor) and prior therapy (two VEGFR TKIs; a prior checkpoint inhibitor plus a prior VEGFR TKI; a prior VEGFR TKI plus any other systemic agent). The primary objective is to compare the progression-free survival (PFS) of subjects randomized to tivozanib with those randomized to sorafenib as assessed by blinded independent radiological review (IRR). Secondary endpoints are overall survival, objective response rate, and duration of response. Clinical trial information: NCT02627963.

TPS4601 Poster Session (Board #273b), Sun, 8:00 AM-11:30 AM

TARIBO trial: Cytoreductive nephrectomy in metastatic renal cell carcinoma patients treated with targeted agents. *First Author: Paolo Grassi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: In the cytokine era cytoreductive nephrectomy (CN) has been shown to increase survival in patients (pts) with metastatic renal cell carcinoma (mRCC). Efficacy of tyrosine kinase inhibitors (TKIs), including first-line sunitinib and pazopanib has been demonstrated. It is unclear if similar survival benefit could be achieved without CN with TKIs since most of pts enrolled into phase III trials had undergone CN. **Methods:** A total of 270 mRCC pts will be randomized to receiveCN followed by TKIs vs upfront TKIs without CN. Patients will receive pazopanib 800 mg orally daily or sunitinib 50 mg daily, 4 weeks on/ 2 weeks off. The choice of TKI will be done according to investigator's clinical practice. Primary objective**: t**o compare clinical benefit, as measured by overall survival (OS), provided by CN followed by TKIs vs upfront TKIs in pts with mRCC. Secondary objectives: i) to compare clinical benefit, as measured by progression-free survival (PFS) and response rate (RR) provided by CN followed by TKIs vs upfront TKIs; ii) Safety; iii) Exploratory analyses: evaluation of the predictive role of circulating tumor cells count and circulating tumor DNA at baseline, before and after surgery (in pts undergoing CN), 24 weeks after randomization and at the time of disease progression. Key inclusion criteria: Favorable or intermediate MSKCC or Heng prognostic risk group; histological diagnosis of RCC with a clear-cell component; resectable asymptomatic mRCC with primary tumor in place; up to three different metastatic sites; $\geq$ 3 metastatic lesions. Key exclusion criteria: Widespread disease ($>$ or = 4 metastatic organ sites); disease suitable of metastasectomy ($<$ 3 lesions confined at one organ site). Statistical plan: The sample size was calculated in order to compare 5-year OS between subjects randomized to receive CN followed by TKIs and those randomized to receive upfront TKIs. A total of 191 deaths will yield 80% power to detect a hazard ratio of 1.5 of upfront TKIs vs CN followed by TKIs with an overall type 1 error of 0.05 (two-sided log-rank test). Such a HR corresponds to an increase in the 5-year OS, from an anticipated value of 10% for TKIs to 21.5% for CN followed by TKIs. To date 10/270 pts have been enrolled. Clinical trial information: NCT02535351.

5000 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Development and validation of a novel clinical-genomic risk group classification for prostate cancer incorporating genomic and clinicopathologic risk. *First Author: Daniel Eidelberg Spratt, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: It is clinically challenging to integrate genomic classifier results that report a continuous numerical risk of recurrence into treatment decisions for prostate cancer (PCa). We aimed to develop a novel clinical-genomic risk system that can readily be incorporated into treatment guidelines for localized PCa. **Methods:** Four multi-center cohorts (n = 6928 men; 5937 prospective samples and 991 retrospective samples with long-term follow-up) were utilized to identify and validate our clinical-genomic risk system in radical prostatectomy (RP) samples and subsequently in pre-treatment biopsy samples. All patients' FFPE tissue underwent microarray analysis, and the expression values for 22 prespecified biomarkers that constitute Decipher were extracted. Cumulative incidence curves were constructed to estimate metastasis risk. C-indices were calculated to compare NCCN and CAPRA score to our clinical-genomic system. **Results:** With a median follow-up of 8 years for men in our RP cohort, the 10-year distant metastasis rates for NCCN low, favorable-intermediate, unfavorable-intermediate, and high-risk were 7.8%, 9.4%, 40.1%, and 41.4%, respectively. Our 3-tier clinical-genomic risk groups had 10-year distant metastasis rates of 3.7%, 30.7%, and 57.7%, for low, intermediate, and high-risk, which were validated in our pre-treatment biopsy cohort with 10-year rate of distant metastasis of 0%, 30.3%, and 63.2%, respectively. C-indices for the clinical-genomic system (0.84, 95%CI 0.62-0.92) were significantly improved over NCCN (0.71, 95%CI 0.59-0.84) and CAPRA (0.71, 95%CI 0.60-0.81) score. A total of 33.4% of men would be reclassified by the clinical-genomic system, and specifically 17.1%, 41.3%, and 19.4% of men in NCCN low, intermediate and high risk groups would be reclassified by our new system. **Conclusions:** The use of a readily available genomic classifier in combination with clinicopathologic variables can generate a simple to use 3-tier clinical-genomic risk system that is highly prognostic for distant metastasis, is more accurate than clinical risk, and can be easily incorporated into NCCN guidelines to inform treatment decisions.

5001 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Abiraterone + prednisone (Abi) +/- veliparib (Vel) for patients (pts) with metastatic castration-resistant prostate cancer (CRPC): NCI 9012 updated clinical and genomics data. *First Author: Maha Hussain, Northwestern University Robert H. Lurie Comprehensive Cancer Center, Chicago, IL*

Background: In preclinical CRPC models, PARP1 inhibition synergizes with AR targeted therapy, especially in ETS fusion-positive tumors. We hypothesized: 1. Co-targeting PARP-1 + AR is superior to AR inhibition and 2. ETS +ve predicts response. **Methods:** Pts had metastatic (mets) disease biopsy (bx), stratified by IHC-ETS status and randomized to Abi (Arm A) or Abi + Vel (Arm B). Primary endpoint: PSA response rate (RR > = 50% decline). Secondary endpoints: safety, objective RR (ORR), progression free survival (PFS), and molecular analysis including if DNA repair gene deficiency (DRD: *BRCA 1, BRCA 2, ATM, FANCA, PALB2, RAD51B, RAD51C*) predicts response. 148 pts stratified by IHC-ETS status were randomized to detect a 20% PSA RR improvement assuming a 5% 1-sided type I error and 80% power. An elastic net multivariable Cox model was used to analyze PFS. Mets bx underwent targeted exon sequencing and capture transcriptome analysis. **Results:** 72 pts were randomly assigned to Arm A and 76 to Arm B. PSA RR: Arm A 63.9%, Arm B 72.4% (p = 0.27). ORR: Arm A 45%, Arm B 52.2%, p = 0.51. Median PFS: Arm A 10.1 months (m), Arm B 11.3 m, p = 0.95. More Arm-B pts were on therapy for 12+ (45% vs 38%) and 18+ cycles (22% vs 17%). ETS status had no impact. Mets tissue sequencing (N = 80): 42 pts (53%) were ETS +ve, 19 (25%) had DRD, 47 (59%) had AR amplification/copy gain, 32 (40%) had PTEN mutation (mut), 33 (41%) had TP53 mut, 37 (46%) had PIK3CA activation (a) and 12 (15%) had WNT-a. Irrespective of arm pts with DRD had a higher PSA and ORR (> = 87%) vs wild type (58%, 39%; p = 0.013, p = 0.002, respectively), higher PSA decline rate of > = 90% (74% vs 26%, p = 0.0004) and longer median PFS (95% CI): DRD 16.6 m (11 - NR) vs wild type: 8 m (5.4 – 13.3); p = 0.02. PFS was longer in pts with normal PTEN (13.5 vs 6.2 m, p = 0.02), TP53 (13.3 vs 7.8 m, p = 0.04) and PIK3CA (10.3 vs 8.3 m, p = 0.03). Controlling for clinical factors, DRD, PTEN, TP53 and PIK3CA are associated with PFS in this order of importance. **Conclusions:** There was a modest trend in favor of Abi + Vel but no difference by ETS. Pts with DRD, normal PTEN,TP53 and PIK3CA had better PFS raising new hypotheses regarding the importance of integrating molecular analysis in therapeutic trials. Clinical trial information: NCT01576172.

5002 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

A randomized phase II cross-over study of abiraterone + prednisone (ABI) vs enzalutamide (ENZ) for patients (pts) with metastatic, castration-resistant prostate cancer (mCRPC). *First Author: Kim N. Chi, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: ABI and ENZ are indicated as 1st line therapy for mCRPC but have not been directly compared. Optimal sequencing of these agents has not been prospectively evaluated and predictive biomarkers are lacking. **Methods:** Multicenter, phase 2 study randomizing treatment-naïve mCRPC pts to ABI vs ENZ, with cross over at PSA progression. Primary endpoints: response and time to PSA progression (TTPP, PCWG3 criteria) after 2nd line therapy. Reported here are secondary endpoints: PSA ≥50% decline (PSA50) from baseline, TTPP with 1stline therapy, and correlation with deep targeted sequencing of 73 mCRPC genes in circulating tumor DNA (ctDNA). **Results:** Accrual completed October 2016 with 202 pts randomized (ABI: ENZ = 101:101). Median follow-up 12.8 months. Baseline characteristics were similar between arms: median for age was 75 years (range 49-94), PSA 36.1 (1.7-2817), HGB 130 (89-165), ALK PHOS 105 (31-6600), LDH 207 (77-3098). ECOG PS was 0-1 in 83%, presence of metastases in bone/liver/lung in 83%/6%/10%. With 1stline therapy for ABI vs ENZ, PSA50 at 12 weeks was 53% vs 73% (P = 0.004), no PSA decline occurred in 21% vs 15% (P = 0.243), and median TTPP was 7.4 vs 8.0 months (HR = 0.88, 95% CI 0.61, 1.27). Baseline ctDNA fraction was >2% in 60% of patients, and associated with worse TTPP (HR 1.80, P=0.005). Baseline pathogenic ctDNA alterations in AR, TP53, RB1, and DNA repair (BRCA2, ATM) genes were associated with a shorter TTPP (univariate analysis: TABLE). On multivariate analysis including clinical factors, TP53 and BRCA2/ATM alterations remained significant (HR = 2.54 (95%CI 1.55-4.19) and HR = 2.68 (1.58-4.54)). Pts with a PSA increase as best response were enriched for alterations in DNA repair (P <0.001), TP53 (P = 0.005), RB1 (P = 0.04), and (in 1 pt) a genomically truncated AR. **Conclusions:** There was a difference in PSA response for 1stline ABI vs ENZ, but no difference for TTPP. Baseline pathogenic ctDNA alterations, particularly in TP53 and BRCA2, identify pts with poor outcomes. Clinical trial information: NCT02125357.

ctDNA	HR (95%CI) for TTPP (altered vs. not)	P
DNA Repair	4.13 (2.55, 6.68)	<0.001
TP53	2.84 (1.90, 4.23)	<0.001
AR	2.04 (1.39, 3.00)	<0.001
RB1	1.96 (1.28, 3.00)	0.002

LBA5003 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Adding abiraterone for men with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): Survival results from STAMPEDE (NCT00268476). *First Author: Nicholas D. James, Queen Elizabeth Hospital, Coventry, United Kingdom*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, June 3, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

5004 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

A phase IV, randomized, double-blind, placebo (PBO)-controlled study of continued enzalutamide (ENZA) post prostate-specific antigen (PSA) progression in men with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC). *First Author: Gerhardt Attard, The Institute of Cancer Research and The Royal Marsden Hospital, Sutton, United Kingdom*

Background: We hypothesized resistance to the androgen receptor inhibitor ENZA is due to increases in androgens and can be overcome by combination with the androgen synthesis inhibitor abiraterone (abi). The phase 4 PLATO trial (NCT01995513) is evaluating the safety and efficacy of continued ENZA + abi/prednisone (abi/P) vs PBO + abi/P after PSA progression on ENZA. **Methods:** In Period (P) 1, men with chemotherapy-naïve mCRPC received ENZA (160 mg); men with no PSA increase from baseline at wk 13 and 21 continued treatment until PSA progression (≥ 25% increase and ≥ 2 ng/mL above nadir). Eligible men were then randomized 1:1 in P2 to ENZA + abi/P (1000 mg/10 mg) or PBO + abi/P. The primary endpoint (EP) was progression-free survival (PFS; radiographic or unequivocal clinical progression, or death on study) in P2, with a prespecified sensitivity analysis of radiographic PFS (rPFS); protected secondary EPs were time to PSA progression (TTPP) and PSA response ≥ 50% in P2. **Results:** 509 men enrolled in P1. At data cutoff (Oct 7, 2016), 84 were active, 174 discontinued, and 251 were randomized in P2 (ENZA + abi/P, n = 126; PBO + abi/P, n = 125). Median treatment duration in P2 was 5.6 mo for both arms. PFS event by radiographic/clinical/death was 38%/25%/2% for ENZA + abi/P and 55%/18%/1% for PBO + abi/P. Median PFS was 5.7 mo for ENZA + abi/P and 5.6 mo for PBO + abi/P (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.61, 1.12; $P = 0.22$). Median TTPP was 2.8 mo for both arms (HR, 0.87; 95% CI, 0.62, 1.24; $P = 0.45$). PSA response rate was 0.8% for ENZA + abi/P and 2.5% for PBO + abi/P ($P = 0.31$). Median rPFS was 10.0 mo for ENZA + abi/P and 7.0 mo for PBO + abi/P (HR, 0.67; 95% CI, 0.47, 0.94; $P = 0.02$). The most common (≥ 15%) adverse events for ENZA + abi/P vs PBO + abi/P were back pain (21% vs 23%), hypertension (20% vs 7%), nausea (17% vs 9%), and fatigue (14% vs 15%). **Conclusions:** ENZA + abi/P post PSA progression on ENZA was associated with increased hypertension and nausea and did not result in a statistically significant improvement in composite PFS. The signal seen in rPFS needs further evaluation. Clinical trial information: NCT01995513.

5005 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Clinical factors associated with AR-V7 detection in ARMOR3-SV, a randomized trial of galeterone (Gal) vs enzalutamide (Enz) in men with AR-V7+ metastatic castration-resistant prostate cancer (mCRPC). *First Author: Mary-Ellen Taplin, Dana-Farber Cancer Institute, Boston, MA*

Background: Presence of the AR-V7 splice variant may predict resistance to Enz and abiraterone in men with mCRPC. Gal is an oral agent that disrupts AR signaling via AR degradation, CYP17 lyase inhibition, and AR antagonism. ARMOR3-SV was designed to test the hypothesis that in mCRPC patients with AR-V7+ CTCs, Gal could improve radiographic progression-free survival (rPFS) versus Enz. **Methods:** In this randomized, open-label, multicenter phase 3 study (NCT02438007), men with treatment-naïve mCRPC were screened for CTC-specific AR-V7 (Qiagen), and AR-V7+ men were randomized 1:1 to Gal or Enz. rPFS (by independent blinded central review) was the primary endpoint. Planned sample size was 148, with 120 rPFS events to achieve 90% power to detect a hazard ratio of ≤0.55. **Results:** 953 patients were screened globally for AR-V7 from Sept 2015 through study closure; 73 men (8%; 95% CI 6-10%) were AR-V7+, 250 (26%) AR-V7–, and 630 (66%) had no CTCs/AR present (unevaluable). AR-V7 detection was associated with higher PSA levels (> vs < median; $P < 0.01$), more bone metastases (> 20 vs 11-20 vs 6-10 vs 0-5; $P < 0.01$), presence of M1 disease at diagnosis (dx) (yes vs no; $P = 0.04$), shorter time from dx to screening (< vs > median; $P < 0.01$), higher ECOG (≥1 vs 0; $P = 0.02$), prior antiandrogen use (yes vs no; $P < 0.01$) and prior docetaxel use (yes vs no; $P < 0.01$). Among the AR-V7+ men, 38 were randomized (19 Gal, 19 Enz), 31 screen failed, and 4 were discontinued from screening at study halt. Baseline characteristics were balanced. On the recommendation of the DSMB, the study was closed early as it was unlikely to meet its primary endpoint. At the time of the study closure, in the Gal and Enz arms respectively, median time on therapy was 2.0 vs 2.8 mo, median time to PSA progression (PCWG1) was 3.9 vs 3.8 mo, PSA_{50} response rates in evaluable patients were 2/16 (13%) and 8/19 (42%), and there were no new safety signals. **Conclusions:** In treatment-naïve mCRPC patients, AR-V7 detection is more common in men with higher disease burden and portends a poor prognosis. Novel study designs and alternative treatment approaches are urgently needed for AR-V7+ mCRPC patients. Clinical trial information: NCT02438007.

5006 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Phase 3 prognostic analysis of the automated bone scan index (aBSI) in men with bone-metastatic castration-resistant prostate cancer (CRPC). *First Author: Andrew J. Armstrong, Division of Medical Oncology and Urology, Duke Cancer Institute, Duke University, Durham, NC*

Background: Quantitative measures of metastatic bone disease are needed in men with mCRPC. We recently demonstrated the validity/reproducibility of a computational approach to bone scan imaging that employs artificial intelligence called the automated BSI (aBSI), which quantifies the percent of skeletal mass involved by cancer. We aimed to extend the prognostic validation of aBSI in a multinational prospective phase 3 clinical study of men with bone-metastatic CRPC. **Methods:** Whole-body bone scans were acquired at screening in a placebo-controlled phase 3 trial of men with mCRPC and bone metastases and treated with tasquinimod/placebo (n = 1,245). The prospective aBSI biomarker analysis plan was locked in Sept 2014 prior to treatment unblinding. All scans generated at 241 trial sites in 37 countries were assessed for image quality and analyzed using the EXINI $bone^{BSI}$ v.2 software and were blindly associated with outcomes. Baseline aBSI was evaluated for its independent prognostic association with overall survival (OS), radiographic progression-free survival (rPFS), and symptomatic skeletal related events (SSEs). **Results:** The aBSI-population (721 pts) was representative of the entire trial population based on patient characteristics at screening and OS outcomes. Median aBSI was 1.07 (SE 0.05). The aBSI-population was divided into quartiles (n = 180-181) with aBSI-levels of 0 - 0.3 (Q1); > 0.3 - 1.1 (Q2); > 1.1 - 4.0 (Q3); and > 4.0 (Q4) and median OS ranging from 35 months (Q1) to 13 mo (Q4) ($p < 0.0001$). Baseline aBSI was significantly associated with OS (HR 1.2 per doubling of BSI; $p < 0.0001$) and remained independently associated with OS after adjustment for treatment, PSA, CRP, LDH and albumin. Baseline aBSI was also strongly associated with rPFS ($p = 0.0005$), time to symptomatic progression ($p < 0.0001$), and time to SSE ($p = 0.001$). **Conclusions:** This analysis represents the first phase 3 evaluation of aBSI as a clinically validated prognostic biomarker for OS, rPFS, and SSEs in men with bone-metastatic CRPC, providing independent prognostic information over commonly measured clinical characteristics. Clinical trial information: NCT01234311.

5007 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Circulating tumor cell (CTC) number as a response endpoint in metastatic castration resistant (mCRPC) compared with PSA across five randomized phase 3 trials. *First Author: Glenn Heller, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Radiographic progression and overall survival (OS) are the traditional clinical benefit measures for mCRPC trials. Reliable indicators of response that occur early are a critical unmet need in practice and clinical research. We explored a week 13 CTC and prostate-specific antigen (PSA) endpoint relative to baseline in 5 prospective randomized phase 3 registration trials that enrolled 5912 pts. OS was the primary endpoint. **Methods:** CTC number (CellSearch) and PSA values in patients who survived at least 13 weeks were evaluated as response endpoints in COU-AA-301, AFFIRM, ELM-PC-5, ELM-PC-4 and COMET-1. Pts with missing values at week 13 were considered non-responders. The endpoints considered are shown in Table 1. **Results:** The discriminatory strength of the response endpoints with respect to OS was estimated using the weighted c-index. To summarize discrimination results for each measure, the mean and the standard deviation based on the weighted c-indices from the 5 studies were computed. **Conclusions:** CTC0 and CTC conversion endpoints had the highest discriminatory power for OS relative to the % decline in CTC or PSA endpoints. The percent of pts eligible and evaluable for the CTC0 endpoint was significantly higher than the conversion endpoint, 75% vs. 51%, respectively. These two absolute measures of CTC can be considered meaningful response indicators in mCRPC clinical trials.

Response	Total survived 12 wks with a baseline value	Total eligible for response	Average proportion eligible from baseline evaluable	Baseline evaluability for response	Week 13 Response criteria
CTC0	4196	3158	0.75	≥1	0
CTC Conversion	4196	2152	0.51	≥5	≤4
% Change CTC	4196	2152	0.51	≥5	30, 50 or 70% decrease
% Change PSA	5464	4995	0.91	≥10ng/mL	30, 50 or 70% decrease

CTC0=No detectable CTC at W13.

	Absolute Measures		Relative Measures					
	CTC0	**CTCconv**	**CTC30**	**CTC50**	**CTC70**	**PSA30**	**PSA50**	**PSA70**
COUAA301	0.78	0.80	0.77	0.77	0.78	0.73	0.75	0.75
AFFIRM	0.86	0.84	0.80	0.80	0.79	0.75	0.77	0.81
ELM-PC-5	0.83	0.78	0.65	0.67	0.70	0.72	0.75	0.77
ELM-PC-4	0.77	0.77	0.67	0.69	0.71	0.68	0.68	0.69
COMET-1	0.79	0.77	0.71	0.69	0.67	0.67	0.63	0.69
Mean	**0.81**	**0.79**	**0.72**	**0.72**	**0.73**	**0.71**	**0.72**	**0.74**
Std dev	**0.04**	**0.03**	**0.06**	**0.06**	**0.05**	**0.03**	**0.06**	**0.05**

5008 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Duration of androgen deprivation therapy in high risk prostate cancer: Final results of a randomized phase III trial. *First Author: Abdenour Nabid, Centre Hospitalier Régional Universitaire, Sherbrooke, QC, Canada*

Background: Long-term androgen deprivation therapy (ADT) combined with radiotherapy (RT) is a standard treatment for patients with high-risk prostate cancer (HRPC). However, the optimal duration of ADT is not yet defined. The aim of this randomized trial (Clinical Trials.gov, #NCT00223171) was to compare outcomes of RT combined with either 36 or 18 months of ADT. **Methods:** Patients with HRPC were randomized to pelvic and prostate RT combined with 36 (arm 1) or 18 months (arm 2) of ADT. Overall survival (OS) and quality of life (QoL) were primary end points. OS rates were compared with Cox Regression model and QoL data were analyzed through mixed linear model. **Results:** 630 patients were randomized, 310 to arm 1 and 320 to arm 2. With a median follow-up of 9.4 years, 290 patients had died (147 arm 1 vs. 143 arm 2). The 10-year OS rate was 62.4% (95% confidence interval [CI] 56.4%, 67.8%) for arm 1 and 62.0% (95% CI 56.1%, 67.3%) for arm 2 ($p = 0.8412$) with a global hazard ratio (HR) of 1.024 (95% CI 0.813-1.289, $p = 0.8411$). QoL analysis showed a significant difference ($p < 0.001$) in 6 scales and 13 items favoring 18 months ADT with two of them presenting a clinically relevant difference in mean scores of ≥ 10 points. **Conclusions:** In HRPC, ADT combined with RT can be safely reduced from 36 to 18 months without compromising outcomes or QoL. 18 months of ADT represents a new standard of care in HRPC. Funded by AstraZeneca Pharmaceuticals Clinical trial information: NCT00223171.

5009 Poster Discussion Session; Displayed in Poster Session (Board #83), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Need for re-evaluation of current guidelines based on results from germline genetic testing in prostate cancer. *First Author: Piper L.W. Nicolosi, Invitae, San Francisco, CA*

Background: Inherited risk for prostate cancer (PCa) is potentially associated with more aggressive disease. Recent data indicate that DNA repair gene abnormalities may be much more common than previously appreciated, especially BRCA2, ATM, CHEK2, BRCA1, RAD51D, and PALB2. Herein, we investigate the efficacy of a targeted gene panel in men with PCa and evaluate clinical factors in relationship to current guidelines for genetic screening. **Methods:** DNA sequencing and exon-level copy number analysis were performed in 1158 PCa patients (pts) between 2013 and 2016 at a commercial diagnostic laboratory. The genes requisitioned varied but consistently included 14 genes on a hereditary PCa panel, most of which were DNA repair genes. Evaluation included Gleason scores and eligibility for genetic screening based on any NCCN testing criteria in pts with positive findings (pathogenic, likely pathogenic, and risk allele). **Results:** Pathogenic findings were identified in 199 of 1158 (17.2%) pts, 13 pts (1.0%) had two variants. Roughly 75% of detected variants were in genes on the hereditary PCa panel, of which 34.4% were BRCA1/2. Positive variants in HOXB13, a gene associated only with PCa risk, were identified in eight (3.8%) pts. DNA mismatch repair variants, alterations with substantial known therapeutic implications, were detected in 1.7% of samples. A total of 12.4% of pts with Gleason scores of ≤ 6, compared with 15.4% of those with scores of ≥ 7 had a pathogenic variant. Within this cohort, 126 (63%) patients with positive results were eligible for genetic testing based on currently available NCCN guidelines, whereas 73 (37%) would not have qualified. **Conclusions:** Current NCCN guidelines and Gleason scores cannot be used to reliably stratify PCa pts for the presence/absence of pathogenic germline variants. Most positive results identified in this study have important management implications for pts and their families. The percentage of pts with germline variants who did not meet current genetic screening criteria underscores the need for revisiting current guidelines which cannot, at this time, reliably be used to predict pathologic findings on genetic testing.

5010 Poster Discussion Session; Displayed in Poster Session (Board #84), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Next-generation sequencing (NGS) of tissue and cell free DNA (cfDNA) to identify somatic and germline alterations in advanced prostate cancer. *First Author: Michael L. Cheng, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: With the goal of accelerating enrollment onto appropriate clinical trials, we performed prospective genomic characterization of pts with advanced prostate cancer. Given the long natural history and osseous disease predominance, we also analyzed plasma cfDNA to assess the feasibility of identifying targetable alterations in pts for whom adequate tumor tissue was unavailable. **Methods:** 1038 tumors from 896 pts along with matched normal DNA were analyzed with a capture-based NGS assay (MSK-IMPACT) targeting 341–468 genes. In 5/2015, the protocol was amended to allow pts to opt-in for a formal germline analysis of 76 genes associated with heritable cancer risk. In select pts, plasma cfDNA was collected and analyzed using the same assay. **Results:** Between 2/2014 and 2/2017, 576 primary tumors and 462 metastases were sequenced. The most notable finding was the high frequency of known or likely pathogenic germline and somatic mutations in genes that regulate DNA damage response (DDR). In the subset with both tumor and germline analysis, 28.84% (169/586) had a DDR mutation identified compared to only 10.65% (33/310) of pts with somatic only analysis. In the subset with tumor and germline analysis, 9.39% (55/586) had somatic only DDR mutations and 16.38% (96/586) had germline only DDR mutations, including 8 pts with two germline mutations. 3.07% (18/586) had co-occurring somatic and germline DDR mutations, with only 0.68% (4/586) involving the same DDR gene (all BRCA2). Prostate cancer had the highest tissue failure rate among the overall MSK-IMPACT solid tumor cohort, and bone biopsy-derived tissue was successfully sequenced in only 42% of pts. Profiling of cfDNA did identify somatic DDR or AR mutations in 12.5% (4/32) of pts without adequate tumor for analysis. **Conclusions:** This prospective genomic profiling effort identified frequent somatic and germline DDR mutations that may guide PARPi or platinum therapy. Both somatic and germline analyses were required to identify all pts with likely pathogenic DDR alterations. NGS-based cfDNA analysis is feasible in advanced prostate cancer and may identify mutations missed by tumor only sequencing.

5011 Poster Discussion Session; Displayed in Poster Session (Board #85), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Whole exome sequencing (WES) of circulating tumor DNA (ctDNA) in patients with neuroendocrine prostate cancer (NEPC) informs tumor heterogeneity. *First Author: Himisha Beltran, Weill Cornell Medical College, New York, NY*

Background: We recently identified mechanisms underlying the clonal evolution of castration-resistant prostate adenocarcinoma (CRPC-Adeno) to a neuroendocrine resistance phenotype (Beltran et al, *Nat Med* 2016). We aimed to develop a non-invasive approach to identify patients that are developing NEPC. **Methods:** We performed whole exome sequencing of matched ctDNA, germline DNA, and metastatic biopsies from patients with CRPC-Adeno and NEPC. After applying ad hoc partial duplication filtering, we used FACETS and extended CLONET to calculate the fraction of tumor DNA and clonality of genomic lesions. **Results:** 64 CRPC patients were prospectively enrolled. The spectrum of alterations captured by WES of ctDNA was consistent with those commonly observed in CRPC validating the feasibility of the approach. The similarity of copy number alterations between tumor tissue and ctDNA was higher in NEPC compared to CRPC-Adeno ($p = 0.0001$) suggesting less heterogeneity in NEPC. There was enrichment of *RB1* and *TP53* loss in NEPC ctDNA and *AR*gains in CRPC-Adeno. The overall fraction of mutations shared by ctDNA and tumoral tissue was ~80%. We compared three different tumor biopsy time-points of patient PM161—CRPC-Adeno (lymph node), CRPC-Adeno (bone), NEPC (liver). Unexpectedly the baseline ctDNA profile (at time of CRPC-Adeno) displayed genomic features most similar to the NEPC liver biopsy. These data suggest that NEPC alterations are detectable in the circulation potentially prior to the development of NEPC clinical features. We compared the ctDNA of another patient PM0 with 6 sites of NEPC metastases obtained 6 days later at autopsy; the relative contribution of tumor alterations in ctDNA was highest for the liver metastasis (similarity 0.59) versus other sites suggesting differential contribution of metastatic sites in the circulation, with implications for the interpretation of single site clinical biopsies. **Conclusions:** This is the first study to show that WES of ctDNA is feasible in CRPC and can help elucidate intra-patient heterogeneity and identify the spectrum and frequency of NEPC genomic changes. ctDNA may improve the detection of patients transforming towards NEPC.

5012 Poster Discussion Session; Displayed in Poster Session (Board #86), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

The benefit of combining docetaxel to androgen deprivation therapy in localized and metastatic castration-sensitive prostate cancer as predicted by ERG status: An analysis of two GETUG phase III trials. *First Author: Shanna Rajpar, Institut Gustave Roussy, Villejuif, France*

Background: Combining docetaxel to androgen deprivation therapy (ADT) improves survival in metastatic castration-sensitive prostate cancer (CSPC) (Vale C, Lancet Oncol 2016; 17: 243-56) and it also improves relapse-free survival (RFS) in high-risk localized CSPC (Fizazi K, Lancet Oncol 2015; 16: 787-94). However it is unlikely that all patients (pts) derive a benefit from docetaxel treatment and identifying predictive biomarkers remains a major unmet need. A subset of prostate cancers contains TMPRSS2-ERG gene fusions leading to ERG overexpression. **Methods:** Pre-treatment prostate core biopsies were collected from 255/413 pts and 79/385 pts enrolled respectively in the GETUG 12 and GETUG 15 (Gravis G, Eur Urol 2016; 70: 256-62) phase 3 trials testing early docetaxel in high-risk localized and metastatic CSPC. ERG, PTEN, Ki67 and Rb expression was assessed using immunohistochemistry. RFS curves were compared using the Logrank test. **Results:** The median age was 63 years (46-77) and 62 years (49-76) in GETUG 12 and GETUG 15. ERG staining was positive in 88/191 (46%) and 33/79 (42%) pts with available tissue, respectively. In GETUG 12, docetaxel-based chemotherapy was associated with improved RFS in pts with ERG+ expression (HR = 0.55 [0.29-1.03]; 6-year RFS : 80% ADT+ docetaxel vs 68% ADT alone), but not in pts with ERG- (HR = 1.10 [0.66-1.85]; 6-year RFS 55% ADT+docetaxel vs 60% ADT alone), interaction test: p = 0.02. Similar findings were observed in GETUG 15, which was used as a validation set: the median RFS was 10.7 (6.5-14.3) and 18.8 (9.8-41) months in pts with ERG+ cancers receiving ADT alone and ADT+docetaxel, and 10.6 (4.8-25.3) and 13.2 (9.4-24) months in pts with ERG- cancers. In contrast, no difference in patient outcome by docetaxel treatment was observed by PTEN, Ki67 and Rb expression. **Conclusions:** Docetaxel-related benefit in men with CSPC is predicted by ERG expression. This biomarker may help better select pts for docetaxel treatment.

5013 Poster Discussion Session; Displayed in Poster Session (Board #87), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

The aggressive variant prostate carcinoma (AVPC) molecular signature (-MS) and platinum-sensitivity in castration resistant prostate cancer (CRPC). *First Author: Ana Aparicio, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The AVPC are a subset of prostate cancers that share the clinical, therapy response and molecular profiles of the small cell prostate carcinomas, a histological variant of the disease that responds poorly to androgen receptor directed therapies. The AVPC are characterized by a molecular signature of combined tumor suppressor defects ($\geq$ 2 alterations in Tp53, RB1 and/or PTEN by immunohistochemistry or genomic analyses). We conducted a randomized phase II study of cabazitaxel (CAB) plus or minus carboplatin (CARB) in men with CRPC and asked whether the AVPC-MS predicted for platinum benefit. **Methods:** 160 men with metastatic CRPC were randomized 1:1 to receive IV CAB (25 mg/m2) or CAB/CARB (25 mg/m2; AUC4) Q21 days with growth factor support until disease progression, unacceptable toxicity or for up to 10 cycles. Imaging occurred every 2 cycles. The primary endpoint was progression free survival (PFS). 73 tumor samples obtained within 1 year of registration from 65 of the 160 patients (pts) were stained for Tp53, RB1, PTEN, AR-N terminus, AR-C terminus and Ki67. DNA of sufficient quantity for sequencing was extracted from 27 tumors and 70 plasma samples. **Results:** At a median follow up of 21.6 months (mo), median PFS (mPFS) in the overall population (n = 160) is 4.6 mo (95% CI 3.5, 5.8) with CAB vs 7.4 mo (95% CI 5.6, 8.3) with CAB/CARB (p = 0.004). Men with AVPC-MS-positive tumors had a mPFS of 4.5 mo (95%CI 1.5, NA) with CAB [n = 9] vs 8.0mo (95%CI 6.11-9.7) with CAB/CARB [n = 23] (p = 0.0036) whereas men with AVPC-MS-negative tumors had a mPFS of 6.8mo (95%CI 5.2, NA) with CAB [n = 12] vs 5.4mo (95%CI 3.72, NA) with CAB/CARB [n = 12] (p = 0.1445). Analysis of plasma DNA samples is ongoing and will be presented at the meeting. **Conclusions:** The AVPC-MS identifies a subset of men platinum-sensitive CRPC tumors. These findings should serve as the foundation for a therapeutically relevant classification of prostate cancer. Clinical trial information: NCT01505868.

5014 Poster Discussion Session; Displayed in Poster Session (Board #88), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Post hoc analysis of a phase III study to test the association between circulating *methylated glutathione s transferase (mGSTP1)* DNA levels and response to docetaxel (DTX) in metastatic castration resistant prostate cancer (mCRPC). *First Author: Kate Lynette Mahon, Chris O'Brien Lifehouse, Camperdown, Australia*

Background: *GSTP1* inactivation is associated with CpG island hypermethylation in > 99% prostate cancers. Detection of circulating *mGSTP1* DNA predicts response to DTX and overall survival (OS) in phase I/II mCRPC cohorts. This post hoc analysis of a phase III study aims to test the association between circulating *mGSTP1* DNA levels and outcomes. **Methods:** The phase III SYNERGY study tested DTX +/- custirsen as 1st line chemotherapy in mCRPC (n = 1022) with no OS benefit in the experimental arm. Serum samples were taken at baseline (BL) and preC3 of DTX +/- custirsen from 600 patients (pts) enrolled on the SYNERGY study. *mGSTP1* levels in free DNA were measured using a sensitive methylation specific PCR assay and correlated with PSA response, time to PSA progression (TTP) and OS. **Results:** On interim analysis of 300 pts, serum *mGSTP1* was detectable at BL in 80% and preC3 in 44%. Undetectable preC3 *mGSTP1* correlated with a $\geq$30% fall in PSA within 3m of starting DTX (p < 0.001). Detectable BL and preC3 *mGSTP1* predicted shorter TTP after DTX (BL; HR 1.6 95%CI 1.1-2.3; p = 0.01 and preC3 HR 2.2 95%CI 1.6-2.9; p < 0.001). Detectable *mGSTP1* at both time points predicted shorter OS (BL; median OS 18.4 vs 33.1m, HR 2.4 95%CI 1.6-3.7; p < 0.001 and preC3; median OS 13.9 vs 29m, HR 2.7 95%CI 2.0-3.6; p < 0.001). In those with detectable BL *mGSTP1*, 50% had undetectable preC3 *mGSTP1* predicting > 30% fall in PSA within 3m (p < 0.001), improved TTP (HR 0.40 95%CI 0.29-0.57; p < 0.001) and improved OS (25.2 vs 13.9 m HR 0.38 95%CI 0.28-0.51; p < 0.001). On multivariable analysis including Hb, Karnofsky PS, LDH, PSA and visceral metastases, detectable preC3 *mGSTP1* independently predicted shorter TTP (HR 1.9 95%CI 1.4-2.6; p < 0.001). Detectable *mGSTP1* at both time points independently predicted OS (BL; HR1.8 95%CI 1.2-2.8; p = 0.006 and preC3; HR 2.2 95%CI 1.6-3.0; p < 0.001). Results from the full cohort of 600 pts will be available for presentation at the meeting. **Conclusions:** This study should validate circulating *mGSTP1* DNA as a marker of therapeutic benefit and prognosis in men with mCRPC receiving DTX and could be utilized for clinical management.

5015 Poster Discussion Session; Displayed in Poster Session (Board #89), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Clinical outcome of metastatic castration-resistant prostate cancer (mCRPC) patients (pts) with a post-treatment circulating tumor cell (CTC) of 0 vs CTC > 0: Post hoc analysis of COU-AA-301. *First Author: Howard I. Scher, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Assessment of radiographic response by RECIST in the majority of mCRPC pts is limited by the lack of measurable disease. Changes in CTC counts (CTCs) enumerated using Veridex CellSearch from unfavorable at baseline (BL [$\geq$ 5 cells/7.5 mL]) to favorable ($\leq$ 4) are prognostic for survival, and the test is FDA cleared as an aid in the monitoring of metastatic PC. The CTC cutpoint of $\geq$ 5 excludes many pts from response assessment. Examining CTCs alone and in combination with other biomarkers as a potential surrogate for clinical benefit was a secondary objective of COU-AA-301, a phase 3 trial of abiraterone acetate + prednisone vs prednisone alone in mCRPC. **Methods:** Pts from both treatment (tmt) groups with BL CTC > 0 were combined to assess CTC = 0 as a response criterion. Association between CTC response, defined as BL CTC > 0 and post-BL CTC = 0, and clinical outcomes was assessed. CTCs were determined at BL and 4, 8, and 12 wks. Pts with BL CTC > 0 and missing post-tmt CTCs were considered nonresponders. Radiographic response was first assessed at Wk 12. Overall survival (OS) was estimated using the Kaplan-Meier method. **Results:** Among739 pts with BL CTC > 0, 141 had measurable disease. At Wk 12, 19% (141/739) of pts were CTC responders and 81% (598/739) were CTC nonresponders. Among CTC responders, 74% (104/141) had stable disease or better by RECIST; 26% (37/141) were either not evaluable or had disease progression by RECIST. Median OS was 23.8 and 10.0 mos for CTC responders (n = 141) and nonresponders (n = 598), respectively. Among pts with liver and/or lung metastases, 86% (24/28) of CTC responders at Wk 12 had stable disease or better by RECIST; 14% (4/28) had disease progression by RECIST. Median OS was 19.9 and 7.1 mos for CTC responders (n = 28) and nonresponders (n = 127), respectively. Similar results were observed in Wk 8 CTC responders. **Conclusions:** For mCRPC pts with BL CTC > 0, CTC response on tmt (CTC = 0) is associated with longer survival and could be considered a response criterion. Additional analysis is required to fully characterize the relationship between CTC = 0 and objective response by RECIST in pts with measurable disease. Clinical trial information: NCT00638690.

5016 Poster Discussion Session; Displayed in Poster Session (Board #90), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Association of androgen receptor (AR) gene status in plasma DNA with outcome on enzalutamide in chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC): Exploratory results from the PREMIERE trial—On behalf of SOGUG. *First Author: Enrique Grande, Hospital Universitario Ramón y Cajal, Madrid, Spain*

Background: Building on previous discoveries studying *AR* status in plasma (Carreira S, Sci Transl Med 2014, Romanel A, Sci Transl Med 2015) and following a road-map for biomarker development, we aimed to clinically qualify *AR* status in chemotherapy-naïve mCRPC using an optimized multiplex droplet digital PCR (ddPCR) assay (Condeduca et al.;ASCO2017; Abstract#). **Methods:** Between February and November 2015, 98 asymptomatic or oligo-symptomatic chemotherapy-naïve mCRPC patients were recruited in 16 Spanish hospitals. Tissue and blood samples were required at study entry. Although initially designed to study the predictive value of TMPRSS2-ETS, data emerging after the trial was initiated led the group to prioritize alternative predefined exploratory biomarkers, including plasma *AR*and CTC characterization (Grande E. ESMO 2016 & Font A. et al; ASCO2017; Abstract #). Outcome measures included PSA-progression-free survival (sPFS), radiographic progression-free survival (rPFS) and overall survival (OS). Cox regression was used for survival analyses and Fisher's exact test for PSA response. **Results:** Ninety-four patients had plasma DNA available for analysis. At baseline, *AR* gain was present in 11 pts (12%) and CTCs in 35 (37%). *AR* gain in CTC-positive and negative patients was 20% and 7%, respectively. At first interim analysis and with a median follow-up of 10.6 months, detection of AR gain was associated with worse sPFS (median, 3.60 versus 15.5 m, HR, 4.33; 95% CI 1.94-9.68; $P < 0.001$), rPFS (median, 3.90 m versus not reached HR, 8.06; 95% CI, 3.26-19.93; $P < 0.001$) and OS (medians not reached, HR, 11.08; 95% CI, 2.16-56.95; $P = 0.004$). These results were independently associated in multivariate analysis including cfDNA and CTCs for all described endpoints. *AR* gain patients were less likely to have a ≥50% decline in PSA (OR, 4.93; 95% CI, 1.30-18.75; $P = 0.025$). **Conclusions:** Detection of *AR* gain in plasma using a robust multiplex ddPCR method predicts an adverse outcome in chemotherapy-naïve mCRPC. Further prospective randomized studies are warranted. Clinical trial information: NCT02288936.

5017 Poster Discussion Session; Displayed in Poster Session (Board #91), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Phase II study of bipolar androgen therapy (BAT) in men with metastatic castration-resistant prostate cancer (mCRPC) and progression on enzalutamide (enza). *First Author: Benjamin A. Teply, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Androgen receptor (AR) overexpression is a common adaptive resistance mechanism in mCRPC. High dose testosterone in this setting may induce tumor responses and restore normal AR expression. To evaluate BAT, we enrolled men with mCRPC progressing on enza to assess (1) responses to BAT and (2) enza re-challenge after BAT. **Methods:** Eligible men had minimally symptomatic mCRPC with progression on enza. Subjects received testosterone cypionate 400mg IM every 28d and continued gonadal suppression, until progression. Subjects were evaluated with PSAs each cycle, and CT/bone scans every 3 cycles. Upon progression on BAT, men were re-challenged with enza. The co-primary endpoints were > 50% PSA responses (PSA_{50}) to BAT and PSA_{50} to enza re-challenge. The null hypothesis was a PSA_{50} rate of 5% for both endpoints, with alternative hypotheses of 20% to BAT and 25% to enza. 30 subjects were required for 90% and 83% power, respectively, with overall type 1 error of 0.1. Secondary endpoints were safety, objective response, progression-free survival (PFS), and effect on circulating tumor cell-based AR and AR-V7 expression. **Results:** 30 eligible subjects were accrued (2014-2016). No dose limiting toxicities were seen. 2 subjects had transient pain flares after BAT initiation. Common grade 1-2 adverse events (AE) were musculoskeletal pain (40%), increased hemoglobin (37%), breast tenderness (17%) and rash (17%). 3 Grade 3-4 AE potentially attributable to BAT occurred (pulmonary embolism, NSTEMI, and urinary obstruction). 9/30 men (30% [95% CI: 17-48%]) achieved a PSA_{50} to BAT. 5/14 men (36%) with measurable disease had an objective response by RECIST 1.1. The median clinical/radiographic PFS on BAT was 8.6 months. 21 subjects proceeded to enza re-challenge, yielding 15 PSA_{50} responses (54% by intention to treat [95% CI: 34-69%]), with a PFS of 4.8 months. 1/3 AR-V7+ subjects responded to BAT, and all had decreased AR-V7/AR ratios (2 converted to AR-V7-) after 3 cycles. **Conclusions:** The study met its primary endpoints, demonstrating preliminary efficacy of BAT in men with progressive mCRPC after enza. A randomized study comparing BAT to enza in mCRPC is ongoing. Clinical trial information: NCT02090114.

5018 Poster Discussion Session; Displayed in Poster Session (Board #92), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Extended versus limited pelvic lymphadenectomy during radical prostatectomy for intermediate- and high-risk prostate cancer: Early outcomes from a randomized controlled phase III study. *First Author: Jean Felipe Prodocimo Lestingi, Sao Paulo State Cancer Institute - University of Sao Paulo, São Paulo, Brazil*

Background: The role of extended pelvic lymph node dissection (ePLND) in treating prostate cancer (PCa) patients remains controversial, mainly by the lack of RCTs. **Methods:** Patients with D'Amico intermediate or high risk PCa, absence of bone metastasis and no previous treatment were prospectively computer randomised to undergo extended or limited PLND (1:1) during radical prostatectomy. Limited PLND (lPLND) included the obturator chain bilaterally; ePLND involved bilaterally chains: obturator, external-, internal-, common-iliac and pre-sacral. Surgical specimens and each chain were analyzed separately, according to College of American Pathologists. All patients signed a free and informed consent and local ethics committee approved the study. The primary endpoint was biochemical recurrence-free survival, analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01812902. **Results:** Since May 2012 until August 2016, 291 patients were randomly assigned, 145 to ePLND and 146 to lPLND. Preoperative data were comparable between groups. Median follow-up was 35.2 months. EPLND increased significantly operative time (54 minutes), estimated blood loss (100 mL), length of hospital stays (1 day) [$p \leq 0.001$], transfusion rate [$p = 0.05$] and postoperative complications according to Clavien scale [$p = 0.03$]. There was no difference in Pathologic Gleason grade, T stage or positive surgical margin. On ePLND and lPLND groups, 59.3% and 61.7% were staged ≥ pT3a, respectively. EPLND and lPLND yielded median (mean) 17 (19.8) and 3 (4.1) nodes, respectively ($p < 0.001$). EPLND showed 6.3 times more lymph node metastases ($p < 0.001$) and only it was able to show positive nodes in intermediate risk. There were no difference in biochemical recurrence (PSA ≥ 0.2 ng/mL) using Kaplan-Meyer method ($p = 0.4$), Radiotherapy, Androgen Deprivation Therapy, bone metastases or death. **Conclusions:** Extended lymphadenectomy in intermediate- and high-risk prostate cancer patients is associated with better tumor staging, increased morbidity and no oncological benefits in this initial short follow-up time. Clinical trial information: NCT01812902.

5019 Poster Discussion Session; Displayed in Poster Session (Board #93), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Adjuvant androgen deprivation (AD) +/- mitoxantrone + prednisone (MP) in patients with high-risk prostate cancer (PC) post radical prostatectomy (RP): Phase III intergroup trial S9921. *First Author: Maha Hussain, Northwestern University Robert H. Lurie Comprehensive Cancer Center, Chicago, IL*

Background: Patients (pts) with high-risk PC post RP are at risk of systemic relapse with related morbidity/mortality. Adjuvant AD can reduce this risk. In 1999, based on available data, we hypothesized that adjuvant MP + 2 years (ys) of AD can further reduce mortality. **Methods:** Eligible pts had cT1-T3, N0 PC with post RP >= 1 high risk factors defined as Gleason sum (GS) ≥ 8, pT3b, pT4, pN+, GS 7 + positive margin or any of these preoperative findings (in pts with neoadjuvant AD): preoperative PSA of > 15 ng/ml, bx GS score > 7, or PSA of > 10 ng/ml + bx GS > 6. Pts had to have post RP PSA = < 0.2 ng/ml, were stratified by T, N, GS, and adjuvant radiation plan and randomized: Arm 1 AD (bicalutamide + goserelin for 2 ys) or Arm 2 AD + 6 cycles m 12 mg/m^2 + P 5mg BID. Primary endpoint: overall survival (OS). Median OS was estimated to be 10 ys in AD arm requiring 680 pts/arm to detect a hazard ratio (HR) of 1.30 with 92% power and one-sided $\alpha = 0.05$. **Results:** 983 pts (961 eligible intent to treat) with median age 60 ys and median PSA 7.6 ng/ml were randomized to AD or AD + MP from 10/99 -1/07 when the DSMC recommended stopping accrual due to higher leukemia rate in Arm 2. 16% had N1 (Group "Gr" 1), 61% GS ≥8 or pT3b (Gr 2),23% other risk factors (Gr 3). Median time to testosterone recovery was 9.5 months. Median follow-up (f/u) 11.2 ys. **Conclusions:** OS was higher than anticipated in both arms; MP did not improve OS and increased other malignancy risk. These data illustrate that systemic therapy benefit cannot be extrapolated from different disease stages and the importance of adequate f/u in adjuvant PCa trials. The remarkable DFS and 10 y OS, irrespective of risk extent, may be result of risk definition, and/or 2 ys AD. Pending definitive data 2 ys adjuvant AD for high-risk PCa post RP is a reasonable option to consider. Clinical trial information: NCT00004124.

Outcome	Arm 1: N = 481	Arm 2: N = 480	P Value	Hazard ratio (95% CI) Arm 2 vs. 1
Survival (10 yr %)	87%	86%	P = 0.70	HR = 1.06 (0.79, 1.43)
DFS (10 yr %)	72%	72%	P = 0.94	HR = 1.01 (0.80, 1.27)
Grade > = 3 AE	30%	56%	< 0.0001	
Deaths, non PCa	82%	78%	0.57	
Other cancer Deaths	15%	32%	0.011	
Risk Group	10 year OS %			HR (95% CI)
Group 1	81%		P = 0.002	2.10 (1.30, 3.41)
Group 2	87%		P = 0.034	1.56 (1.03, 2.35)
Group 3	90%			Reference 1.0

5020 Poster Discussion Session; Displayed in Poster Session (Board #94), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Stereotactic ablative radiation therapy for the treatment of oligometastatic prostate cancer. *First Author: Phuoc T. Tran, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: The importance of local treatment in oligometastatic prostate cancer (OPC) is unknown. Stereotactic ablative radiotherapy (SABR) is highly focused, high-dose radiation that is well suited for treatment of oligometastases. Here we report on the safety and preliminary clinical outcomes of SABR in a modern cohort of OPC men. **Methods:** Eighty four men who satisfied criteria of OPC diagnosed on imaging underwent consolidative SABR were then followed prospectively on our IRB approved registry by our GU multidisciplinary team. We collected demographic, clinical, toxicity and efficacy information. We examined the first 66 men in this preliminary report to allow for a minimum of 4.5 months follow-up. SABR was delivered in 1-5 fractions of 5-18 Gy. Kaplan-Meier method was used to assess local progression-free survival (LPFS), biochemical progression-free survival (bPFS; PSA nadir+2), distant progression free survival (DPFS), ADT-free survival (ADT-FS) and time-to-next intervention (TTNI). **Results:** Of the 66 OPC patients analyzed, 25 (38%) men presented as synchronous OPC and the remaining 41 had recurrent OPC. Median and mean follow-up was 61 and 66 weeks, respectively. Patient and disease factors as listed in the Table. Crude Grade 1 and 2 acute toxicities were 36% and 11%, respectively, with no Grade $>$ 2 toxicity. SABR was delivered to 134 metastases: 89 bone (66%), 40 nodal (30%) and 5 (4%) visceral metastases. Overall LPFS at 1-year was 92%. The bPFS and DPFS at 1-year were 69% and 69%, respectively. Median TTNI was not reached yet. Of the 18 men with hormone sensitive prostate cancer who had their ADT deferred, 11/18 (56%) remain free of disease following SABR (1-year ADT-FS was 78%) and in 17 castration resistant men, 11 had $>$ 50% PSA declines with 1-year TTNI of 30% with a median of 45 weeks. **Conclusions:** Consolidative SABRfor OPCis feasible and well tolerated. The preliminary clinical outcomes in our series is limited by heterogeneity and size but our data suggests that this approach is worthy of further prospective study.

Table. Patient and disease properties (n = 66).

Factors	n (%)	Median (range)
Age		65 (47-84)
HSPC	49 (74)	
CRPC	17 (26)	
Concurrent ADT	53 (80)	
Pre-SABR PSA (ng/mL)		1.2 ($<$ 0.1-96)

5021 Poster Session (Board #95), Mon, 1:15 PM-4:45 PM

A randomized phase II study of pelareorep (REO) plus docetaxel vs. docetaxel alone in patients with metastatic castration resistant prostate cancer (mCRPC): Canadian Cancer Trials Group study IND 209. *First Author: Bernhard J. Eigl, BC Cancer Agency, Vancouver, BC, Canada*

Background: Pelareorep (REO) is an oncolytic virus with in vitro and in vivo activity in many cancers, including prostate. It has in vitro synergism with microtubule targeted agents especially taxanes. We undertook a clinical trial to evaluate REO in mCRPC patients (pts) receiving docetaxel. **Methods:** In this randomized, open-label multicenter phase II study, pts received docetaxel 75mg/m2 on day 1 of a 21-day cycle in combination with REO given as 3x1010 TCID50 IV daily on days 1-5 (arm A), or alone (arm B). The primary endpoint was 12-week lack of disease progression (LPD) rate. Secondary endpoints included objective response rate; survival; circulating tumor cell (CTC) enumeration at 0, 6 and 12 weeks; PSA response rate and biomarkers. **Results:** Eighty-five pts were randomized. Median age was 69, ECOG performance status (PS) was 0/1/2 in 31%/66%/3% of pts. Bone/regional lymph node/liver metastases were present in 98%/24%/6% of pts. More pts in arm A had poor prognostic factors for survival at baseline (median prognostic index 1.44 vs. 1.29). The median number of cycles delivered for arms A/B was 7/9 (range 1-10 and 1-13). In arm A, 51%/68% of pts received $\geq$90% of planned dose intensity of docetaxel/REO respectively, vs. 76% of pts for docetaxel in arm B. Adverse events (AE) were as expected for docetaxel therapy but more prevalent in arm A (grade 3 or higher all AEs 80 vs. 74%). A higher rate of grade 4 febrile neutropenia was noted in arm A (7 vs. 0%) but may represent virus related fevers. The 12-week LPD rate was 61% and 52.4% in A/B respectively (p = 0.51). OS was worse in arm A vs. B (HR 1.95; 95% CI 0.94-4.06; p = 0.07 after adjusting for age, PS and baseline prognostic score). There was no difference between arms in CTC favourable status at any timepoint. No survival benefit of REO with D was found in any subset from the biomarker analysis. **Conclusions:** While the combination of REO with D for patients with mCRPC was tolerable and LPD rate was comparable in both arms, docetaxel dose intensity and survival were inferior and so this combination, as tested, does not merit further study. Clinical trial information: NCT01619813.

5022 Poster Session (Board #96), Mon, 1:15 PM-4:45 PM

Development and validation of a prognostic model for overall survival in chemotherapy-naive men with metastatic castration-resistant prostate cancer (mCRPC) from the phase 3 prevail clinical trial. *First Author: Andrew J. Armstrong, Division of Medical Oncology and Urology, Duke Cancer Institute, Duke University, Durham, NC*

Background: Prognostic models require updating to reflect contemporary medical practice. In a post hoc analysis of the phase 3 PREVAIL trial (enzalutamide vs placebo), we identified prognostic factors for overall survival (OS) in chemotherapy-naive men with mCRPC. **Methods:** Patients were randomly divided 2:1 into training (n = 1159) and testing (n = 550) sets. Using the training set, 23 predefined candidate prognostic factors (including treatment) were analyzed in a multivariable Cox model with stepwise procedures and in a penalized Cox proportional hazards model using the adaptive least absolute shrinkage and selection operator (LASSO) penalty (data cutoff June 1, 2014). A multivariable model predicting OS was developed using the training set; the predictive accuracy was assessed in the testing set using time-dependent area under the curve (tAUC). The testing set was stratified based on risk score tertiles (low, intermediate, high), and OS was analyzed using Kaplan-Meier methodology. **Results:** Demographics, disease characteristics, and OS were balanced between the training and testing sets; median OS was 32.7 months for both datasets. There were no enzalutamide treatment-prognostic factor interactions (predictors). The final multivariable model included 11 prognostic factors: prostate-specific antigen, treatment, hemoglobin, neutrophil-lymphocyte ratio, liver metastases, time from diagnosis to randomization, lactate dehydrogenase, $\geq$ 10 bone metastases, pain, albumin, and alkaline phosphatase. The tAUC was 0.74 in the testing set. Median (95% confidence interval [CI]) OS for the low-, intermediate-, and high-risk groups (testing set) were not yet reached (NYR) (NYR–NYR), 34.2 months (31.5–NYR), and 21.1 months (17.5–25.0). The hazard ratios (95% CI) for OS in the low- and intermediate-risk groups vs the high-risk group were 0.20 (0.14–0.29) and 0.40 (0.30–0.53), respectively. **Conclusions:** Our validated prognostic model incorporates factors routinely collected in chemotherapy-naive men with mCRPC treated with enzalutamide and identifies subsets of men with widely differing survival times. Clinical trial information: NCT01212991.

5023 Poster Session (Board #97), Mon, 1:15 PM-4:45 PM

Impact of timing of administration of bone supportive therapy on pain palliation from radium-223. *First Author: Kelly Khai Li Yap, Keck School of Medicine of University of Southern California, Los Angeles, CA*

Background: Skeletal-related events (SREs) drive morbidity in patients with metastatic castration-resistant prostate cancer (mCRPC). In the ALSYMPCA study, Radium-223 (Ra223) was found to palliate pain in addition to prolonging survival and reducing SREs. Earlier onset of pain relief was noted when zoledronic acid (ZA) was administered within 24-48 hours of samarium; we evaluated whether the timing of bone supportive therapy (BST) affected pain palliation fromRa223. **Methods:** We identified patients who received Ra223 at University of Southern California or Mayo Clinic Arizona. Data extracted: Ra223 administration dates, pain scores, pain medications, ZA or denosumab administration dates, alkaline phosphatase (ALP) levels, prostate specific antigen (PSA) levels, and concurrent prostate cancer therapy. Patients were evaluable for pain response if they had at least 2 pain scores documented before and after Ra223 with pain medication use data. Pain response was defined as $>$ 2 point decrease in pain on a 10 point scale; flare was defined as $>$ 2 point increase followed by return to baseline or lower. **Results:** Of 65 patients, 20 had baseline pain score $>$ 0 and 34 were evaluable. Median #doses Ra223 was 5 (range 2-6). 18 patients received concurrent abiraterone (abi) or enzalutamide (enza), 16 did not. Pain response occurred in 6/6 (100%) patients who received BST within 1 month prior to first Ra223 dose and 4/8 (50%) patients who did not receive BST. Pain flare occurred in 6/21 patients (29%) without BST and 2/13 (15%) with BST. 6/10 (60%) patients with pain response had ALP decline but there was no consistent pattern of ALP changes in patients with flare. 8/8 patients with pain response had no PSA decline (6 increased, 2 stable). 6/12 (50%) and 2/22 (9%) patients on abi/enza had pain response and flare respectively, and 4/8 (50%) and 6/19 (32%) patients without concurrent abi/enza had response/flare. **Conclusions:** BST within 1 month prior to first Ra223 may be associated with increased likelihood of pain palliation and may prevent pain flare. PSA/ALP changes do not predict pain response. Concurrent use of abi/enza does not increase the likelihood of pain response and may decrease the likelihood of flare.

5024 Poster Session (Board #98), Mon, 1:15 PM-4:45 PM

***BRCA1/2* reversion mutations in prostate cancer identified from clinical tissue and liquid biopsy samples.** *First Author: Sugganth Daniel, Foudation Medicine, Inc., Morrisville, NC*

Background: Prostate tumors with genomic alterations (GA) in *BRCA1* or *BRCA2* (*BRCA*) may be sensitive to treatment with PARP inhibitors (PARPi). However, secondary reversion mutations (revGA) can arise that may restore *BRCA* function and underlie reduced sensitivity to PARPi or platinum (Pt)-based therapy. Comprehensive genomic profiling (CGP), using either tissue or liquid biopsies, can detect the variety of clinically relevant revGA that can arise. **Methods:** DNA extracted from FFPE tumor tissue or blood samples obtained during routine clinical care for 1911 patients with predominantly relapsed, refractory or metastatic prostate carcinoma was analyzed by hybrid-capture, next-generation sequencing for all classes of GA: base substitutions, indels, rearrangements, and copy number changes. RevGA were any GA that could restore the reading frame if in cis with a nonsense or frameshift (fs) GA. **Results:** 216/1911 (11.3% ± 1.4%) tumors had ≥1 deleterious *BRCA* GA. Of these, 7 samples harbored potential revGA in *BRCA1* (1) or *BRCA2* (6): prostate acinar adenocarcinoma (5), neuroendocrine carcinoma (1), or undifferentiated carcinoma (1). Of these, 2 samples were liquid biopsies (blood), 4 were FFPE tissue samples (liver), and 1 sample was a bone marrow core biopsy. All samples with revGA were metastases. Potential revGA were of 3 types: overlapping indel (4), compensatory fs (2), and missense (1). One case harbored 2 revGA, an overlapping indel and a compensatory fs. Alteration frequencies for *TMPRSS2* (fusions), *PTEN*, and *AR* were similar with or without *BRCA* mutations; revGA-positive samples had a modest increase in *PTEN* alterations (42.9% vs 33.8%, NS). The frequency of *CDK12* alterations was significantly reduced in *BRCA*-mutated tumors (0.9% vs 6.9%, p = 0.00002). Clinical histories for patients with reversion mutations will be presented. **Conclusions:** CGP of 1911 prostate carcinomas reveals ≥1 deleterious *BRCA1/2* in 11.3% of samples. From these, a series of 7 cases, all metastases, with co-occurring potential revGA were identified. Although rare, revGA can be acquired during treatment and may underlie resistance to PARPi or Pt-based therapy. *BRCA* revGA can be detected from both tissue and liquid biopsies.

5026 Poster Session (Board #100), Mon, 1:15 PM-4:45 PM

Combination of PDL-1 and PARP inhibition in an unselected population with metastatic castrate-resistant prostate cancer (mCRPC). *First Author: Fatima Karzai, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: About 30% of sporadic mCRPC has defects in DNA repair pathways which may confer sensitivity to PARP inhibition. There is limited data about PDL1 inhibition in mCRPC. We hypothesize increased DNA damage by olaparib (O) will complement anti-tumor activity of immune checkpoint blocking antibody, durvalumab (D), in mCRPC:NCT02484404. **Methods:** Single arm pilot study with accrual of 25 patients (pts) with mCRPC and biopsiable disease. Prior treatment with enzalutamide and/or abiraterone is required. D is given at 1500 mg iv q28 days + O 300 mg po q12 h. Primary endpoint is PFS. Pretreatment and on-study core biopsies undergo mutational analysis. **Results:** 10 pts have enrolled (median age 65 yr [range 51-79], median baseline PSA: 85.78 [22.17-809.9 ng/mL]). 7 pts have GS ≥ 8. Grade 3/4 adverse events include anemia 2/7 (29%), thrombocytopenia, lymphopenia, neutropenia, nausea, fatigue, UTI, and lung infection [1/7 each, (14%)]. 5/7 pts (71%) on-study >2 months (mos) have PSA declines > 50%. Median PFS is 7.8 mos (95% CI: 1.8 mos-undefined). **Conclusions:** Preliminary data shows D+O is well tolerated with activity in an unselected population. Accrual is ongoing with biomarker analysis. Clinical trial information: NCT02484404.

Time on-study (mos)	Disease Location	Prior treatments	Mutation	Best PSA response
7	Bone and soft tissue/viscera (A)	androgen deprivation therapy (ADT), enzalutamide/PROSTVAC, docetaxel, abiraterone	None identified in DNA damage repair pathways (NI)	-79%
10	A	ADT, abiraterone, docetaxel, enzalutamide, sipuleucel-T	NI	-94%* *Partial Response, RECISTv1.1
2	A	ADT, casodex, docetaxel, abiraterone+radium-223	NI	15%
2	Bone only (B)	ADT, cetuximab, abiraterone, enzalutamide, docetaxel, sipuleucel-T	NI	35%
7	A	ADT, sipuleucel-T, enzalutamide/ PROSTVAC, doxetaxel+cabozantinib	NI	-73%
6	B	ADT, sipuleucel-T, enzalutamide, docetaxel+dendritic cell vaccine	BRCA2(germline)	-59%
4	B	ADT, zometa vs. placebo, nonsteroidal estrogen, abiraterone+radium 223, enzalutamide	No tumor cells seen on biopsy (NT)	-99%
2	A	ADT, docetaxel x 6 cycles, sipuleucel-T, abiraterone, enzalutamide/ bromodomain inhibitor	BRCA2 (germline)	-26%
2	B	ADT, enzalutamide	NT	-23%
<2	A	ADT, enzalutamide	BRCA2(somatic)	pending

5027 Poster Session (Board #101), Mon, 1:15 PM-4:45 PM

Time to metastasis or death in non-metastatic castrate resistant prostate cancer (nmCRPC) patients by National Comprehensive Cancer Network (NCCN) risk groups. *First Author: Brian Macomson, Janssen Scientific Affairs, LLC, Horsham, PA*

Background: Interventions in nmCRPC are the last defense against metastasis, which drives health care cost and mortality. To assess the value of such interventions we must analyze risk factors for metastasis and death. **Methods:** This was a retrospective study of data (Optum electronic health record database, 2007 – 2016) from men with a prostate cancer diagnosis, 2 rising PSA levels ≥1 week apart, castrate level (< 50 ng/dL) testosterone (T) and no ICD-9/10 code or therapy indicating metastasis. Gleason grade (G) and PSA data up to and including nmCRPC index date (ie, date of 2nd PSA rise) were used to assign NCCN risk groups: Low (G ≤6 and PSA < 10 ng/mL), Intermediate (IM) (G = 7 or 10 ≤ PSA ≤ 20 ng/mL) or High (G ≥ 8 or PSA > 20 ng/mL). The LP/NG group comprised men with PSA < 10 ng/mL (LP) and missing G (NG). A Cox proportional hazard model, adjusted for age, race, comorbidity index score, T level, therapy type and bone scans was used to compare LP/NG, IM and High with the Low risk group. **Results:** Among 1008 men with nmCRPC (mean age 76 years; 12% African American), 553 developed metastases and 430 died during follow-up. Mean time to metastasis was 28, 22, 15, 13 months in the Low, LP/NG, IM, and High groups, respectively. In the Low group, 9 of 29 (31%) men developed metastases, vs 131/285 (46%) in the LP/NG group (hazard ratio [HR] = 1.70, 95% confidence interval [CI]: 0.86-3.35), 175/320 (55%) in the IM group (HR = 2.52, 95% CI: 1.28-4.91) and 238/374 (64%) in the High group (HR = 3.63, 95% CI: 1.85-7.10). Mean time to death was 32, 30, 24, 21 months in the Low, LP/NG, IM, High groups, respectively. There were 8 deaths in the Low group (27.6%), vs 101 (35.4%) (HR = 1.35, 95% CI: 0.65-2.79) in the LP/NG group, 124 (38.8%) (HR = 1.79, 95% CI: 0.87-3.70) in the IM group and 197 (52.7%) (HR = 2.96, 95% CI: 1.45-6.05) in the High group. The High risk group was more likely to develop metastasis during the first year and die within the first 2 years. **Conclusions:** Metastasis and death occurred earlier and more frequently in the Intermediate and High groups relative to the Low risk group. These findings may further inform diagnostic and management strategies for combating disease progression.

5028 Poster Session (Board #102), Mon, 1:15 PM-4:45 PM

Real-world outcomes in second-line treatment of metastatic castration-resistant prostate cancer (mCRPC): The Prostate Cancer Registry. *First Author: Simon Chowdhury, Guy's Hospital, London, United Kingdom*

Background: The Prostate Cancer Registry is a prospective, international observational study that began in June 2013 and will assess the characteristics and management of > 3000 mCRPC patients (pts) in routine clinical practice for ≤ 3 years. **Methods:** Data were collected from men with mCRPC irrespective of treatment (tx). This interim analysis reports baseline characteristics, txs and outcomes in pts with ≥ 12-month follow-up receiving second-line mCRPC tx following docetaxel as the only prior mCRPC tx. **Results:** The most commonly initiated second-line mCPRC txs (n ≥ 50) were abiraterone acetate + prednisone (AAP, n = 177), enzalutamide (ENZ, n = 94), or cabazitaxel (CAB, n = 70). Characteristics and outcomes are shown in the table below. TTP was not significantly different for AAP vs ENZ, AAP vs CAB or ENZ vs CAB (propensity score adjusted $p = 0.5954$, $p = 0.5888$ and $p = 0.4808$, respectively). **Conclusions:** In this real-world study, clinical outcomes reveal that, in pts receiving second-line mCRPC tx after docetaxel, TTP was similar across tx groups; QoL improved most in AAP and ENZ groups and no deterioration was observed most in AAP and CAB groups. Clinical trial information: NCT02236637.

Tx	AAP (n = 177)	ENZ (n = 94)	CAB (n = 70)
Gleason score ≥ 8 at initial diagnosis, n (%)[a]	102 (62.2)	55 (63.2)	41 (63.1)
At enrolment:			
Age, mean yrs (SD)	71.1 (7.8)	72.2 (6.6)	68.1 (7.7)
Bone lesions ≥ 5, n (%)[a]	54 (47.4)	34 (50.0)	26 (60.5)
Strong opioid use, n (%)	26 (14.7)	19 (20.2)	10 (14.3)
TTP, median mo (95% CI)	9.0 (6.0-10.8)	7.1 (5.4-10.6)	6.9 (5.0-9.0)
Prostate-specific antigen response, n (%)[a, b]	54 (36.2)	41 (50.6)	21 (36.8)
Clinically meaningful change in QoL (FACT-P), n (%)[a]			
Improvement[c]			
Global score[e]	27 (33.3)[h]	9 (27.3)[i]	6 (17.1)[j]
Prostate cancer subscale[f]	36 (44.4)[h]	13 (39.4)[i]	9 (28.1)[k]
Pain subscale[g]	29 (36.3)[i]	11 (33.3)[i]	10 (31.3)[k]
No deterioration[d]			
Global score[e]	50 (61.7)[h]	15 (45.5)[i]	23 (65.7)[j]
Prostate cancer subscale[f]	44 (54.3)[h]	15 (45.5)[i]	19 (59.4)[k]
Pain subscale[g]	50 (62.5)[i]	19 (57.6)[i]	23 (71.9)[k]

[a]Data are % pts with measurement/record; [b]≥ 50% decrease within 6 months. Change [c]any time/[d]all time points during tx (points): [e]≥ 10, [f]≥ 3, [g]≥ 2; [h]n = 81; [i]n = 33; [j]n = 35; [k]n = 32; [l]n = 80. Abbreviations: FACT-P, Functional Assessment of Cancer Therapy-Prostate; QoL, quality of life; TTP, time to progression.

5029 Poster Session (Board #103), Mon, 1:15 PM-4:45 PM

Rovalpituzumab tesirine (Rova-T) as a therapeutic agent for Neuroendocrine Prostate Cancer (NEPC). *First Author: Loredana Puca, Weill Cornell Medical College, New York, NY*

Background: TheNotch ligand Delta like ligand 3 (DLL3) is aberrantly expressed on the cell surface of small cell lung cancer (SCLC), and the DLL3-antibody drug conjugate, Rova-T, has shown promise for patients with SCLC (Rudin et al, Lancet Onc 2017). NEPC is a late stage subtype of castration resistant prostate cancer with limited therapeutic options. Based on clinical and molecular similarities with SCLC, we investigated expression of DLL3 and the use of Rova-T in NEPC. **Methods:** We evaluated mRNA and/or protein expression of DLL3 in a cohort of 395 patients (535 samples) ranging from benign prostate (BEN), localized prostate adenocarcinoma (PCA), castration resistant adenocarcinoma (CRPC), and NEPC and correlated with pathologic and genomic features. Prostate cancer cell lines and patient-derived organoids were treated with Rova-T (SC16LD6.5) in vitro and in vivo. **Results:** DLL3 was expressed at the mRNA and/or protein level in 0/143 BEN (0%), 4/266 PCA (1%), 8/76 CRPC (10%), 33/50 NEPC (66%). DLL3 IHC was of higher intensity in NEPC and co-localized with classical NE marker expression (SYP, CGA). DLL3 was amongst the most differentially expressed genes by RNA-seq in NEPC versus CRPC ($p = < 0.0001$, fold change = 71), correlated with ASCL1 expression ($r = 0.88$) and RB1 genomic loss (83%), and inversely with AR expression. Although treatment with the Notch inhibitor DAPT suppressed Notch target gene expression in NEPC, DAPT did not have significant effect on cellular proliferation. siRNA knockdown of DLL3 or DAPT did not alter AR signaling or NE markers. Rova-T (SC16LD6.5) was active in DLL3-positive NEPC cell lines with an IC50 of 580pM compared to the control IgG1LD6.5 (IC50 = 6.3nM), whereas CRPC lines were insensitive. **Conclusions:** DLL3 is a cell surface protein aberrantly expressed in the majority of NEPC and a subset of CRPC, and is not expressed in primary prostate cancer or benign tissues. The DLL3 antibody-drug conjugate Rova-T demonstrates preferential preclinical activity in NEPC compared to prostate adenocarcinoma. These data support further investigation of Rova-T as a potential therapeutic agent for NEPC. A phase I trial with dedicated NEPC arm is currently accruing patients (NCT02709889).

5030 Poster Session (Board #104), Mon, 1:15 PM-4:45 PM

Outcomes of metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated with different new agents (NAs) sequence in post-docetaxel (DOC) setting: Final analysis from a multicenter Italian study. *First Author: Orazio Caffo, Medical Oncology, Santa Chiara Hospital, Trento, Italy*

Background: Abiraterone acetate (AA), cabazitaxel (CABA), and enzalutamide (ENZ) may prolong survival in mCRPC pts progressing after DOC, although it is not clear how to use NAs to best exploit their efficacy and avoiding their possible cross resistances. In 2015, we reported the outcomes of a series of 260 mCRPC pts, receiving at least 2 NAs, after DOC progression in routine clinical practice (Eur Urol. 2015;68:147-53). In the present study we updated the analysis with longer follow-up and by assessing a larger series of pts. **Methods:** Based on a multi-institutional collaboration, we collected data of pts who received at least 2 NAs after DOC: we assessed biochemical (bRR) and objective response rates (oRR) and progression free survival (PFS) of each NA by treatment line; moreover, we evaluated the overall survival (OS) from the second line start by sequence strategy. For the OS analysis we differentiated three different types of NAs sequences after DOC: one new hormone agent (AA or ENZ) followed by CABA (NHA→CABA); CABA followed by AA or ENZ (CABA →NHA); one NHA followed by the other NHA (NHA →NHA). **Results:** A consecutive series of 476 mCRPC pts with bone (86%), nodal (56%) or visceral (15%) mets, was collected. All received NAs as 2nd and 3rdline after DOC. The outcomes by both treatment lines and NAs are detailed in the table. We observed a statistically significant difference in terms of OS when compared the three sequence strategies: the median OS of pts treated with NHA→CABA, CABA→NHA, and NHA→NHA was respectively 12.9 mos, 14.2 mos, and 8.8 mos, respectively ($p = 0.01$). **Conclusions:** At our knowledge this retrospective study reports the highest number of pts treated post-DOC with at least 2 NAs. Our data confirmed that the activity of NAs decreased in the 3rd line compared to the 2nd line and suggested a cumulative OS advantage when CABA is used in the sequence.

	Second line				Third line			
	# pts	bRR	oRR	Median PFS	# pts	bRR	oRR	Median PFS
AA	261	39.8%	17.6%	7.9 mos	136	29.4%	15.4%	6.1 mos
CABA	151	35.7%	15.9%	6.1 mos	220	27.7%	12.2%	4.7 mos
ENZ	64	48.4%	15.6%	6.2 mos	120	23.3%	9.1%	3.7 mos

5031 Poster Session (Board #105), Mon, 1:15 PM-4:45 PM

Circulating tumor cell subsets and macrophage polarization to predict efficacy of cabozantinib in advanced prostate cancer with visceral metastases. *First Author: Edwin M. Posadas, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: The presence of VM in metastatic, castration-resistant prostate cancer (mCRPC) predicts poor survival. Cabozantinib (cabo) is a multi-kinase inhibitor that has clinical activity that did not improve survival in an unselected mCRPC population. Subgroup analyses suggested that the benefit may exist for patients (pts) with mCRPC-VM. The effect of cabo includes the tumor microenvironment, monocytes in particular, which in turn can alter tumor behavior. **Methods:** We conducted a single-arm study of cabo in men with mCRPC-VM. Pts received cabo 60 mg daily. Radiographs were used to assess response. Correlative blood samples were collected for the enumeration and characterization of circulating tumor cells using the NanoVelcro Assay and analysis of circulating monocytes by FACS. **Results:** A total of 17 pts enrolled with 16 evaluable for response. At 12 weeks, 19% experienced partial responses (PR), 44% stable disease (SD), and 38% progressive disease. The clinical benefit rate (PR+SD) at 12 weeks was 63%. Safety profile was consistent with previous reports. CTCs were detected in 80% of pts. NanoVelcro CTC counts showed reduction by week 8 in both PR+SD (88%) and PD (71%) groups with re-emergence at progression. Among pts with liver metastases, very-small-nuclear CTCs ($< 8.5\ \mu m$) were seen in 29% of pts with clinical benefit compared to 60% in non-benefiters. Analysis of monocyte polarization after initiation of therapy showed that reduction of M1 polarization was associated with improvement in bone pain and/or bone scan. **Conclusions:** In heavily-pretreated mCRPC-VM, cabo provided clinical benefit with acceptable toxicity. Circulating biomarkers related to both tumor and microenvironment may be useful in identifying patients who benefit from this type of therapeutic approach. Clinical trial information: NCT01834651.

5032 Poster Session (Board #106), Mon, 1:15 PM-4:45 PM

Efficacy, safety, tolerability, and pharmacokinetics of EPI-506 (ralaniten acetate), a novel androgen receptor (AR) N-terminal domain (NTD) inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC) progressing after enzalutamide and/or abiraterone. *First Author: Kim N. Chi, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: EPI-506 (ralaniten acetate) is a first-in-class small molecule transcription inhibitor of the AR NTD. Nonclinical studies demonstrated activity against both full length and resistance-related AR species, including AR-v7. **Methods:** Open-label, single-arm, Phase 1/2 study evaluating EPI-506 administered orally once-daily. The Phase 1 is a 3+3 design to establish the safety, pharmacokinetic (PK) profile, and recommended phase 2 dose of EPI-506. Anti-tumor activity is also evaluated. Inclusion criteria included: mCRPC with progression after ≥1 line of hormonal therapy or chemotherapy, and progression on enzalutamide and/or abiraterone. **Results:** Eighteen patients (pts) have been enrolled in the dose escalation phase over 5 dose levels (80, 160, 320, 640, 1280 mg). Median age was 71 (range 58-87). Prior treatments included enzalutamide only (N = 7), abiraterone only (N = 2) or both (N = 9). Six pts have had prior chemotherapy. Seven pts have discontinued due to disease progression and 2 pts due to adverse events (AEs): Grade 4 elevated amylase (related) and Grade 4 gastrointestinal bleeding (unrelated). Median exposure was 98.5 days (range 26-338). Most frequently reported treatment emergent AEs were diarrhea (N = 7), nausea (N = 5) and fatigue (N = 3). One Grade 3 AE (AST elevation) at 1280 mg and one Grade 4 AE (increased amylase) at 640 mg were reported. PK data demonstrate a dose-proportional profile for C_{max} and AUC coupled with an initial negative food effect up to 640 mg. At week 4 of continuous dosing, 3 of 18 evaluable pts demonstrated PSA declines ranging from 9 to 18% receiving doses ≥640 mg. **Conclusions:** EPI-506 is well-tolerated with a favorable safety profile. PK indicates dose-proportionality. PSA declines have been observed at doses associated with sub-therapeutic exposure in preclinical studies. This study is the first to evaluate targeting the AR NTD, a region critical for transcriptional function of all known AR species. Clinical trial information: NCT02606123.

5033 Poster Session (Board #107), Mon, 1:15 PM-4:45 PM

Efficacy of cabazitaxel (CABA) rechallenge in heavily-treated patients with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Constance Thibault, European George Pompidou Hospital, Paris, France*

Background: Only 2 chemotherapies have shown an overall survival (OS) benefit in mCRPC: docetaxel (DOC) and CABA. In patients (pts) previously treated with a new hormonal therapy (NHT: enzalutamide or abiraterone), DOC and CABA, therapeutic options are limited. We previously reported some activity of DOC rechallenge in good responders to first-line DOC. We present here the results of a retrospective study evaluating the efficacy and safety of CABA rechallenge. **Methods:** Records of 70 mCRPC pts rechallenged with CABA were collected in 17 centers (France, Italy, UK, Austria). To be included, pts should have previously received DOC, NHT and CABA with a good response to CABA. **Results:** Of these 70 pts, 52 received DOC-NHT-CABA, 15 DOC-CABA-NHT and 3 NHT-DOC-CABA. At rechallenge, 83% had a high-volume disease (CHAARTED definition), 10% had visceral mets, 66% consumed narcotic analgesics, 68 % were ECOG 0-1 and median neutrophil/lymphocyte ratio (NLR) was 3.1. CABA was rechallenged for a median of 6 cycles (25 mg/m^2 q3w, 59%; 20 mg/m^2, 27%; 16 mg/m^{2}q3w 11%) with prophylactic G-CSF in 47%. Median time from last CABA cycle was 8.6 months (mo). CABA rechallenge had an acceptable tolerability: 7 pts (10%) had grade 3-4 toxicity (neutropenia). Data on efficacy are reported in Table 1. Median progression-free survival (PFS) was 11.3 mo with DOC, 12 mo with NHT, 11.9 mo with first CABA (median 8 cycles), and 7.8 mo with CABA rechallenge. Median OS calculated from the first life-extending therapy was 59.9 mo (95% CI 47.8; 66.4). **Conclusions:** This retrospective cohort of heavily treated mCRPC pts suggests that CABA rechallenge has a good activity with a manageable toxicity. CABA rechallenge might be an option in heavily treated pts still fit to receive chemotherapy.

Efficacy of CABA and CABA rechallenge.

	CABA	CABA rechallenge
Best clinical benefit*		
Improved	51%	34%
Stable	46%	48.5%
Progression	3%	17.5%
PSA response		
Decrease > 50%	71%	24%
Decrease ≥ 30%	77%	41%
Median PFS (mo)	11.9 [10.58; 14.72]	7.8 [4.60; 10.12]
Median OS (mo)	30.6 [24.28; 37.36]	13.4 [8.31; 15.08]

*Based on ECOG performance status, pain and analgesic consumption

5034 Poster Session (Board #108), Mon, 1:15 PM-4:45 PM

Circulating tumor cells (CTCs) N-terminal androgen receptor expression to identify patients (pts) with castrate resistant prostate cancer (CRPC) who are more sensitive to chemotherapy. *First Author: Susan F. Slovin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Loss of the retinoblastoma tumor suppressor (RB) function was identified as a major means to develop CRPC; the expression of the androgen receptor (AR) is under stringent RB control; and tumors devoid of RB function are hypersensitive to treatment with chemotherapy. Exploratory analysis evaluated baseline N-terminal AR expression in CTCs in men with chemotherapy-naïve CPRC and correlated to changes in PSA, leading us to inquire if this biomarker may identify pts sensitive to chemotherapy. **Methods:** In a multicenter phase II randomized trial of approved doses of abiraterone acetate/prednisone (AA-Arm 1) or combination AA and standard doses of cabazitaxel (AA/CBZ-Arm 2). Patients on AA received CBZ upon progression. Baseline CTCs were obtained on all pts and expression of N-terminal AR expression was performed by Epic Sciences. Positive AR N-terminal expression (AR$^+$) was based on the presence of at least 1 CTC or CK$^-$ cell with AR N-terminal signal expression above the 3.0 positivity threshold. Serial PSAs were determined at baseline and every 3 weeks with routine labs and imaging every 12 weeks. **Results:** To date, 42 of 80 pts have been enrolled: 22 pts to AA, and 20 pts to AA/CBZ. Both regimens were well tolerated with 8/42 (19%) pts experiencing treatment-related grade 3 or 4 toxicities. Blood from 35 patients underwent CTC analysis. Seventy-seven percent of pts (27/35) had detectable CTCs; 11 of 35 pts (31%) had AR overexpression. Of the pts with AR+ CTCs, 1/5 pts treated with AA, and 5/6 pts treated with AA/CBZ had a PSA decline > 50% from baseline. **Conclusions:** Real-time CTC analysis of N-terminal AR expression was feasible and data suggests that this may identify a cohort of pts who may benefit from the combination of CBZ with AA. Further studies are ongoing to evaluate whether cellular heterogeneity and RB expression in CTCs play a role in identifying pts who would benefit from chemotherapy. The trial is coordinated by the Prostate Cancer Clinical Trials Consortium, LLC and funded by Sanofi US Services Inc. and Prostate Cancer Foundation. Clinical trial information: NCT02218606.

5035 Poster Session (Board #109), Mon, 1:15 PM-4:45 PM

Phase 2 biomarker-driven study of ipilimumab plus nivolumab (Ipi/Nivo) for ARV7-positive metastatic castrate-resistant prostate cancer (mCRPC). *First Author: Karim Boudadi, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: ARV7+ mCRPC is an aggressive phenotype with a median PFS of 3-4 mo and OS of 7-9 mo. We hypothesized that ARV7+ tumors would be enriched for DNA repair mutations, rendering them more responsive to combined immune checkpoint blockade. **Methods:** We enrolled 15 mCRPC pts with ARV7+ CTCs (using a CLIA-certified assay) into a single arm phase 2 study. Pts received Nivo 3 mg/kg plus Ipi 1 mg/kg every 3 wk x 4 doses, then maintenance Nivo 3 mg/kg every 2 wk. Targeted sequencing for DNA repair defects was performed on pretreatment tumor biopsies (n=11) or cell-free DNA (n=4). Primary endpoint: PSA_{50}response rate. Secondary endpoints: objective response rate (ORR) in pts with measurable disease, durable PFS (lack of progression ≥24 wk), PSA-PFS, radiographic (r) PFS, overall survival (OS), and frequency/intensity of AEs. **Results:** 15 ARV7+ men were enrolled, with median f/u 8.4 (range 1.9–10.5) mo. Median age was 65, 47% had ECOG ≥1, median PSA was 115 ng/mL, 67% had visceral/nodal mets, all had bone mets, and 60% had ≥4 prior regimens for mCRPC. Mean ARV7/AR ratio was 23% (range 3–75%). 6/15 men (40%) had pathogenic DNA repair gene mutations (*BRCA2, ATM, MSH6, FANCM, FANCA, POLH*). Overall, the PSA_{50}rate was 1/15 (7%), ORR was 2/8 (25%), durable PFS rate was 3/15 (20%), PSA-PFS was 3.0 (95%CI 2.1–4.9) mo, rPFS was 3.9 (95%CI 2.8–5.5) mo, and OS was 9.5 (95%CI 7.2–NA) mo. Outcomes appeared better in DNA repair deficient (DRD+) tumors vs. DNA repair proficient (DRD–) tumors (TABLE). 15 grade 3-4 treatment-related AEs occurred in 7/15 (46%) men (including 2 hepatitis, 2 colitis, 1 pneumonitis); there were no treatment-related deaths. **Conclusions:** In this first study targeting ARV7+ mCRPC, treatment with Ipi/Nivo had acceptable safety and encouraging efficacy, particularly in men with DRD+ tumors. DNA repair mutations may be enriched in ARV7+ prostate cancer. Clinical trial information: NCT02601014.

	DRD+ Tumors (N=6)	DRD– Tumors (N=9)	HR (95%CI)	*P*
PSA_{50}	17%	0%		0.400
ORR	40% (2/5)	0% (0/3)		0.464
Durable PFS	50%	0%		0.044
PSA-PFS (mo)	4.9 (95%CI 3.0–4.9)	2.1 (95%CI 1.7–2.3)	0.14 (0.04–0.46)	0.001
rPFS (mo)	7.5 (95%CI 3.9–7.5)	2.9 (95%CI 1.9–4.0)	0.28 (0.09–0.86)	0.027
OS (mo)	9.5 (95%CI 8.2–NA)	7.2 (95%CI 3.5–9.5)	0.61 (0.15–2.44)	0.421

5036 Poster Session (Board #110), Mon, 1:15 PM-4:45 PM

Assessment of quality of life (QOL), cognitive function and depression in a randomized phase II study of abiraterone acetate (ABI) plus prednisone (P) vs enzalutamide (ENZA) for metastatic castrate-resistant prostate cancer (mCRPC). *First Author: Daniel Khalaf, BC Cancer Agency, Vancouver, BC, Canada*

Background: ABI + P and ENZA treatments are associated with side effects that may impair QOL. ENZA has been associated with cognitive and memory impairment. There has been no direct comparison between these agents and their effect on these domains. **Methods:** Randomized phase II trial of ABI + P vs ENZA as 1st-line therapy for mCRPC (ClinicalTrials.gov: NCT02125357). FACT-P QOL questionnaire, patient health questionnaire (PHQ-9) and Montreal Cognitive Assessment (MoCA) were completed throughout the study. The proportion of patients with a clinically significant change in FACT-P (10 points total FACT-P score, 3 points FACT-P subscales), worsening of PHQ-9 depression symptom severity (none = 0-4, mild = 5-9, moderate = 10-14, moderate-severe = 15-19, severe ≥20) and decline in MoCA cognitive impairment level (normal = 27-30, mild = 18-26, moderate = 10-17, severe < 10) at week 12 was compared between study arms for this analysis. **Results:** From 202 patients (pts) accrued, there were 162, 145 and 142 pts with baseline and 12-week FACT-P, PHQ-9 and MoCA assessment. Median baseline FACT-P, PHQ-9 and MoCA scores were similar in both arms. From baseline to 12 weeks, the median total FACT-P score improved in the ABI + P arm (115 to 128, P = 0.02), but there was no change in the ENZA arm (114 to 114, P = 1.00). There was a higher rate of significant worsening for the physical well-being (PWB) subscale for ENZA vs ABI + P (TABLE), but not for the other FACT-P subscales. There was a higher rate of worsening in depression severity in the ENZA arm (TABLE), although worsening to a moderate-severe/severe level occurred in only 2 patients. There was also a trend for worsening in cognitive impairment for the ENZA arm (TABLE). **Conclusions:** These data suggest there are distinct differences between ABI + P vs ENZA and their effects on QOL, mood symptoms and cognitive function. Clinical trial information: NCT02125357.

	At 12 weeks of treatment				
	ABI + P		ENZA		
	Unchanged/ Improved	Worsened	Unchanged/ Improved	Worsened	P
Total FACT-P score	92%	8%	84%	16%	0.099
FACT-P PWB subscale	94%	6%	71%	29%	0.0004
PHQ-9 depression severity	93%	7%	74%	26%	0.003
MoCA impairment level	94%	6%	84%	16%	0.06

5037 Poster Session (Board #111), Mon, 1:15 PM-4:45 PM

Avelumab in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Farhad Fakhrejahani, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Despite recent progress, mCRPC remains a lethal disease. While programmed cell death 1 (PD-1) and PD-1 ligand (PD-L1) inhibitors have shown activity in variety of cancers, to this point there is minimal evidence of activity in mCRPC. This is a report of avelumab, anti-PDL1 in mCRPC patients (pts). **Methods:** This is an expansion cohort of the first in human, phase I trial (JAVELIN Solid Tumor; EMR100070-001) that evaluated 10 mg/kg of avelumab in pts with mCRPC who had progressive disease (PD) on previous treatment. Pts who had PD on an androgen receptor antagonist (ARA) could enroll on trial and continue their ARA. Avelumab was administered as a 1-hour intravenous infusion every 2 weeks (w) with restaging scans every 6 w. Prostate cancer working group 2 criteria were used to determine PD. **Results:** 18 patients were enrolled on this cohort; the median age of pts was 67 years. Median on study PSA was 11ng/mL. 11 pts had Gleason score (GS) $\geq$ 8 and 7 had GS of 7. 3 pts had previous chemotherapy with docetaxel, 8 pts received previous vaccine treatment including 4 pts with sipuleucel-T and 4 pts with Prostvac. Overall avelumab treatment appears safe and tolerable. 15 pts experienced grade $\leq$ 2 treatment related adverse events (TRAEs), fatigue being the most common one. 4 pts developed treatment related hypothyroidism, 3 with grade 2 and 1 with grade 1. In addition, 2 pts had grade 3 asymptomatic TRAEs (amylase & lipase elevations). 7 pts had stable disease (SD) $>$ 24 w post treatment, 6 pts had PD after first restaging scans at 6 w which was reconfirmed in 2nd restaging scan at 12 w. PSA doubling time (PSADT) prior to avelumab was compared with PSADT after 3 months (m) of treatment. Among 17 pts with available data, 3 pts had a prolonged PSADT which was defined at 3 m (twice as high as on-study PSADT), 7 pts had stable PSADT and 7 had decreased PSADT. 5 of 18 pts enrolled while on enzalutamide with a rising PSA. Among these pts 1 had prolonged PSADT, 2 had a stable PSADT and 2 with decreased PSADT after 3 m of follow up. 3 of 5 pts had SD $>$ 24 m, 1 had SD for 13 w and 1 had PD at first restaging scans. **Conclusions:** These data provide safety data of avelumab on a population of pts with mCRPC. Immune analysis is under way to determine correlation with immune responses in the pts on this trial that had prolonged SD. Clinical trial information: NCT01772004.

5038 Poster Session (Board #112), Mon, 1:15 PM-4:45 PM

Phase 1 study of the PSMA-targeted small-molecule drug conjugate EC1169 in patients with metastatic castrate-resistant prostate cancer (mCRPC). *First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancers, but not in most normal tissues, making it a potential therapeutic target. We are conducting a two-part phase 1 dose escalation/expansion study of EC1169, a PSMA-targeted conjugate of the microtubule inhibitor tubulysin B hydrazide in mCRPC. The utility of the PSMA-targeted companion imaging agent ^{99m}Tc-EC0652 is also being evaluated as a patient selection tool. The safety, efficacy, and imaging-based PSMA selection strategy are being investigated in Part A (dose escalation) and Part B (2-stage, 2-cohort expansion). **Methods:** Part A pts were eligible if they progressed on abiraterone or enzalutamide, and were treated with a taxane. EC1169 was administered as an IV bolus on days 1, 8 every 21 days. Part B pts are enrolled in 1 of 2 cohorts, mCRPC taxane naïve (cohort 1, 45 pts) and taxane exposed (cohort 2, 40 pts). Prior to treatment, pts undergo a ^{99m}Tc-EC0652 SPECT scan. The primary endpoint of Part B is median radiographic progression-free survival (rPFS). Other study evaluations are OS, PSA, and CTC-based biomarkers. **Results:** Part A is now complete: the RP2 dose is 6.5 mg/m^2, on the basis of non-DLT transaminitis. 20 Part A/B pts have been treated at the RP2 dose (7 taxane naïve, 13 taxane exposed). Median age is 69 (range: 59-82). Median number of cycles is 2 (range: 1-7). 10 pts (50%) reported at least 1 treatment related AE. Most treatment related AEs are Gr1 and 2; G3 thrombocytopenia, fatigue, and constipation have occurred in 1 pt each. No Grade 4 treatment related AEs have been reported. No DLT or toxicity requiring dose reductions occurred. Four taxane-exposed pts in Part B have reached their first 9 wk radiographic assessment, of which two have soft tissue disease. One of those two patients (50%) has achieved an unconfirmed RECIST PR. **Conclusions:** The RP2 dose of EC1169 is 6.5 mg/m^2. EC1169 has been well tolerated in 20 pts at the RP2 dose. Imaging with ^{99m}Tc-EC0652 suggests excellent disease localization supporting a PSMA-targeted therapeutic strategy. There is evidence of anti-tumor activity in both the dose escalation and expansion cohorts. Clinical trial information: NCT02202447.

5039 Poster Session (Board #113), Mon, 1:15 PM-4:45 PM

Prognostic value of free testosterone (FT) levels during chemotherapy with carboplatin plus weekly docetaxel in metastatic castration- and docetaxel-resistant prostate cancer (mDRPC). *First Author: Christoph Reuter, Department of Hematology, Hemostaseology, Oncology, and Stem Cell Transplantation, Medizinische Hochschule Hannover, Hanover, Germany*

Background: Carboplatin plus docetaxel (DC) may be effective in mDRPC. Platinum(II)-complexes interfere with steroid biosynthesis lowering testosterone levels by inhibiting the cholesterol side chain cleavage enzyme (CYP11A1), 3β-hydroxysteroid dehydrogenase (HSD3B1,2) and 17α hydroxylase/C17,20-lyase (CYP17A1). **Methods:** Docetaxel failure/resistance was defined according to the Prostate Cancer Working Group (PCWG2 2007) criteria. Treatment consisted of at least two cycles of carboplatin AUC5 iv for 30 min on day 1 every 4 weeks (q4w), docetaxel at a dose of 35 mg/m2 iv for one hour on days 1, 8, (15) plus prednisone 2x5mg/day orally after receiving informed consent until disease progression or occurrence of intolerable adverse effects. Efficacy measures were done following PCWG2 recommendations. Free testosterone levels were measured before (n = 77) and during DC chemotherapy (n = 69). **Results:** Of the 100 pts. treated since February 2005, 96% had bone metastases, 45% had lymph node, 27% liver and 21% lung involvement. At the time of the current analysis, the median follow-up was 13.6 months, 93 pts. had died and 97 had progressive disease. The objective response rate was 36.5% in the 63 pts. with measureable disease. Response of prostate-specific antigen ($\geq$50%) was observed in 50% of patients. Median progression-free survival (PFS) for all patients was 6.9 months (CI 95% 5.5, 8.3) and median OS was 15.4 months (CI 95% 11.5, 19.4). The most common reversible grade 3/4 toxicity was leukopenia/ neutropenia (40/32%). Median free testosterone levels were 0.61 pg/ml before and $<$ 0.18 pg/ml during carboplatin/docetaxel treatment (nadir levels, $p < 0.001$; detection limit $<$ 0.18 pg/ml). Median serum androgene levels (T+DHT) were 0.1 ng/ml before and below the detection limit of $<$ 0.05 ng/ml during DC treatment. In multivariate analyses, LDH, PSA response, free testosterone nadir levels below the detection limit ($<$ 0.18 pg/mL) during DC treatment were associated with longer OS ($p < 0.05$). **Conclusions:** These data suggest that carboplatin plus weekly docetaxel may be an important salvage treatment option for DRPC patients.

5040 Poster Session (Board #114), Mon, 1:15 PM-4:45 PM

A phase II trial of abiraterone acetate (AA) without prednisone in castration resistant prostate cancer (CRPC). *First Author: Rana R. McKay, Dana-Farber Cancer Institute, Boston, MA*

Background: AA blocks CYP17 and suppresses adrenal androgens and glucocorticoids. Given the risk of mineralocorticoid excess (ME), AA is administered with corticosteroids. In this phase II multicenter, single-arm study, we assess the safety of AA without steroids in CRPC. The primary objective is to determine the proportion of men requiring prednisone to manage ME. **Methods:** Eligible patients had CRPC with controlled blood pressure (BP) ($<$ 140/90 on $\leq$3 agents) and a normal or $\geq$3.5 mmol/L potassium. Patients initially received AA (1000 mg daily) alone. Patients who developed a BP $\geq$ 140/90 were treated with anti-hypertensives (HTN) and/or a mineralocorticoid antagonist (MA) prior to steroids. Hypokalemia was treated with supplementation or a MA. Patients with persistent or severe ME were initiated on prednisone (5 mg twice daily). To assess response to steroids, prednisone was added to AA at PSA progression. Therapy was continued until radiographic progression, toxicity, or withdrawal. **Results:** 60 patients were enrolled of whom 51 (83%) had metastases 16 (27%) received prior chemotherapy, 6 (10%) enzalutamide, and 4 (7%) ketoconazole. Grade (G) 3-4 adverse events (AEs) of interest included HTN (G3 n = 8, 13%; G4 n = 1, 2%), hypokalemia (G3 n = 4, 7%; G4 n = 0), fatigue (G3 n = 1, 2%; G4 n = 0). There was no G $\geq$3 edema. 9 patients (15%) initiated prednisone for toxicity: HTN (n = 3, 5%), hypokalemia (n = 4, 7%), fatigue (n = 2, 3%). Baseline PSA was 15.4 ng/mL. Time to nadir PSA was 2.5 months (IQR 1.4, 6.3) and median nadir PSA was 2.1 ng/mL. 67% of patients (n = 40) experienced a $\geq$50% PSA decline and 35% (n = 21) experienced a $\geq$90% decline. 19 patients (32%) initiated prednisone for PSA progression. Median time to prednisone initiation in patients with PSA progression was 6.1 months (IQR 4.9, 11.7); 5 patients (8.3%) had a PSA decline and 1 achieved a $\geq$50% decline. Levels of corticosteroids will be reported. **Conclusions:** In CRPC, AA without steroids is feasible, however clinically significant AEs, particularly HTN, can occur in a minority of patients. HTN and hypokalemia can be treated with anti-HTN agents or potassium without steroids in the majority. Use of AA without prednisone needs to be balanced with the potential risk of toxicity. Clinical trial information: NCT02025010.

5041 Poster Session (Board #115), Mon, 1:15 PM-4:45 PM

Clinical activity and safety of ASN001, a selective CYP17 lyase inhibitor, administered without prednisone in men with metastatic castration-resistant prostate cancer (mCRPC): A phase 1/2 clinical trial. *First Author: Jorge A. Garcia, Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH*

Background: ASN001 is a novel, non-steroidal, potent inhibitor of CYP17 lyase that selectively inhibits synthesis of testosterone over cortisol in the adrenals to avoid the need for co-administration of prednisone. ASN001 also exhibits high oral bioavailability and low potential for drug-drug interaction. **Methods:** This Phase (Ph) 1/2 clinical trial in men with progressive mCRPC evaluates once-daily, oral ASN001 at escalating doses of 50, 100, 200, 300 and 400 mg (NCT02349139). While Ph 1 also allowed enrollment of pretreated patients, no prior enzalutamide (ENZA) or abiraterone (ABI) is permitted in Ph 2. Endpoints include maximum dose (MTD) and dose limiting toxicities, recommended Ph 2 dose, PK, effect on steroid hormone biosynthesis and clinical efficacy (PSA and imaging). **Results:** To date, 26 mCRPC pts have been enrolled. No prednisone was administered and no mineralocorticoid excess has been reported. Overall, ASN001 was well tolerated. Most drug-related adverse events were Gr 1/2 and included fatigue, constipation and nausea. At 400mg, two pts experienced asymptomatic, reversible Gr 3 ALT/AST elevation, but no recurrence when retreated at 300mg. Enrollment of ABI/ENZA naïve patients continues at lower doses to further evaluate safety and efficacy. Testosterone decrease to below quantifiable limits and DHEA decrease of up to 80% was observed. Systemic exposure was high (C_{max}, AUC and $T_{1/2}$ at 300 mg QD were 6.7 μM, 80 μM.h and 21.5 h, respectively). Stable disease up to 18+ months has been observed despite prior ABI and ENZA exposure. PSA decline of $>$ 50% (up to 93% decline) and up to 37+ wks duration was observed in 3 of 4 ABI/ENZA naïve patients at starting doses of 300/400mg. **Conclusions:** Overall, ASN001 was safe and well tolerated. Prednisone co-administration was not needed. Encouraging preliminary evidence of efficacy is reflected by PSA declines in evaluable mCRPC pts not pretreated with ABI or ENZA and by durable disease stabilization in refractory disease. Enrollment is ongoing at doses below 400mg QD in ABI/ENZA naïve mCRPC pts. Updated and detailed results will be presented at the meeting. Clinical trial information: NCT02349139.

5042 Poster Session (Board #116), Mon, 1:15 PM-4:45 PM

Patient (pt) characteristics and treatment patterns in the radium (Ra)-223 REASSURE observational study. *First Author: Celestia S. Higano, University of Washington Fred Hutchinson Cancer Center, Seattle, WA*

Background: Ra-223, a targeted alpha therapy, prolonged survival with good safety in metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 ALSYMPCA trial. REASSURE will evaluate Ra-223 short- and long-term safety in routine clinical practice settings. This is the first planned interim analysis (median 7 mo observation). **Methods:** This global, prospective, single-arm, observational study enrolled pts with mCRPC with bone metastases (mets) for whom Ra-223 therapy was planned. Follow-up will continue up to 7 years after last Ra-223 dose. **Results:** 1106 pts (437 N. America, 665 Europe, 4 not recorded) enrolled from 2 Sep 2014 to 22 Sep 2016. Baseline data are available from 583 pts receiving 1st- (1L), 2nd- (2L), or ≥3rd-line (≥3L) Ra-223 for mCRPC(Table). The majority of pts (n=369, 63%) completed 5–6 doses (1L, 70%; 2L, 64%; ≥3L, 49%); median 6 doses (1L,6; 2L, 6; ≥3L, 4). Treatment-emergent drug-related AEs occurred in 215 pts (37%). Post-treatment grade 3/4 thrombocytopenia occurred in 14 pts (2.4%) and anemia in 45 (7.7%). **Conclusions:** In routine clinical practice, Ra-223 was associated with no short-term safety concerns and appeared to be used in pts with less advanced mCRPC than in ALSYMPCA. The majority of pts on 1L/2L Ra-223 therapy received 5–6 doses. Ra-223 was often used with abiraterone or enzalutamide, but not chemotherapy. The next interim analysis in 2019 will report long-term safety and outcomes on all pts. Clinical trial information: NCT02141438.

Baseline characteristics and treatment patterns.

	Total pts* N=583	1L n=282 (48%)	2L n=162 (28%)	≥3L n=139 (24%)
ECOG 0–1, n (%)	451 (77)	232 (82)	118 (73)	101 (73)
No. of mets†, n (%)				
<6	165 (30)	92 (36)	37 (24)	36 (27)
6–20	302 (56)	144 (56)	90 (58)	68 (52)
>20	106 (20)	35 (14)	39 (25)	32 (24)
Superscan	40 (7)	16 (4)	15 (10)	9 (7)
ALP (U/L), median	134	112	145	167
<140 U/L, n (%)	211 (36)	105 (37)	59 (36)	47 (34)
≥140 U/L, n (%)	199 (34)	74 (26)	64 (40)	61 (44)
PSA (ng/mL), median	61	28	74	145
LDH (U/L), median	273	260	272	320
Concomitant use§, n (%)				
Abiraterone or enzalutamide	153 (26)	86 (31)	47 (29)	20 (14)
Docetaxel or cabazitaxel	19 (3)	10 (4)	5 (3)	4 (3)

*Totals <100% due to missing data. †Some pts undergoing >1 imaging modality reported in >1 category. §Concomitant = any overlap with Ra-223.

5044 Poster Session (Board #118), Mon, 1:15 PM-4:45 PM

Androgen deprivation therapy in the treatment of prostate cancer and dementia risk: A systematic review and meta-analysis. *First Author: Kevin Thomas Nead, Department of Medicine, Hospital of the University of Pennsylvania, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

Background: Androgen deprivation therapy (ADT) to treat prostate cancer may be associated with an increased risk of dementia, but existing studies have shown conflicting results. Here we conduct a systematic review and meta-analysis on the association of ADT in the treatment of prostate cancer with the risk of dementia. **Methods:** We conducted a systematic review of articles reporting the outcome of dementia among individuals with prostate cancer in those exposed to ADT versus a lesser-exposed comparison group (e.g. no ADT, intermittent ADT) using the PRISMA statement guidelines. Two authors independently carried out searches in PubMed (1966–present), Web of Science (1945–present), Embase (1966–present), and PsycINFO (1806–present). The search was undertaken December 4th, 2016. We assessed the validity of each study per the Newcastle-Ottawa Scale criteria. We meta-analyzed studies reporting an effect estimate and controlling for confounding.Random- or fixed-effects meta-analytic models were used in the presence or absence of heterogeneity, respectively, per the I^2statistic. Small study effects were evaluated using Egger and Begg's tests. **Results:** Nine studies were included in the systematic review. Seven studies reported an adjusted effect estimate for dementia risk. A random-effects meta-analysis of studies reporting any dementia outcome, which included 50,541 individuals, showed an increased risk of dementia among ADT users (hazard ratio [HR], 1.47; 95% confidence interval [CI], 1.08–2.00; p = 0.02). We separately meta-analyzed studies reporting all-cause dementia (HR, 1.46; 95% CI, 1.05–2.02; p < 0.001) and Alzheimer's disease (HR, 1.25; 95% CI, 0.99–1.57; p = 0.06). The I^2statistic to evaluate the proportion of heterogeneity due to study variation was 76% (95% CI, 47–89; p < 0.001) for the primary analysis. There was no evidence of bias from small study effects (Egger, p = 0.19; Begg, p = 1.00). **Conclusions:** The currently available combined evidence suggests that ADT in the treatment of prostate cancer may be associated with an increased risk of dementia. The potential for neurocognitive deficits secondary to ADT should be discussed with patients and evaluated prospectively.

5045 Poster Session (Board #119), Mon, 1:15 PM-4:45 PM

Trop-2 expression on treatment resistant cancer cells in castrate-resistant prostate cancer (CRPC) as a predictive biomarker for targeted therapy. *First Author: Kimberly Peihsi Ku, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Trophoblastic cell-surface antigen (Trop-2) is a transmembrane glycoprotein that is highly expressed in many solid tumors. Sacituzumab govitecan (IMMU-132) is an antibody-drug conjugate of an anti-Trop-2 humanized antibody with SN-38. Early clinical trials have shown high response rates in a broad range of diseases including triple negative breast and urothelial cancers. We evaluated Trop-2 expression in tumor biopsies and circulating tumor cells (CTCs) from men with mCRPC (metastatic castrate-resistant prostate cancer). **Methods:** Trop-2 expression was evaluated from mCRPC biopsies from patients (Pts) treated with abiraterone acetate (AA) on the PROMOTE clinical trial, CTCs from a separate cohort treated with either enzalutamide or AA. Trop-2 CTCs were compared with EpCAM captured CTCs using a microscale technology termed the VERSA (Vertical Exclusion-based Rare Sample Analysis) platform to compare protein and gene expression signatures of resistance to these agents. **Results:** RNA sequencing identified Trop-2 gene expression in > 70% of metastatic biopsies. The AR splice variant V7 was found in 48 biopsies that also expressed Trop-2. Trop-2 expression was not altered by treatment with AA at 12 weeks. The number of CTCs captured from 25 pts with Trop-2 or EpCAM were closely correlated (R^2= 0.84). Gene expression analysis showed similar patterns of expression for the TROP-2 and EPCAM captured cells. AR splice variant expression (AR-V7, AR-V9) in Trop-2 and EpCAM CTCs was detected in 33% of patients. Expression of neuroendocrine markers was identified in 40% of Trop-2 CTCs. **Conclusions:** Trop-2 is frequently expressed in mCRPC and co-expressed in tumors that express AR splice variants. Trop-2 CTCs are detected in CRPC pts previously treated with AA or Enzalutamide that also express multiple AR splice variants and neuroendocrine markers. The results support Trop-2 expression as predictive biomarker of sensitivity to targeted therapies tumors resistant to AA or Enzalutamide. Men with mCRPC are being enrolled on a Phase I trial with IMMU-132, and multi-site Phase II clinical trial in men who have progressed on AA or Enzalutamide is being finalized.

5046 Poster Session (Board #120), Mon, 1:15 PM-4:45 PM

Sipuleucel-T (sip-T) to induce cytolytic T lymphocyte (CTL) activity against target antigens in men with hormone-sensitive and castration-resistant prostate cancer (CRPC). *First Author: Charles G. Drake, Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY*

Background: Sip-T is an FDA-approved autologous cellular immunotherapy for patients with asymptomatic or minimally symptomatic metastatic CRPC (mCRPC), manufactured from peripheral blood mononuclear cells (PBMCs) cultured with the immunogen PA2024 (prostatic acid phosphatase [PAP] conjugated to granulocyte macrophage colony-stimulating factor). Treatment with sip-T induces cellular and humoral immune responses to both PA2024 and PAP (Antonarakis, ASCO 2015; Petrylak, ECC 2015; Small *Clin Cancer Res* 2015). To further elucidate the mechanism of sip-T–induced immune responses, we evaluated proliferative and cytolytic characteristics of PA2024- and PAP-specific T cells. **Methods:** Antigen-specific proliferation of CD4 (T helper [T_H]) and CD8 (CTL) T cells was quantified using flow cytometry. To assess CTL lytic activity, cell-surface CD107a expression, indicating lysosomal fusion with the cell membrane and expulsion of lytic enzymes, was measured after stimulation with PAP or PA2024. CTL lytic activity was assessed in 13 patients (from 3 sip-T trials [NCT01431391, NCT01981122, and NCT01487863] in hormone-sensitive PC and mCRPC patients) and 1 healthy donor (control). **Results:** In sip-T–treated patients, a significant increase in proliferation of both CTLs and T_H cells was detected in response to PA2024 ($p < 0.05$) and PAP ($p < 0.10$) at week 6 compared with baseline. Increased PA2024-specific proliferation was maintained in T_H cells through week 26 ($p < 0.05$). CTL CD107a expression increased in sip-T patient samples stimulated with PAP and PA2024 but not in the healthy donor control. Preliminary analyses suggest that patients with longer overall survival (OS) may have greater CTL CD107a activity. **Conclusions:** Sip-T treatment was associated with well-maintained antigen-specific cellular responses, including robust CTL responses, demonstrating sip-T induces antigen-specific tumor lysis and providing a biologic basis for OS benefit in mCRPC patients. Ongoing work will examine whether patients with longer OS display greater CTL activity. Clinical trial information: NCT01431391; NCT01981122; NCT01487863.

5047 Poster Session (Board #121), Mon, 1:15 PM-4:45 PM

Comparison of biochemical recurrence free survival after radical prostatectomy triggered by grade reclassification on active surveillance, and men newly diagnosed with similar grade disease. *First Author: Clarissa P. Diniz, The Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Evaluate the biochemical recurrence free survival (bRFS) in men after radical prostatectomy (RP) triggered by Gleason score (GS) grade reclassification (GR) during active surveillance (AS) in order to inform patient decisions. **Methods:** We conducted a retrospective analysis of men undergoing RP from 1995 - 2015 at Johns Hopkins and identified 4 groups; 94 men in AS that underwent RP following GR from Gleason score (GS) 6 to GS $\geq$ 7(3+4) [grade groups $\geq$ 2], 3,504 men that underwent IRP following a diagnosis of grade groups $\geq$ 2, 56 men in AS that underwent RP following GR to GS 7(3+4) [grade group 2], and 1,979 men that underwent IRP following a diagnosis of grade group 2. The outcome of interest was bRFS, assessed using Kaplan Meir analysis and a multivariate Cox regression model. **Results:** Men on AS had a lower PSA density distribution (0.11 vs. 0.13, p = 0.022; 0.12 vs. 0.12, p = 0.043), and a higher proportion of low volume cancers (46.2% vs. 15.3%, 46.4% vs. 16.7%, both $p < 0.001$) as compared to the IRP groups for both biopsy grade groups $\geq$ 2 and biopsy grade group 2, respectively. The proportions of men with biochemical recurrence (BCR) in the AS and IRP groups were 13.8% vs. 29.1% (p = 0.008 for grade groups $\geq$ 2) and 8.9% vs. 21.7% (p = 0.022 for grade group 2), respectively. One, 5, 10-year bRFS for men in the AS group vs the IRP group was 97.9%, 76.6%, 69.0% vs 85.5%, 65.1% ,54.2%%, respectively for biopsy grade groups $\geq$ 2 (log-rank test, p = 0.009), and 96.4%, 89.6%, 89.6% vs 91.2%, 74.0%, 63.9%, respectively for biopsy grade group 2 (log-rank test, p = 0.071). For biopsy grade groups $\geq$ 2, there was no significant difference in BCR between groups after adjustment for age at treatment, biopsy extent of cancer, and PSA density; HR = 0.78 (95% CI 0.43 – 1.43, p = 0.426). **Conclusions:** AS patients that are reclassified to grade groups $\geq$ 2 have no greater risk of treatment failure as compared to men newly diagnosed with similar grades. These data could help inform decisions regarding management of low grade prostate cancer.

5048 Poster Session (Board #122), Mon, 1:15 PM-4:45 PM

Predictors of post-surgical race-specific prostate cancer progression. *First Author: Jennifer Cullen, Center for Prostate Disease Research, Rockville, MD*

Background: Disparity in prostate cancer (CaP) incidence and mortality for African American (AA) versus Caucasian American (CA) men may reflect tumor biology, comorbidity, treatment, follow-up care, and/or health care access. In a racially diverse cohort of patients undergoing radical prostatectomy (RP), this study examined how race, comorbidity, and PSA doubling time (PSADT) impact CaP progression. **Methods:** Enrollees in the Center for Prostate Disease Research (CPDR) Multi-Center National Database from 1989-2014 who underwent RP within 12 months of CaP diagnosis were eligible. Biochemical recurrence (BCR) was defined as PSA $\geq$0.2 ng/mL post-RP. Comorbid conditions included coronary artery disease (CAD), cerebral vascular incident (CVI), Type II diabetes (DB), hypertension (HT), elevated cholesterol (EC), lung disease (COPD), prostatitis (PS), renal insufficiency (RI) and other cancer (OC). Multivariable Cox proportional hazards (PH) analysis was used to examine comorbid conditions (yes vs. no) and PSADT ($<$ 3, 3-8.9, 9-14.9, and $\geq$15 mos) to predict BCR, controlling for age at RP, D'Amico risk stratum, pathology features, and adjuvant treatment. **Results:** A total of 6,785 patients were eligible; 22% AA and 78% CA. Median age and follow-up was 62 and 6.1 years, respectively. Across race, comparable median follow-up time, distributions of pathologic features and adjuvant treatments were observed. However, AA vs. CA patients had greater HT (53 vs. 39% $p < 0.0001$), DB (17 vs. 7%, $p < 0.0001$), and RI (3 vs. 1%, p = 0.002). Alternatively, CA vs. AA patients had greater CVD (10 vs. 7%, p = 0.0008) and OC (3 vs. 0.5%, $p < 0.0001$). Cox PH analysis showed poorer BCR-free survival for AA vs. CA men (HR = 1.28, CI = 1.11, 1.48, p = 0.0009) adjusting for D'Amico risk stratum, pathology, and treatment. PSADT, not comorbidity, was a critical predictor of BCR, with poorest outcome at extremes: HR PSADT $<$ 3 vs. $>$ = 15 months = 41.5, CI = 33.6, 51.3, $p < 0.0001$). **Conclusions:** Despite comparable health care access and distribution in clinical risk stratum and pathology features, race persisted in predicting poor CaP outcome. Disparate comorbidity for AA and CA men did not eliminate this difference. PSADT remained the most striking determinant of poor BCR-free survival.

5049 Poster Session (Board #123), Mon, 1:15 PM-4:45 PM

Circulating tumour cells and survival in abiraterone- and enzalutamide-treated patients with castration-resistant prostate cancer. *First Author: Bram De Laere, Center for Oncological Research (CORE), University of Antwerp, Antwerp, Belgium*

Background: A heterogeneous landscape of patients with metastatic castration-resistant prostate cancer (mCRPC) exists in current clinical practice. We investigated the prognostic value of CTC enumeration and dynamics, in the context of second-line endocrine therapies (i.e. abiraterone or enzalutamide). **Methods:** In a prospective, multicentre study blood samples were collected from patients with mCRPC at baseline (n = 147) and follow-up (n = 95/147 (64.6%)). At baseline, patients were stratified in favourable ($<$ 5 CTCs/7.5mL) and unfavourable ($\geq$5 CTCs/7.5mL) groups, whereas at follow-up, in those demonstrating a stable, in- or decreasing CTC count. PFS and OS were compared between groups. PSA changes at 10-12 weeks were evaluable in 83 patients. **Results:** Patients with $\geq$5 CTCs/7.5 mL (n = 59) at baseline had a shorter PFS (3.9 vs. 11.3 months, $p< 0.0001$) and OS (9.34 months vs. not reached, $p< 0.0001$). Patients demonstrating increasing CTCs (n = 21) on therapy had a shorter PFS (4.03 vs. 10.36 vs. 13.08 months, $p < 0.0001$) and OS (11.2 months vs. not reached, $p < 0.0001$), compared to patients with decreasing (n = 41) and stable (n = 33) CTCs, respectively. Multivariate Cox regression showed that the number of CTCs (HR (95%CI): 1.0054 (1.0006–1.010), p= 0.0260) and an increasing follow-up CTC count (HR (95%CI): 2.8987 (1.2856–6.536), p= 0.0103) were independent predictors of PFS. CTC increase was the sole independent predictor for OS (HR (95%CI): 7.3512 (1.7953–30.101), p= 0.0055). At 10-12 weeks, a PSA response of $\geq$30% and $\geq$50% was achieved in 46/83 (55.4%) and 33/83 (39.8%) patients, respectively, which was statistically different between chemo-naive or -pretreated patients ($\geq$30%: p= 0.0395), patients with increasing, stable or decreasing CTC counts ($\geq$30%: p= 0.0019; $\geq$50%: p= 0.0032), and patients with increasing or stable/decreasing CTC counts ($\geq$30%: p= 0.0006; $\geq$50%: p= 0.0014). **Conclusions:** CTC levels are associated with PFS and OS in mCRPC patients, starting a new line of endocrine therapy. Follow-up CTC enumeration is associated with PSA response and its dynamics is an independent predictor of PFS and OS, thereby demonstrating the pharmacodynamic properties of CTCs.

5050 Poster Session (Board #124), Mon, 1:15 PM-4:45 PM

***HSD3B1* genotype and response to androgen deprivation therapy for biochemical recurrence after radiotherapy for localized prostate cancer.** *First Author: Jason W. D. Hearn, University of Michigan, Ann Arbor, MI*

Background: The enzyme encoded by the *HSD3B1*(1245C) variant allele has been shown to promote castration-resistant prostate cancer by increasing intratumoral dihydrotestosterone synthesis. In the setting of biochemical recurrence (BCR) following prostatectomy, inheritance of the variant allele has been associated with inferior clinical outcomes for men treated with androgen deprivation therapy (ADT). Whether the same is true in the context of BCR after radiotherapy (RT) is unknown. **Methods:** We determined *HSD3B1* genotype retrospectively in men treated with ADT for post-RT BCR using an established biorepository at a large academic center. We analyzed time-to-progression (TTP), time-to-metastasis (TTM), and overall survival (OS) according to *HSD3B1*genotype using an additive genetic model with the log-rank trend test. Multivariable analyses (MVA) were performed to adjust for known prognostic factors with Cox regression. **Results:** We identified 218 men treated with ADT for BCR after RT, of whom 213 (98%) were successfully genotyped (46%, 45% and 9% carrying 0, 1, and 2 variant alleles, respectively). Median follow-up was 7.9 years (yrs). Demographic and treatment factors were similar across genotypes. Median TTP was 2.3 (95% CI: 1.6, 3.1) yrs in men who inherited 0 variant alleles, 2.3 (1.5, 3.3) yrs with 1 variant allele, and 1.4 (0.7, 3.3) yrs with 2 variant alleles (P = 0.683). Median TTM diminished with the number of variant alleles inherited (7.4 [6.7, 9.7], 5.8 [4.9, 6.5] and 4.4 [3.0, 5.7] yrs, respectively (P = 0.030). No difference in OS was detected (P = 0.305). On MVA with 0 variant alleles as the reference, the adjusted hazard ratio (HR) for metastasis was (1.19 [0.74, 1.92]; P = 0.480) for 1 allele and (2.01 [1.02, 3.97]; P = 0.045) for 2 alleles. MVA did not demonstrate significant differences in TTP or OS. **Conclusions:** The *HSD3B1*(1245C) allele that enhances dihydrotestosterone synthesis is associated with time-to-metastasis in men treated with ADT for BCR after RT for prostate cancer. Notably, 49% of men had received prior ADT as part of local therapy and 56% received an anti-androgen during ADT for BCR, which may blunt the effect of the variant allele.

5051 Poster Session (Board #125), Mon, 1:15 PM-4:45 PM

Clinical implications of the 2012 US Preventive Services Task Force (USPSTF) PSA screening recommendation in prostate cancer diagnoses and 5-year survival at a Minnesota safety net health care system. *First Author: Kevin Gale, Hennepin County Medical Center, Minneapolis, MN*

Background: Prostate specific antigen (PSA) screening for prostate cancer has declined following the USPSTF 2012 recommendation. How screening rates and prostate cancer diagnoses have subsequently changed in a racially diverse patient population is not well defined. In this study, we aim to determine the impact of the USPSTF screening recommendation in the Hennepin Healthcare System (HHS) in the state of Minnesota. **Methods:** A single-institution retrospective analysis of data from our electronic health record, to identify the characteristics of PSA screening and new prostate cancer diagnoses for men ≥50 years between 2008 and 2015. Data before and after May 2012 were compared. P-values were calculated using binominal and generalized linear models. **Results:** Nearly 22,000 patients underwent PSA screening from 2008 to 2015. PSA screening rates decreased after May 2012 for the four largest demographics represented ($p < 0.001$). Hispanics and Blacks were more likely to be screened when compared to Whites and Asians ($p < 0.05$). 319 cases of prostate cancer were diagnosed from 2008 to 2015 with 87 cases (27.3%) diagnosed by PSA-screening. The number needed to screen to diagnose one patient with prostate cancer at HHS was 137.5, and 9.5% of patients (1146 patients) had a false positive PSA that led to further testing or a biopsy. $56,090 was spent in screening costs per diagnosis of early stage prostate cancer via screening. Patients diagnosed from screening were less likely to present with high Gleason scores (8-10) compared to non-screening diagnosis (8% vs 23.3%, $p < 0.01$). The 5-year survival percentage (prostate cancer mortality) was improved for those patients diagnosed by PSA screening vs the non-screened group (100% vs 89.3%, $p < 0.05$). **Conclusions:** PSA screening has declined at HHS since the USPSTF recommendation against prostate cancer screening. Implementation of PSA screening in our healthcare system is expensive and leads to a high number of false positives. Despite this, the 5-year survival from prostate cancer is significantly higher when patients are diagnosed by PSA screening.

5052 Poster Session (Board #126), Mon, 1:15 PM-4:45 PM

Association of CTC detection by AdnaTest with outcome on enzalutamide in chemotherapy-naïve castration-resistant prostate cancer: Exploratory results from PREMIERE—A SOGUG trial. *First Author: Albert Font Pous, Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain*

Background: Circulating tumor cells (CTCs) enumeration using CellSearch correlates with clinical outcome in prostate cancer, but is limited for gene expression analysis. AdnaTest ProstateCancer is a commercially available CTC immune-enrichment and PCR-related detection method that allows gene expression studies (Antonarakis E, NEJM 2014). It has demonstrated incremental detection of CTCs in patients with no CTCs identified by CellSearch (Samoila A, ASCO 2013) but needs to be clinically qualified. There is a strong need for studies to assess the association with the clinical outcome in CRPC. **Methods:** Between February and November 2015, 98 asymptomatic or oligo-symptomatic chemotherapy-naïve mCRPC pts were recruited in 16 institutions. Although initially designed to study the predictive value of TMPRSS2-ETS, data emerging after the trial was initiated led the group to prioritize alternative predefined exploratory biomarkers, including plasma *AR* (Grande E, ASCO 2017 #) and CTC characterization (Grande E, ESMO 2016). Outcome measures included PSA-PFS (sPFS), radiographic PFS (rPFS) and OS. Cox regression was used for survival analyses and Fisher's exact test for PSA response. **Results:** Ninety-eight patients had CTC blood samples available. CTCs were detected at baseline, 12 weeks and progression in 36% (35/98), 27% (26/95) and 78% (32/41), respectively. The CTC conversion rate (positive to negative after 12 w) was 43% (15/35). All CTC conversions had ≥50% decline in PSA (15/15) whereas only 35% (7/20) of pts with persistent CTCs. At first interim analysis, with a median follow-up of 10.6 months, detection of CTCs at baseline was associated with worse sPFS (median, 7.59 m versus NR, HR, 3.67; 95% CI 1.90-7.10; $P < 0.001$), rPFS (median, 12.9 m versus NR; HR, 7.61; 95% CI, 2.80-20.64; $P < 0.001$) and OS (medians NR, HR, 9.51; 95% CI, 1.11-81.52; P = 0.0398). CTC positive pts were less likely to have a ≥90% decline in PSA (OR, 2.88; 95% CI, 1.13-7.72; P = 0.02). **Conclusions:** CTC detection using AdnaTest is associated with an adverse outcome in chemotherapy-naïve asymptomatic or oligo-symptomatic mCRPC pts. Clinical trial information: NCT02288936.

5053 Poster Session (Board #127), Mon, 1:15 PM-4:45 PM

Genome-wide analysis of metastases to reveal association of pathway activation with abiraterone acetate/prednisone (AA/P) primary resistance and cell cycle proliferation pathway activation with response duration in metastatic castrate resistant prostate cancer (mCRPC). *First Author: Manish Kohli, Mayo Clinic, Rochester, MN*

Background: Genomic aberrations associated with resistance/response to AA/P are not known. In a prospective study we assessed whole-exome/RNA-seq based aberrations in CRPC metastatic biopsies for identifying molecular markers associated with primary resistance and response duration. **Methods:** Sequencing of metastatic biopsies was performed for analyzing molecular aberrations that predict primary resistance (defined as progression at 12-weeks of therapy (non-responders) using PSA, RECIST, bone scan criteria per PCWG2). Gene network analysis was performed in genes mutated more frequently in non-responders and in genes differentially expressed between non-responders and responders using a "risk ratio" (RR) of ≥2. Cox regression models with multiple gene network pathways were used for determining association with time to treatment change (TTTC). **Results:** Of 92 enrolled pts 82 had complete whole-exome, RNA-seq & 12-week outcome data available for analysis. At 12-weeks 33/82 had progressed. Using a RR of ≥2, 113 genes were more frequently mutated in non-responders & 292 in responders. In non-responders, gene network analysis revealed frequent mutations in *Wnt/β*-catenin pathway genes; frequent deletion of negative regulators of *Wnt* pathway (*DKK4*, *SFRP2*, *LRP6)*. Gene expression analyses revealed significantly reduced expression levels of *Wnt/β*-catenin pathway inhibitors and increased expression levels of cell cycle proliferation (CCP) genes in non-responders. Median study follow up was 32 months during which time 58/82 pts progressed and switched treatments. Median TTTC was 10.1 months (IQR: 4.4-24.1). In multivariate analysis CCP scores of ≥50 predicted shorter TTTC (HR = 2.11, 95% CI: 1.17-3.80; p = 0.01). **Conclusions:** In metastases *Wnt/β*-catenin pathway activation is associated with primary AA/P resistance and increased CCP with acquired drug resistance. These findings offer molecular based predictive biomarkers in CRPC stage treatment. Clinical trial information: NCT#01953640.

5054 Poster Session (Board #128), Mon, 1:15 PM-4:45 PM

The immunomodulatory protein Dickkopf-1 (DKK1) defines a non-neuroendocrine subtype of metastatic castration-resistant prostate cancer (mCRPC) with low AR and low PSA expression. *First Author: David Wise, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Advanced stagemCRPC can manifest AR-signaling independent growth typified by loss of AR and/or PSA expression in the absence of neuroendocrine (NE) features on biopsy. We sought to identify therapeutically relevant biomarkers of this highly resistant prostate cancer subtype. **Methods:** An unbiased differential gene expression analysis of non-neuroendocrine mCRPC biopsies was carried out comparing patients with AR^{low} to patients with AR^{high} disease in a discovery cohort (SU2C/PCF, 18 pts: 8 AR^{low}, 10 AR^{high}) and validation cohort (Fred Hutchinson, 76 pts: 12 AR^{low}, 64 AR^{high}). The AR and NE status of the biopsies were defined by AR and PSA mRNA expression and gene signatures representative of AR activity and NE lineage. An RNA sequencing-based signature of immune cell subsets was calculated using the *Cibersort* algorithm. **Results:** Differential gene expression analysis identified the secreted Wnt antagonist, DKK1, as significantly upregulated in AR^{low} cases compared to AR^{high} cases (11.2 RPKM vs. 0.28 RPKM, $p < 0.03$) in our discovery cohort and confirmed in our validation cohort (9.2 FPKM vs. 0.99 FPKM, $p < 0.001$). DKK1 protein was also found to be increased in non-neuroendocrine AR^{low} relative to AR^{high} prostate cancer in vitro cell and organoid models (858 pg/mg total protein vs. 2 pg/mg total protein, $p < 0.05$) and patient-derived xenografts (28.6 FPKM vs. 0.78 FPKM, $p < 0.0001$). Consistent with the role of DKK1 as a negative modulator of anti-tumor immunity, patient biopsies with the highest quartile of DKK1 expression showed an RNA signature consistent with lower levels of active NK cells (0.2% vs. 1.8%, $p < 0.005$), and lower levels of CD8+ T cells (3.7% vs. 9.7%, $p < 0.005$) compared to those with the lowest quartile of DKK1 expression. **Conclusions:** DKK1 represents a secreted biomarker that is disproportionately enriched in non-neuroendocrine mCRPCs that lack AR expression. Because DKK1 has been implicated as a suppressor of anti-tumor immunity and is a target of an existing neutralizing antibody, our results support the clinical evaluation of the role of DKK1 blockade in DKK1-positive AR-negative prostate cancer.

5055 Poster Session (Board #129), Mon, 1:15 PM-4:45 PM

The plasma lipidome in castration-resistant prostate cancer. *First Author: Lisa Horvath, Chris O'Brien Lifehouse, Sydney, Australia*

Background: Biomarker studies of metastatic castration-resistant prostate cancer (CRPC) have mainly focused on changes in the cancer, however, the host environment and its interactions with cancer is increasingly important, especially given the increasing association of PC outcomes and obesity. We sought associations between the plasma lipidome and clinical outcome in CRPC. **Methods:** Plasma samples were obtained from a Phase 1 discovery cohort of 96 CRPC patients before and after the first cycle of docetaxel chemotherapy. Lipidomic profiling of the plasma samples was performed by liquid chromatography and electrospray ionisation-tandem mass spectrometry. Results were subsequently assessed in a Phase 2 validation cohort of 63 CRPC patients. **Results:** Lipidomic profiling detected 323 lipid species in plasma samples from the Phase 1 cohort. Patients could be classified into two subgroups with significant survival differences according to their baseline lipidomic profiles (median overall survival 13.7 vs 21.7 months; HR 2.31, 95% CI 1.44-3.68, $p = 0.0005$). The baseline levels of 46 lipids were individually prognostic ($p < 0.01$) and predominantly sphingolipids. A prognostic three-lipid signature was derived (ceramide (d18:1/24:1), sphingomyelin (d18:2/16:0), phosphatidylcholine (16:0/16:0)) (11.7 versus 21.7 months, $p = 0.00001$; HR 2.94, 95% CI 1.80-4.81, $p = 0.00002$). The signature was associated with shorter overall survival in the Phase 2 cohort (HR 4.78, 95% CI 2.06-11.1, $p = 0.0003$), and was an independent prognostic factor when modeled with clinicopathological factors and metabolic characteristics (BMI, cholesterol and triacylglycerol). The AUC of ROC analysis of 12 month survival for a clinicopathological model (AUC 0.70, 95% CI 0.54-0.87, $p = 0.03$) was enhanced by the addition of the 3-lipid signature (AUC 0.73, 95% CI 0.57-0.89, $p = 0.01$). **Conclusions:** Our study is the first to comprehensively profile the plasma lipidome of men with CRPC using cutting-edge lipidomic profiling technology, to identify a plasma lipid signature that can reproducibly predict outcome in CRPC and can improve on clinicopathological models. Therapeutic modulation of the levels of these lipids by targeting their metabolic pathways may improve patient outcome.

5056 Poster Session (Board #130), Mon, 1:15 PM-4:45 PM

Incidence of intrathoracic (IT) metastases detected by ^{68}Ga-PSMA-11 PET in early stage prostate cancer (PC). *First Author: Rahul Raj Aggarwal, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Standard imaging in early stage PC has focused on detecting metastases (mets) within the abdomen and pelvis. The incidence of IT mets (lung, mediastinal, or supraclavicular) mets is unknown, but presumed to be negligible. Whole body ^{68}Ga-PSMA PET has greater sensitivity compared to conventional imaging, affording the opportunity to estimate the incidence of IT mets. **Methods:** Newly diagnosed or biochemically recurrent (BCR) PC patients (pts) with apparent localized disease on standard imaging were enrolled on a prospective study of ^{68}Ga-PSMA PET imaging between June 2015 and January 2017 and were analyzed for incidence of IT mets. Positive lesions were defined as uptake higher than blood pool. When appropriate, patients underwent confirmatory biopsy of the PSMA-avid IT lesions. **Results:** 364 pts underwent ^{68}Ga-PSMA PET imaging, including 121 (33%) pts with newly diagnosed PC and 243 (67%) pts with BCR. 145 pts (40%) had at least 1 PSMA-avid metastasis. PSMA-avid IT mets were detected in 20 pts (5.5% of overall cohort; 13.8% of those with ≥ 1 PET-positive mets), including 3 newly diagnosed (2.5%) pts and 17 (7.0%) pts with BCR. 9 of 20 pts (45%) had IT mets as the only detectable site of metastasis on PET. Biopsy of the PSMA-avid IT lesion was found to harbor PC in 5/5 patients (100%). Sites of detection included: supraclavicular node, n = 9 (2.5%); mediastinal node(s), n = 10 (3.6%), and visceral lung, n = 4 (1.0%). In the entire study cohort of 364 pts, 43% of pts had a Gleason Score ≥ 8 at diagnosis, median PSA was 4.87 ng/mL (range: 0.04 – 83.7), and the median PSA doubling time was 6.2 months (range: 0.4 – 78.3) in patients with BCR. There were no significant differences in PSA, PSA doubling time, Gleason grade, or stage between patients harboring IT metastases vs. those who did not. **Conclusions:** IT mets are detected by ^{68}Ga-PSMA PET imaging at an appreciable frequency in early stage PC with apparent localized disease by conventional imaging, which may significantly impact management in these cases. Further studies are warranted to validate these findings and determine the optimal strategy for the detection and treatment of supradiaphragmatic metastases in newly diagnosed and biochemically recurrent PC. Clinical trial information: NCT02918357.

5057 Poster Session (Board #131), Mon, 1:15 PM-4:45 PM

Effect of Ga-68 PSMA-11 PET on management in patients with recurrent prostate cancer. *First Author: Tom Hope, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: PET imaging of prostate specific membrane antigen (PSMA) has been shown to have a higher sensitivity and specificity compared to conventional imaging. The objective was to evaluate the impact of PSMA PET on the management of prostate cancer patients with biochemical recurrence following local therapy. **Methods:** In our initial Ga-68-PSMA-11 PET protocol (NCT02611882), 150 patients with biochemical recurrence were imaged. 63 patients were imaged using PET/CT (GE Discovery VCT) and 63 patients using PET/MRI (GE Signa 3.0T PET/MRI). 110 patients received Lasix injections. Referring clinicians filled out a pretreatment management form and a management form based on the imaging results. Changes in management were graded as major, minor, no change or unknown based upon the responses. **Results:** We received both pre and post imaging forms in 126 patients, for an 84% response rate. The average PSA in the population was 5.9 ± 5.4 ng/mL with an average doubling time of 9.7 ± 11.0 months, and 60 patients had a PSA of less than 2.0 at the time of imaging. The average time between prior treatment and imaging (RP and/or radiation) was 5.3 ± 5.4 years, with 46 patients imaged within two years of their most recent treatment. 43 patients had a prior prostatectomy, 41 prior radiation, and 33 patients had both. 103 patients (82%) had disease localized on PSMA imaging. Of the 126 patients, 67 (53%) of the imaging studies resulted in a major change in management. The most common major change was converting from active surveillance to radiation therapy (15 patients, 12%), changing from ADT to radiation therapy (16 patients, 13%), and converting from radiation therapy to either active surveillance (6 patients, 5%) or to ADT alone (3 patients, 2%). 10 patients (8%) had a minor change, 42 patients (33%) had no change, and 7 patients (6%) had an unknown change in management. **Conclusions:** The results of our surveys demonstrate a substantial impact of PSMA PET on the intended patient management. The majority of changes involved converting a targeted therapy to systemic treatment or systemic treatment to a targeted therapy. Prospective studies are warranted to determine whether directed treatment towards PSMA-avid lesions affects long-term disease outcomes. Clinical trial information: NCT02611882.

5058 Poster Session (Board #132), Mon, 1:15 PM-4:45 PM

Whole blood androgen receptor (AR) variant (ARV12, ARV14) expression and overall survival (OS) in metastatic castrate resistant prostate cancer (mCRPC). *First Author: Karthik Giridhar, Mayo Clinic, Rochester, MN*

Background: The detection of full length AR (AR-FL) or AR variants (AR-Vs) in blood and association with outcomes in mCRPC is unknown. We compared whole blood mRNA expression of AR-FL and AR-Vs to circulating tumor cells (CTCs) for predicting OS and time to treatment failure (TTF). **Methods:** We isolated RNA from whole blood collected in PAXgene RNA tubes and concurrent metastatic tissue biopsy from 51 men with mCRPC prior to initiation of abiraterone acetate in a prospective clinical trial (NCT#01953640). Whole transcriptome sequencing (RNAseq) was performed on blood samples and paired biopsies to detect AR-FL, ARV1, ARV3, ARV7, ARV8, AR12, ARV14, and ARV45. Reads were aligned to the GRCh38 reference genome with the spliced-alignment TopHat2 package. The Pearson correlation coefficient was calculated between AR-FL in blood and matched bone biopsy. CTCs were determined using the CELLSEARCH assay. Cox proportional hazard regression analysis was performed on AR-FL, each AR-V, and CTCs for association with OS and TTF. We compared the area under the curve (AUC) using CTCs alone to a multivariable model that included AR-Vs for predicting OS. **Results:** The median follow up was 3.0 years, (range 0.3-3.5); the median CTC count was 3 (range 0-372); 34/53 men were deceased. Blood based AR-FL or AR-Vs were detected in 50/53 patients with following distribution: AR-FL (41/53), ARV3 (9/53), ARV45 (8/53), ARV12 (4/53), ARV14 (4/53), ARV7 (2/53), and ARV8 (2/53). Whole blood AR-FL transcripts were highly correlated to paired bone biopsy (r^2= 0.76). Elevated transcripts of either ARV12 or ARV14 were associated with decreased OS [hazard ratio (HR) 3.46, p = 0.006]. CTC count ≥5 was associated with poorer OS [HR 3.42, p = 0.02] and shorter TTF [HR 3.52, p = < 0.001]. Adjusting for CTC counts, in a multivariate model, blood AR12 expression was associated with poor OS [HR = 6.33, p = 0.009]. AR12 and CTCs trended toward improved AUC compared to CTC alone (0.78 vs 0.71, p = 0.07). **Conclusions:** AR-FL and AR-Vs are detectable in whole blood and are highly correlated with metastatic bone AR-FL expression. AR-Vs may add to prognostication in mCRPC and further validation is needed. Clinical trial information: NCT#01953640.

5059 Poster Session (Board #133), Mon, 1:15 PM-4:45 PM

Ten-year overall and prostate cancer (PCa)-specific mortality in high-risk patients after high-dose-rate brachytherapy combined with external beam radiation therapy (HDR-BT/EBRT) compared with EBRT alone. *First Author: Trude Baastad Wedde, Oslo University Hospital, Oslo, Norway*

Background: The effect of dose-escalation with HDR-BT boost for high-risk PCa is not known. The objective is to compare 10-year PCa-specific mortality (PCSM) and overall mortality (OM) in non-metastatic patients treated with HDR-BT/EBRT (2004-2010) to EBRT alone (historical RCT, SPCG-7, 1996-2003). **Methods:** HDR-BT boosts (10 Gy x 2) were given 2 weeks apart followed by 50 Gy conformal EBRT (2 Gy x 25) to the prostate and seminal vesicles (assuming alpha/beta ratio of 3, EQD2 = 102 Gy). The HDR-BT/EBRT group (N:325) received Androgen Deprivation Therapy (ADT) for a total of 2 years. Patients in the control group (N:296) received 70 Gy (2Gy x 35) to the prostate and seminal vesicles with lifelong Anti-Androgen Treatment (AA). cT1-cT2 vs cT3 tumours and Gleason score 6-7 vs 8-10 were analysed. For each treatment group PCSM and OM were established by Kaplan-Meier (KM) analyses, and inter-treatment differences were tested by the logrank tests. Cox regression analysis evaluated the significance of available pre-treatment variables. Significance level $p < 0.05$. **Results:** In both groups the median age was 66 years. Median follow-up was 104 (range 13-120) and 120 (range 3-120) months for the HDR-BT/EBRT and EBRT groups respectively. KM plots revealed an 1.8% risk of PCSM in the HDR-BT/EBRT patient group and an 8.4% risk in the EBRT cohort (p = 0.001). For OM, the figures were 12.3% in the HDR-BT/EBRT group compared to 23.3% in the EBRT group (p = 0.014). In the Cox regression analysis, treatment (HR = 3.9, CI95% 1.8-8.3) and Gleason score (HR = 3.2, CI95% 1.8-5.9) were significantly associated with PCSM whilst T-stage, age and PSA levels were not. Treatment (HR = 1.7, CI95% = 1.1-2.6) was the only factor significantly associated with OM. **Conclusions:** In men with high-risk PCa dose-escalation with HDR-BT/EBRT compared to EBRT alone resulted in a significantly decreased risk of 10-year PCSM and OM despite shorter length of hormonal therapy. PCSM was significantly influenced by both Gleason score and type of treatment, whereas treatment remained the only significant covariate for OM.

5060 Poster Session (Board #134), Mon, 1:15 PM-4:45 PM

Association of androgen receptor (AR) status in plasma DNA with outcome on enzalutamide (enza) or abiraterone (abi) for castration resistant prostate cancer (CRPC). *First Author: Vincenza Conteduca, Centre for Evolution and Cancer, The Institute of Cancer Research, London SW7 3RP, UK, London, United Kingdom*

Background: There is an urgent need to identify biomarkers to guide personalized therapy in CRPC. We aimed to clinically qualify the association of *AR* status in plasma DNA with worse outcome in pre- and post-docetaxel (doc) CRPC. **Methods:** We used droplet digital (dd)PCR to assess *AR* copy number (CN) and mutations (mut) (2105T > A (p.L702H) and 2632A > G (p.T878A) status in plasma DNA from 171 patients (pts) treated with abi/enza in biomarker protocols at 2 institutions. The aim to evaluate plasma *AR* was defined after sample collection but prior to analysis. **Results:** We first optimised multiplex ddPCR to accurately define *AR* status and identified an *AR* CN cutpoint = 2.01 as having the greatest likelihood to split pts into 2 prognostic groups. We confirmed a strong agreement between ddPCR and NGS for quantitating *AR* CN and mut allelic frequency (Bland-Altman test: mean difference -0.02 95%CI -2.45 to 2.41; mean difference -0.01 95%CI -0.015 to 0.016 respectively). *AR* CN gain was observed in 10 (14%) pre- and 33 (34%) postdoc pts and associated with a worse OS (HR 3.98 95%CI 1.74-9.10 p < 0.001; HR 3.81 95%CI 2.28-6.37 p < 0.001 respectively), PFS (HR 2.18 95%CI 1.08-4.39 p = 0.03; HR 1.95 95%CI 1.23-3.11 p = 0.01 respectively) and PSA decline ≥50% (OR 4.7 95%CI 1.17-19.17 p = 0.035; OR 5.0 95%CI 1.70-14.91 p = 0.003 respectively). *AR* mut were observed in 8 (11%) postdoc but no pre-doc abi-treated pts and also associated with worse OS (HR 3.26 95%CI 1.47-not reached p = 0.004). There was no interaction between *AR* and doc status (p = 0.83 for OS, p = 0.99 for PFS). Multivariate analysis, adjusting for *AR* CN and mut, previous doc, double stranded DNA concentration, LDH, confirmed *AR* status was independently associated with OS (HR 3.77 95%CI 2.42-5.88 p < 0.001 and HR 2.76 95%CI 1.26-6.07 p = 0.011 for *AR* CN and mut respectively) and PFS (HR 1.96 95% CI 1.32-2.93 p = 0.001). **Conclusions:** Plasma *AR* status assessment using multiplex ddPCR identifies CRPC with worse outcome to enza/abi in pre/postdoc CRPC. Additional clinical qualification is available from the PREMIERE study (Grande et al;ASCO2017;Abstract#). Prospective evaluation of treatment decisions based on plasma *AR* is now required.

5061 Poster Session (Board #135), Mon, 1:15 PM-4:45 PM

Comprehensive molecular profiling of multi-focal prostate cancer and concomitant lymph node metastasis: Implications for tissue-based prognostic biomarkers. *First Author: Simpa Samuel Salami, University of Michigan, Ann Arbor, MI*

Background: Current tissue-based prognostic biomarker assays claim that assessment of a single biopsy focus is sufficient to predict disease behavior. We analyzed and compared the genetic profiles of multifocal prostate cancer (PCa) with concordant lymph node metastasis (LNM) to determine if expression-based prognostic tests are robust to multifocality. **Methods:** This IRB-approved study comprised patients who underwent radical prostatectomy and lymph node dissection that revealed N1 or discordant multifocal (low- and high-grade foci) disease. DNA and RNA were co-isolated from each tumor focus pre-identified on formalin fixed paraffin embedded specimens. High depth, targeted DNA and RNA next generation sequencing was performed to characterize the molecular profile of each sample, using the Oncomine Comprehensive (11 patients) or Comprehensive Cancer (DNA, 3 patients) Panels and a custom targeted RNAseq panel comprising genes for deriving prognostic signatures. **Results:** A total of 67 primary tumor and 17 LNM foci from 14 patients were analyzed. We observed significant intra- and inter-patient molecular heterogeneity. For example, in patient #1, while all 4 regions of high-grade primary tumor showed *TP53* somatic mutations and some copy number alterations (CNAs) with two samples from the LNM, tumor areas near the positive margin showed more complete concordance than intraprostatic regions. Critically, a low-grade primary tumor focus in this case showed no somatic mutation or CNA overlap with the high-grade or LNM samples. In patient #4, all tumor and LNM foci shared a large number of somatic mutations, including a frameshift mutation in *PTEN*, with no high level CNA, consistent with a hypermutated genotype. By targeted RNAseq, low- and high-grade tumors from the same patient showed distinct expression profiles using genes included in prognostic signatures. **Conclusions:** Our results challenge the claim that expression-based prognostic tests are robust to multifocality. Further studies are needed to better characterize the biologically dominant lesion in multifocal PCa and hold promise for the development of improved prognostic biomarkers.

5062 Poster Session (Board #136), Mon, 1:15 PM-4:45 PM

Association of loss of tumor suppressor ZFP36 with lethal prostate cancer. *First Author: Christopher Sweeney, Department of Medical Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA*

Background: Inflammation has been linked to prostate cancer (PCa) progression which may be mediated by the transcription factor nuclear factor kappa B (NFκB). Using a bioinformatic screen focused on NFκB pathway activation in lethal PCa, we identified the tumor suppressor *ZFP36* as a key node of the NFκB network. We also showed in vitro that *ZFP36* expression was inversely associated with both NFκB-controlled gene levels and proliferation and sensitivity to enzalutamide. We examined the role of *ZFP36* and PCa progression in patient cohorts. **Methods:** The association between low mRNA expression of *ZFP36* (levels in the lower quartile) and lethal PCa (defined as metastatic disease or death) was assessed with logistic regression among men with localized PCa in two independent cohorts treated with radical prostatectomy (RP). The discovery cohort was RP samples from Health Professional Follow-up Study and Physicians Health Study and the validation cohort was RP samples from Cleveland Clinic, Mayo Clinic, Johns Hopkins and MSKCC. In a third cohort from Cornell University, *ZFP36* expression levels were assessed in RP samples from patients with localized PCa and biopsies of metastatic castration resistant prostate cancer (mCRPC). **Results:** Table 1 shows men with localized PCa and lower quartile of tumor *ZFP36* expression had a nearly 2-fold higher risk of lethal PCa after adjusting for known clinical and histological prognostic features (age, RP Gleason score, T-stage); an association confirmed in the validation cohort. *ZFP36* gene expression was also significantly lower in mCRPC (n=53) compared with a localized RP cohort (n=68) (p-value <0.0001). **Conclusions:** In humans lower *ZFP36* in RP specimens is associated with clinically significant risk of lethal PCa after treatment with curative intent and lower *ZFP36*levels are found in metastatic tissue.

	HPFS/PHS Cohort (Discovery)	Multi-institutional (Validation)
Platform	Affymetrix HuGene 1.0 ST	Affymetrix HuExon 1.0 ST
Sample Size	404	788
Median Age (yrs)	66 (IQR: 62-70)	63 (IQR: 57-67)
% Gleason ≥8	26%	52%
Number "lethal"	113 (28%)	399 (51%)
Univariate OR (95% CI)	3.52 (2.18,5.69) p<0.0001	1.93 (1.26,2.44) p=0.0002
Multivariate OR (95% CI)	1.97 (1.09-3.55) p=0.02	1.84 (1.24,2.75) p=0.003

5063 Poster Session (Board #137), Mon, 1:15 PM-4:45 PM

A 17-gene panel for prediction of adverse surgical pathology in the setting of MRI-guided prostate biopsy. *First Author: Amirali Salmasi, University of California, Los Angeles, Los Angeles, CA*

Background: A 17 gene panel (Oncotype Dx Genomic Prostate Score, GPS) has been validated as an independent predictor of adverse pathology (AP, defined as pathological GS 4+3 or higher and/or pT3+) in men treated with radical prostatectomy (RP) for prostate cancer (PCa). Multiparametric Magnetic Resonance Imaging (mpMRI) may help guide prostate biopsies. We explored synergies between GPS and mpMRI to aid in PCa management decisions. **Methods:** A cohort of men with NCCN Low and Intermediate-Risk PCa who were managed with RP was identified from a clinical database. Patients were required to have had a simultaneous mpMRI-guided and systematic biopsy and to have undergone RP within 6 months. Biopsy tissue of the highest Gleason pattern was used for calculation of GPS. The primary endpoint was AP. Secondary endpoints included the range of GPS within UCLA prostate MRI risk groups and median GPS when there was discrepancy between MRI and systematic biopsy Gleason Score (GS). Logistic regression models were fit to evaluate the relationship between GPS (per 20 units) and AP. **Results:** 134 men met criteria for the primary endpoint. Median age was 62 years (range 46-77). NCCN Low & Intermediate-Risk PCa was present in 16%, and 84% of men, respectively. Biopsy GS 3+3/3+4/4+3 was present in 19%, 67%, and 13%, respectively. In a univariable model, GPS was associated with AP (OR 3.8, 95% CI 2.1 to 7.4, $p < 0.001$). After adjustment for highest biopsy GS and clinical T-stage, GPS remained significantly associated with AP (OR 3.4, 95% CI 1.8 to 6.8, $p = 0.0004$). A wide and overlapping distribution of GPS was noted across UCLA MRI prostate risk groups, indicating that GPS provides information that is distinct from what can be determined from mpMRI. When there was a discrepancy between mpMRI and systematic biopsy GS, mpMRI targeted lesions with higher GS had higher median GPS (33, range 13-70) than systematic biopsies with higher GS (median GPS 25, range 15-55). **Conclusions:** GPS provides independent and complementary prognostic information to mpMRI-guided biopsies. The combination of mpMRI for biopsy guidance and GPS for molecular analysis may optimize prediction of AP and improve patient selection for treatment versus surveillance.

5064 Poster Session (Board #138), Mon, 1:15 PM-4:45 PM

P53 status in primary tumor predicts efficacy of first-line abiraterone and enzalutamide in castration-resistant prostate cancer patients. *First Author: Benjamin Louis Maughan, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: We tested whether tissue-based analysis of p53 and PTEN genomic status, measured predominantly in primary tumor samples, may be predictive for sensitivity to abiraterone and enzalutamide in castration resistant prostate cancer (CRPC). **Methods:** We performed a retrospective analysis of 309 consecutive patients with CRPC treated with first-line abiraterone or enzalutamide. Of these, 116 men (38%) had available tumor tissue for analysis, and formed the basis of this study. Deleterious *TP53* missense mutations and *PTEN* deletions were interrogated using genetically validated immunohistochemical assays for p53 protein nuclear accumulation and PTEN protein loss. OS and PFS were compared between patients with and without p53 and/or PTEN alterations. **Results:** 46% of evaluable cases had PTEN loss and 27% had p53 nuclear accumulation. 45% (53/118) of cases underwent targeted next generation sequencing and p53 nuclear accumulation was 91% sensitive and 90% specific for underlying *TP53* missense mutation. OS and PFS did not differ significantly according to PTEN status but were associated with p53 status. Median OS was 15.8 months (95% CI, 15.8–23.9) and 28.7 months (95% CI, 28.7–42.7) for men with and without p53 nuclear accumulation, respectively (HR 1.98; P = 0.007). Median PFS was 5.5 months (95% CI, 3.53–10.5 months) and 10.2 months (95% CI, 7.37–13.3 months) in men with and without p53 nuclear accumulation, respectively (HR 1.73; P = 0.013). In multivariable analyses, p53 status was independently associated with both OS (HR 2.13; P = 0.016) and PFS (HR 1.83; P = 0.034). This effect was also seen in the subset of patients with prostatectomy tissue only. In patients with p53 nuclear accumulation median PFS ($p < 0.001$) and median OS ($p < 0.001$) were decreased compared to wild-type patients. No effect was seen with PTEN loss in either PFS ($p = 0.12$) or OS ($p = 0.50$). **Conclusions:** p53 status may be a biomarker of sensitivity to novel hormonal therapies in CRPC. PTEN was not a biomarker of sensitivity in our study. These results require prospective validation.

5065 Poster Session (Board #139), Mon, 1:15 PM-4:45 PM

Linking tumor mutational load to clinical responses to ipilimumab (IPI) in men with advanced prostate cancer (PCa). *First Author: Sumit Kumar Subudhi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tumor mutational load and neoantigens have been associated with responses to immune checkpoint therapies in patients (pts) with melanoma and lung cancer. We designed a clinical trial (NCT02113657) in advanced PCa to determine whether the induction of antitumor responses by IPI correlate with T cell responses to PCa neoantigens. **Methods:** All advanced PCa pts enrolled into this study had sufficient DNA/RNA from tumor tissue obtained prior to receiving IPI (3 mg/kg every 21 days for up to 4 doses) for whole-exosome sequencing (WES) and RNA-seq. **Results:** Twenty-one of 30 pts have been enrolled. Nine (43%) have received all 4 doses of IPI. IPI was discontinued prematurely in 9 pts (43%) due to drug-related toxicities and in 3 (14%) due to disease progression. All 3 of the latter had liver metastases. To date, tumors from 13 pts have been comprehensively analyzed by WES and RNA-seq. The median time from IPI #1 to the next systemic therapy for these pts was 24 weeks (IQR, 18.3 – 54.3). Responders (R) were defined as pts whose time to next systemic therapy was > 24 weeks. The median time to next systemic therapy for R (n = 7, 54%) is 55 weeks (IQR, 52.0 – 89.0; 2 pts with ongoing responses) versus 18 weeks (IQR, 10.5 – 23.0) for non-responders (NR; n = 6, 46%). In an analysis of all 13 pts, including those with liver metastases, tumor mutational load and frequency of expressed non-synonymous mutations were similar for R and NR pts. However, a subset analysis, excluding pts with liver metastases, revealed > 100 total mutations and/or > 10 expressed non-synonymous mutations in 7/7 R versus 1/4 NR. **Conclusions:** For advanced PCa pts without liver metastases, tumor mutational load may be associated with responses to IPI. Identification of immunodominant neoantigens may lead to the development of personalized vaccines to be combined with immune checkpoint therapies for the effective treatment of pts with PCa. Clinical trial information: NCT02113657.

5066 Poster Session (Board #140), Mon, 1:15 PM-4:45 PM

History of PSA screening on prostate cancer aggressiveness. *First Author: Jennifer Cullen, Center for Prostate Disease Research, Rockville, MD*

Background: In 2012, PSA screening for prostate cancer (CaP) detection was given a "Grade D" recommendation for all men by the USPSTF. Recent U.S. studies report declines in PSA screening with concomitant increases in advanced CaP at diagnosis. This study examined the association between PSA screening history and CaP aggressiveness in a racially diverse, military cohort with equal health care access. **Methods:** This retrospective cohort study evaluated CaP patients undergoing radical prostatectomy (RP) from 1994-2015 at Walter Reed National Military Medical Center. Whole-mounted prostatectomy specimens were classified using 2014 ISUP Gleason grading system. Excluding the diagnostic PSA, screening history was categorized as: ≥ 6 PSA's prior to CaP diagnosis (uppermost quartile), 1-5 (lower 3 quartiles), vs. no screening history. Multivariable logistic regression (MLR) was used to examine NCCN risk stratum (intermediate-high vs. low) and Gleason upgrade (GU) from biopsy to RP. Multivariable Cox proportional hazards (Cox PH) analyses were used to model time to biochemical recurrence (BCR). Multivariable models controlled for age at RP, race, family history and obesity (BMI $>$ 30 vs. $\leq$ 30 kg/m^2). The GU and BCR models also controlled for NCCN risk classification. **Results:** There were 1,772 eligible patients with a median follow-up and age at RP of 7.0 and 59.8 years, respectively. Prior to CaP diagnosis, 42% and 19% of men had 1-5 and $\geq$ 6 PSA's screenings, respectively. MLR showed greater odds of intermediate or high vs. low risk disease for PSA screening history of none vs. 1-5 (OR = 1.33, CI = 1.03-1.70, p = 0.028) but not for none vs. $\geq$ 6 (p = 0.44). MLR showed increased odds of GU for none vs. $\geq$ 6 (OR = 1.81, CI = 1.23-2.7, $p < 0.001$). Multivariable Cox PH models showed incrementally poorer BCR-free survival as screening history decreased ($HR_{None\ vs.\ \geq 6} = 2.27$, CI = 1.54-3.33, $p < 0.001$; $HR_{None\ vs.\ 1\text{-}5} = 1.49$, CI = 1.15-1.92, p = 0.002). **Conclusions:** In this RP cohort, higher risk stratum, increased GU, and poorer BCR-free survival were associated with no PSA screening history. BCR-free survival was incrementally worsened by less PSA screening. A complete absence of PSA screening may lead to more aggressive disease at presentation and poorer clinical outcomes.

5067 Poster Session (Board #141), Mon, 1:15 PM-4:45 PM

Serum androgens and survival in metastatic castration resistant prostate cancer (mCRPC) patients treated with docetaxel and prednisone: Results from CALGB 90401 (Alliance). *First Author: Charles J. Ryan, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Higher baseline androgens have been previously shown to be associated with an improved overall survival (OS) in mCRPC patients treated with the androgen synthesis inhibitors, ketoconazole or abiraterone. The purpose of this analysis was to determine whether baseline serum androgen levels (Testosterone (T), Androstenedione (A) and DHEA (D) are associated with OS in mCRPC patients treated with docetaxel-based chemotherapy. **Methods:** Data from 1,050 men treated on CALGB 90401 with docetaxel, prednisone and either bevacizumab or placebo were used. Eligibility required progressive mCRPC and no prior chemotherapy. Pre-treatment serum assays for T, A and D were performed via tandem Liquid Chromatography-Mass Spectrometry (LC-MS/MS) at NMS labs. The proportional hazards model was used to assess the prognostic significance of T, A, and D in predicting OS adjusting for known prognostic factors. **Results:** Median values for T, A, and, D were 1.00, 13.00 and 8.12, ng/dL respectively.Values above the median were defined as low, above as high. Median OS for low vs high levels was 22.7 and 23.1 month for T, 22.4 and 21.7 month for A and 21.8 and 24.0 month for D, respectively, all NS. In multivariable analysis adjusting for 10 known prognostic values and prior keto use in mCRPC (Halabi JCO 2014), A (p-value = 0.013) levels were associated with OS. The HR for A was = 0.99 (95% CI = 0.98-0.99). **Conclusions:** In multivariate analysis, baseline androstenedione levels are prognostic factors for OS in mCRPC patients receiving chemotherapy. Low or undetectable levels of other androgens are associated with shorter OS, consistent with prior results in androgen synthesis inhibitor treated pts in both the chemotherapy naive and post chemotherapy settings. This relationship may reflect more aggressive tumor biology that evolves in an extreme androgen deprived milieu. Clinical trial information: NCT00110214.

5068 Poster Session (Board #142), Mon, 1:15 PM-4:45 PM

Translating prostate cancer working group (PCWG) criteria into a quantitative progression biomarker in metastatic castration resistant prostate cancer (mCRPC). *First Author: Aseem Anand, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: mCRPC is a bone dominant lethal disease. A validated endpoint in mCRPC trials is bone scan progression, which is semi-quantitative and rely on the appearance of new lesions as proposed by the PCWG. The validated automated bone scan index (BSI) quantifies the bone tumor burden as the fraction of total skeletal weight. To build on the current definition of disease progression, we sought to compare the association of time to progression with overall survival (OS) using PCWG criteria and BSI increase. **Methods:** mCRPC patients (pts) enrolled on trials of agents targeting androgen-receptor (AR) were assessed. Pts were required to have a raw bone scan image for BSI analysis concurrent with disease assessments. The EXINI automated computing platform generated the BSI values. Thresholds for the absolute and relative increase in BSI from 1st follow-up ($\leq$12 weeks) were explored for the time to BSI progression. The association with survival time was computed for each threshold defined time to BSI progression. Kendall's Tau, derived from the Clayton copula, was used to associate time to BSI progression with survival time, where both endpoints may be censored. **Results:** A total of 257 pts were assessed, of whom 169 had raw bone scans images needed for the BSI analysis. 90 pts (53%) met progression by PCWG criteria, the association between the time to PCWG progression and OS was 0.52. The association between time to BSI progression and OS was comparable to the PCWG progression when the absolute increase in BSI was 0.6 or more (table below). **Conclusions:** Progression in bone can be expressed as a single quantitative metric that describes the increase in total disease burden while retaining the same association that PCWG has with OS. These data represent the first steps to a quantitative expression of bone disease progression as a clinical trials endpoint.

		Proportion progressed	OS correlation
Absolute BSI increase			
	0.2	0.58	0.34
	0.4	0.47	0.41
	0.6	0.41	0.51
	0.8	0.36	0.52
	1.0	0.29	0.52
Relative BSI Increase			
	30%	0.53	0.25
	60%	0.39	0.29
	90%	0.31	0.41
	120%	0.26	0.49
	150%	0.23	0.50

5069 Poster Session (Board #143), Mon, 1:15 PM-4:45 PM

Validation of cAMP phosphodiesterase-4D7 (PDE4D7) for its independent contribution to risk stratification in a prostate cancer patient cohort with longitudinal biological outcomes. *First Author: Jos Rijntjes, Philips Research Europe, Eindhoven, Netherlands*

Background: In this study we present the retrospective validation of the prognostic prostate cancer biomarker PDE4D7 in predicting longitudinal biological outcomes in a historical cohort of radical prostatectomy patients. **Methods:** Biopsy punches from 550 patients were collected from a representative tumor area of FFPE surgical resections. RNA was extracted and PDE4D7 quantified by one-step RT-qPCR. PDE4D7 scores were calculated by normalization of PDE4D7 to the averaged expression of four reference genes. The independent prognostic value of the PDE4D7 scores were evaluated using uni- and multivariate Cox proportional hazard regression. Multivariate analyses were adjusted for clinical prognostic variables. Post-surgical outcomes tested were: PSA relapse, start of salvage treatment, progression to metastases, overall and prostate cancer specific mortality. Logistic regression was used to create a combined prognostic model of PDE4D7 with clinical risk and tested in outcome prediction. **Results:** The PDE4D7 score was significantly associated with time to PSA failure after prostatectomy (HR 0.53; 95% CI 0.41-0.67 for each unit increase; $p < 1.0E\text{-}04$). After adjustment for pathology Gleason, pT stage, surgical margin status, and seminal vesicle invasion the HR was 0.55 (95% CI 0.43-0.72; $p < 1.0E\text{-}04$). Patients with a high PDE4D7 score that were clinically classified as intermediate to high risk of progression were re-classified into a group with an average progression risk less than the average cohort risk of clinically very low risk patients. The maximum benefit, compared to Gleason score, was observed in the clinically intermediate favorable risk group. Combining clinical risk with PDE4D7 scores improved the overall risk stratification. **Conclusions:** The PDE4D7 score has potential to provide independent risk information and, in particular, to re-stratify patients with clinical intermediate to high risk characteristics to a very low risk profile.

5070 Poster Session (Board #144), Mon, 1:15 PM-4:45 PM

Baseline CTC subtype to predict outcomes on mCRPC patients (pts) receiving enzalutamide (E) compared to abiraterone (A). *First Author: Howard I. Scher, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Prior response to A or E does not predict sensitivity to E following A or A following E. The detection of AR-V7 predicts insensitivity to either drug, but identifies only a portion of non-responders. We previously identified 15 CTC subtypes based on unique phenotypic features in mCRPC pts, each with unique biology and different degree of likelihood of predicting resistance to either drug. Here we explored the relationship between individual subtypes and sensitivity to A vs. E, but not both. **Methods:** 107 pre-treatment blood samples from mCRPC pts starting A (n = 47) or E (n = 60) as a 1st or 2nd line of Tx were analyzed for CTCs utilizing the Epic Sciences platform. Samples were assayed for CTC subtypes based upon 15 pre-defined phenotypic CTC classifiers (Type A-O). Treatment outcomes were assessed by serial PSA changes and landmarked percent time of therapy progression on radiographs, and overall survival following either A or E. Cell type prevalence was also analyzed in relation to clinical outcomes, and subsets of the CTC subtypes subject to single cell NGS to ascertain genomic drivers common to each subtype. **Results:** CTCs were identified in 94% (101/107) of pt samples. One, cell Type K, found in 25% (27/107) of pts, was associated with a statistically significant inferior outcomes on E for all measures. Whereas similar outcomes were seen between K+ & K- pts treated with A. The distinct features of Cell Type K include a large nucleus, high nuclear entropy and high Nuclear/cytoplasmic AR terminal ratio; and a unique genomic profile enriched for cell cycle and DNA repair alterations relative to other CTC subtypes. **Conclusions:** The presence of specific CTC subtypes in pre-Rx phlebotomy samples associated with outcomes on A or E. A CTC subtype (Cell Type K) helped to identify pts with poor outcomes on E but not A vs. those without the cell type. Further biologic interrogation of K cells and ongoing clincial validation of the CTC subtype is planned.

Pt outcomes on E by baseline Cell K status.

Cell K Status	% of Pts by status	% of Pts w/>50% PSA decline	% of Pts w/ >6 mo Time on Tx	% of Pts w/ >6 mo rPFS	% of Pts w/ >1 y OS
K+ (n=14)	23%	29%	43%	43%	29%
K- (n=46)	77%	63%	74%	74%	71%

5071 Poster Session (Board #145), Mon, 1:15 PM-4:45 PM

Phase 1-2 study of progesterone receptor (PR) inhibition with extended-release (ER) onapristone (ONA) alone or in combination with abiraterone (AA) in patients (pts) with castration-resistant prostate cancer (CRPC) incorporating plasma DNA analysis to define androgen receptor (AR) status. *First Author: Anuradha Jayaram, Institute of Cancer Research and The Royal Marsden NHS Trust Foundation, Sutton, United Kingdom*

Background: An urgent need exists for new therapies after progression (PD) onAA and enzalutamide (ENZ). Increased PR expression or progesterone-activating AR mutations have been associated with resistance to AR targeting. We aimed to test ONA, a type I PR antagonist with clinical activity in PR^{pos} cancers, in AA/enz-resistant CRPC. In a prospectively defined exploratory analysis, we aimed to report outcome by plasma *AR* status (*pAR*). **Methods:** This was a multi-institution, open label phase I/II clinical trial in pts progressing after ENZ/AA. Pts were first treated with single agent (SA) ONA using a randomised dose escalation design. ONA at 2 doses was then combined with AA (1000mg od with pred 5mg bid) in pts progressing on AA. The primary end-points were safety, pharmacokinetics (PK) and anti-tumor activity split by p*AR*. Archival and metastatic biopsies were collected when possible and tested for PR status. p*AR* was studied using previous methods (Romanel STM 2015). **Results:** 21 pts received SA ONA (5 = 10mg/ 5 = 20mg/ 4 = 30mg/ 4 = 40mg /3 = 50mg BID) and 15 pts received ONA-AA combination (5 = 30mg ONA BID, 10 = 50mg ONA BID). There were not DLTs or significant LFT abnormalities and no G3/4 adverse events (AE), no treatment discontinuations due to AEs and no SAEs considered related to ONA. PK in SA ONA observed active plasma concentrations and no interaction with AA. Of 32 evaluated pts 15 had a 2105T > A (p.L702H) or 2632A > G (p.T878A) AR mutation detected in plasma pre-treatment and 1 had AR copy number gain. PSA declines were not observed with SA ONA but in 2 pts with combination (-30%, -7%) who were AR normal. The rPFS on SA ONA was 2.8 months for AR normal and 2.6 for AR aberrant (Hazard ratio (HR) 1.41; 95% CI, 0.62-3.72; P 0.48) and on combination was 4.4 months for AR normal (8/15) and 2.2 for AR aberrant (7/15) (HR 6.08; 95% CI, 6.32-221.9; P < 0.001). **Conclusions:** ONA is safe in CRPC as SA and in combination with AA. There was no difference in rPFS by p*AR* status for SA ONA but on the combination with AA, pts who were plasma *AR* normal had a significantly longer rPFS. Clinical trial information: NCT02049190.

5072 Poster Session (Board #146), Mon, 1:15 PM-4:45 PM

Indentification of a CTC-based gene expression signature predicting resistance to abiraterone and enzalutamide in mCRPC. *First Author: Todd Matthew Morgan, University of Michigan, Ann Arbor, MI*

Background: Circulating tumor cell (CTC)-based detection of AR-V7 has been shown to be one potential marker for predicting response to 2nd generation androgen receptor (AR) therapies. However, the apparent rarity of AR-V7 positivity is indicative of the importance of other drivers of resistance in this setting. We sought to utilize a multiplex gene expression platform for assessing CTCs in order to determine other predictive biomarkers of response. **Methods:** Whole blood (~5mL) was obtained from 37 patients with mCRPC starting enzalutamide (n=16) or abiraterone (n=21). CTCs were isolated using anti-EpCAM-conjugated magnetic beads. Following cell lysis, mRNA was extracted followed by multiplex qRT-PCR for 92 prostate cancer-related genes. Samples were considered CTC-positive based on a previously established set of epithelial markers. We identified genes associated with PSA and radioclinical progression free survival (PFS) using Cox regression analysis. Muli-gene models were tested using ROC analysis. **Results:** We identified 20 patients (54%) with detectable CTCs, and patients were followed for a median of 10 months (IQR 3.9-19.4 months). Seven genes were associated with both PSA PFS and radioclinical PFS in the Cox analyses (Table). Combing the 7 genes into a single model gave AUC values of 0.88 for PSA PFS and 0.89 for radioclinical PFS. In comparison, the AR-V7-only model resulted in AUC values of 0.65 and 0.66. **Conclusions:** We identified seven prostate cancer-related genes that can be determined from CTCs and appear to predict short time to progression in men with mCRPC being treated with 2nd generation hormonal therapies. While this is a small cohort and prospective validation is needed, these findings highlight the potential role for this approach in helping guide therapy choice.

	PSA PFS			Radioclinical PFS		
Gene	HR	95% CI	p Value	HR	95% CI	p Value
AR	3.61	1.06-12.29	0.040	4.91	1.38-17.48	0.014
AR-V7	4.35	1.27-14.91	0.019	5.43	1.52-19.35	0.009
ANXA2	3.53	1.06-11.70	0.039	7.90	1.83-34.05	0.006
SOX2	3.70	1.11-12.25	0.032	4.81	1.35-17.05	0.015
PSCA	4.35	1.27-14.91	0.019	5.43	1.52-19.36	0.009
PSA	7.12	1.63-31.03	0.009	6.37	1.75-23.07	0.005
WNT5B	5.40	1.54-18.95	0.008	4.78	1.40-16.25	0.012

5073 Poster Session (Board #147), Mon, 1:15 PM-4:45 PM

Development and external validation of a novel risk score to identify insignificant prostate cancer. *First Author: Lorenzo Dutto, Klinik für Urologie, Kinderurologie und Urologische Onkologie, Prostatazentrum Nordwest, St. Antonius-Hospital, Gronau, Germany*

Background: Active surveillance is increasingly used for insignificant prostate cancer (PCa). In order to identify suitable patients, risk scores have been developed which use pre-operative factors. We evaluated the accuracy of 9 separate tools developed to identify patients harbouring insignificant PCa in 2613 patients who underwent radical prostatectomy for Gleason 3+3 PCa. We have developed and validated a novel risk score to correctly identify insignificant PCa for use in unscreened patient cohorts using non-dichotomised clinical predictors. **Methods:** 2799 patients who would have been candidates for AS (Gleason score 6 only) patients underwent robotic radical prostatectomy between 2006 and 2016 at a tertiary referral center. The volume and grade of tumour in the resected prostate was analysed. Insignificant PCa was defined as Gleason 3+3 only, index tumour volume <1.3 cm3 , total tumour volume <2.5 cm3 (updated ERSPC definition). 2613 patients were included in the final analysis. We computed the accuracy (specificity, sensitivity and area under the curve (AUC) of the receiver operator characteristic) of 9 predictive tools. Multivariate logistic regression with elastic net regularisation was used to develop a novel tool to predict insignificant prostate cancer using age at diagnosis, baseline PSA, TRUS volume, clinical T-stage, number of positive cores and percentage of positive cores as predictors. This tool was validated in an external cohort of 441 unscreened patients undergoing surgery for Gleason 6 PCa. **Results:** All of the predefined tools rated poorly as predictors of insignificant disease as none of them reached the required AUC threshold of 0.7. The new tool performed well in training and validation cohorts. **Conclusions:** Pre-existing predictive tools to identify indolent PCa have a poor predictive value when applied to an unscreened cohort of patients. Our novel tool shows good predictive power for insignificant PCa in this population in training and validation cohorts. The inherent selection bias due to analysis of a surgical cohort is acknowledged.

	Training data	Validation data
N-Total	2799	441
N-insignificant PCa	1045	65
AUC (95% CI)	0.756 (0.737- 0.774)	0.757 (0.699- 0.815)

5074 Poster Session (Board #148), Mon, 1:15 PM-4:45 PM

Association of risk of clinical recurrence (CR) and prostate cancer death (PCD) with a 17-gene genomic prostate score (GPS) value <20. *First Author: Phillip G. Febbo, Genomic Health, Redwood City, CA*

Background: Over-treatment of localized prostate cancer (PC) can result from over-estimation of a patient's risk of CR and PCD. GPS (scale 0-100) has been validated to predict adverse pathology, biochemical recurrence, metastasis, and PCD and provides a more accurate overall assessment of patient risk than clinical risk factors alone. A recent validation study found that no patients with AUA Low- or Intermediate-risk disease and a GPS of <20 developed PC metastases or PCD. Here, 2 large longitudinal PC cohorts were analyzed to estimate the risk of CR and PCD for GPS <or >20 units. **Methods:** Data from Klein et al. European Urology (EU) 2014 and Cullen et al. EU 2014 were analyzed to establish the risk of CR and PCD associated with a pre-established GPS cut-point of 20. Patients were divided based on the value of GPS (≤20, >20). Cox regression analyses accounted for cohort sampling weights. Since GPS was developed using Klein et al, standardized hazard ratios (std HR, HR for 1 SD change in the covariate) for GPS and CR and PCD survival curves for the 2 groups were estimated correcting for regression to the mean (RM). **Results:** Of the 402 patients in Cullen et al. (median follow up 5.2 years), only 5 patients developed metastases; all 5 had GPS >20. For Klein et al., of 426 patients with a median follow up of 6.6 years, there were 109 CR (metastasis and local recurrence) and 39 PCD; only one patient with events had a GPS <20. Overall 28% of patients had GPS <20. GPS was a significant predictor for both CR (std HR 2.50 (95%CI 1.99, 3.15, p <0.001, RM-corrected std HR 2.16, FDR <0.1%) and PCD (std HR 2.90 (95% CI 2.06,4.06, p<0.001, RM-corrected std HR 1.96, FDR <0.1%) after adjustment for AUA group. Men with intermediate risk prostate cancer and a GPS score of < 20 have a 2.6% and 0.7% 10-year RM-corrected risk of CR and PCD, respectively (Table 1). **Conclusions:** GPS strongly predicts risk of CR and PCD in men with AUA Low- or Intermediate-risk PC. Patients with a GPS score <20 have a very low risk of CR or PCD and should be considered for AS.

Estimated 10-year RM-corrected risk of CR PCD.

AUA Risk Group	GPS Group	CR risk	PCD Risk
Low	≤ 20	1.8%	0.5%
	> 20	4.3%	1.0%
Intermediate	≤ 20	2.6%	0.7%
	> 20	10.9%	3.1%
High	≤ 20	6.0%	2.1%
	> 20	21.2%	7.8%

5075 Poster Session (Board #149), Mon, 1:15 PM-4:45 PM

PSA doubling time (PSADT) and proximal PSA value predict metastasis-free survival (MFS) in men with biochemically recurrent prostate cancer (BRPC) after radical prostatectomy (RP). *First Author: Mark Christopher Markowski, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: We previously reported a relationship between PSADT and MFS in BRPC post RP (Pound 1999; Freedland 2007; Antonarakis 2012). In men with PSADT<12 months, who are at high risk of lethal PCa, we sought to identify a PSA cutpoint (proximal PSA; PP) that indicates the imminent emergence of metastasis (M+). In this report we combined Center for Prostate Disease Research and Johns Hopkins (CPDR/JHU) databases to investigate the association of the PP value on MFS in men with BRPC and PSADT <12 mos. **Methods:** In the CPDR/JHU RP database (31,296), 513 men with BCR (>0.2ng/ml) with PSADT <12 mos who received no adjuvant/salvage ADT/RT were prospectively followed until radiological evidence of M+ are included in this analysis. All patients were evaluated yearly with >1 PSA and scans at regular intervals until M+. Associations with MFS were compared using logrank test and Cox regression. The PP is the most recent value >6 months prior to M+/censor. **Results:** M+ occurred in 218 of 513 patients with BRPC (median follow up 9 years). Risk of M+ increased successively for PSADT 6.0-7.5, 4.5-6, 3.0-4.5, and <3.0 months, adjusted for pT stage and Gleason score. PP ≥10ng/ml significantly increased risk of M+ in pts with PSADT <12 mos, regardless of PSADT subgroup, hazard ratio=2.95, p<.0001. Median MFS was 4.0 years at PP >10ng/ml vs 20 years at PP <10ng/ml. Table 1 shows median MFS and 3, 5, and 7 year MFS rates in subgroups with PSADT <3 and 3.01-6 months representing the highest risk groups. **Conclusions:** In men with PSADT<12 months, PSADT subgroups <7.5 months and PP >10ng/ml are independent predictors of MFS, adjusted for pT stage and Gleason score. PP ≥10ng/ml further define risk of M+ in BRPC with PSADT<12 months. These data can assist physicians in patient counseling and clinical trial design.

	PSADT < 3 mos			PSADT 3.01-6.0 mos		
MFS	PP <10 (48 pts)	PP >10 (21 pts)	P Value*	PP <10 (106 pts)	PP ≥10 (47 pts)	P Value*
3years	49.44%	19.05%	0.058	68.13%	46.47%	0.0009
5years	42.78%	19.05%		61.38%	29.21%	
7years	42.78%	12.70%		49.87%	18.93%	
Median MFS	3 years	1 year		7 years	3 years	

*Based on logrank analysis

5076 Poster Session (Board #150), Mon, 1:15 PM-4:45 PM

Changes in CTC burden and prevalence of specific CTC subtypes in mCRPC patients (pts) receiving alpharadin (Ra-223) as single agent or in combination with other therapuetics (Tx). *First Author: Ryan Vance Dittamore, Epic Sciences, Inc., San Diego, CA*

Background: Ra-223 prolongs life in mCRPC pts with symptomatic osseous metastasis with inconsistent effects on PSA. Survival times are prolonged further when combined with Abi/Enza. Data from preclinical studies suggest that Ra-223 may sensitize tumors to DDR agents and/or biologic therapies. But predictive biomarkers of benefit to each or both combinationso are lacking. We studied CTC counts and the prevelance of specific CTC subtypes in patients before and following Ra-223 therapy, both as a single agent and in combination, to identify biomarkers of sensitivity and treatement efficacy, and effects of Ra-223 on tumor biology. **Methods:** Pre and ~4 week post RA-223 therapy blood samples were collected from 35 pts (2 samples each) given as a single agent (n = 20 pts) or in combination with other therapies (n = 15 pts, 9 w/ Enza, 5 w/ Abi, 1 w/ Taxane). Samples were processed and CTCs analyzed using the Epic Sciences platform. Total CTC count and the prevalence of specific CTC phenotypes present pre and post Rx were identified utilizing high content digital pathology and associated with therapy type and post-treatment change. **Results:** CTC declines were observed in 55% (11/20) and 60% (9/15) of pts treated with single agent and combination respectively. In Ra-223 alone pts, a novel CTC subtype (high N/C ratio, high nuclear area) was identified at baseline 11/20 samples (med = 33% of CTCs). Which was no longer detected in 10 (90%) of the pts treated. This contrasts with a second novel CTC subtype present at baseline in 4 pts (med CTC = 9%) that increased to 9 cases (med CTC = 18%) at follow-up. **Conclusions:** A subset of pts demonstrate post-therapy CTC declines following Ra-223 alone or in combination. A novel CTC subtype resolved by RA-223 in conjunction with total CTC kinetics may indicate pt benefit from Ra-223. A novel emergent CTC subtype has also been identified in pts already receiving Ra-223. Single CTC sequencing and protein analysys of these CTC subtypes are ongoing, and may help describe tumor evolution and sensitization to novel therapuetics.

5077 Poster Session (Board #151), Mon, 1:15 PM-4:45 PM

Neoadjuvant randomized trial of degarelix (Deg) ± cyclophosphamide/GVAX (Cy/GVAX) in men with high-risk prostate cancer (PCa) undergoing radical prostatectomy (RP). *First Author: Emmanuel S. Antonarakis, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: GVAX-Prostate is a GM-CSF–secreting allogeneic cellular vaccine, whose immunogenicity may be enhanced by androgen ablation as well as low-dose Cy. We conducted a neoadjuvant immunologic study comparing Deg vs. Cy/GVAX→Deg. **Methods:** Men with high-risk PCa (T1c–3b N0 M0, Gleason 7–10) were randomized 1:1 to Deg(240 mg SQ) vs. Cy(200 mg/m^2 IV)/GVAX(2.5×10^8 PC3 cells, 1.6×10^8 LNCaP cells) given 2 wk before Deg; all pts then had RP 2 wk after Deg. CD8+ T cell and Treg densities in the primary tumor were quantified by IHC (cells/mm^2). Clinical endpoints were time-to-PSA-relapse, time-to-next-therapy, and time-to-metastasis. The study was powered (α = 0.05, β = 0.18) to show a 2-fold increase in mean CD8+ density with Cy/GVAX→Deg (Arm B) vs. Deg (Arm A). **Results:** 28 men were enrolled (Arm A = 15, Arm B = 13). A concurrent control group (N = 20) who did not receive neoadjuvant therapy provided untreated RP tumor samples. Baseline variables were balanced across study arms: 64% had Gleason ≥8, 56% were pT3b, 18% were pN1. There were nonsignificant increases in CD8+ and Treg densities in Arm B vs. A, and statistically significant increases in CD8+ and Treg densities in both arms (A, B) compared to group C (TABLE). CD8+ and Treg densities were strongly correlated. Outcomes were numerically better in Arm B vs A with respect to time-to-PSA-relapse (HR 0.42, 95%CI 0.13–1.38, *P*= 0.15) and time-to-next-therapy (HR 0.43, 95%CI 0.13–1.39, *P*= 0.16), although not statistically significant. **Conclusions:** Intratumoral immune infiltrates were marginally augmented by Cy/GVAX→Deg vs. Deg alone, while CD8+ and Treg densities were significantly greater in both study arms vs. control, supporting the immunogenic effects of androgen ablation. CD8+ / Treg ratios were remarkably consistent across groups. Clinical trial information: NCT01696877.

	Arm A (Deg) N = 15	Arm B (Cy/GVAX→Deg) N = 13	Control (C) N = 20	*P*
CD8+ T cell density (mean, 95%CI)	205 (121–289)	263 (129–397)	96 (72–120)	0.35 (A vs B) < 0.01 (B vs C) 0.03 (A vs C)
Treg density (mean, 95%CI)	59 (34–85)	78 (48–107)	29 (21–36)	0.18 (A vs B) < 0.01 (B vs C) 0.02 (A vs C)
CD8+ / Treg ratio (mean, 95%CI)	4.0% (2.7–5.3%)	3.9% (2.2–5.7%)	3.7% (2.9–4.6%)	0.66 (A vs B) 0.87 (B vs C) 0.68 (A vs C)

5078 Poster Session (Board #152), Mon, 1:15 PM-4:45 PM

A secondary analysis of PSA response in NRG Oncology/RTOG 9902: A phase III trial of adjuvant chemotherapy with androgen suppression and radiation for high-risk prostate cancer (CaP). *First Author: Stephen Andrew Mihalcik, Harvard Radiation Oncology Residency Program, Massachusetts General Hospital, Boston, MA*

Background: RTOG 9902 was a randomized controlled trial of the addition of adjuvant chemotherapy (CT; paclitaxel, oral etoposide, and estramustine x4 cycles) to 24 mo of androgen suppression (AS) and radiation (RT) for patients (pts) with high-risk CaP., beginning with an initial 4 mo of AS; RT began after 2 mo. 9902 accrued 397 pts and closed early due to excess toxicity. At a median follow-up of 9.2 years, there was no benefit to CT, but it is hypothesized that a subset analysis by post-RT PSA identifies pts that benefit from treatment intensification with CT. **Methods:** Post-RT PSA status was dichotomized at $>$ 0.2 ng/mL within 1 mo of RT. Landmark analysis redefined starting times for disease-free survival (DFS), time to distant metastasis (TDM) and overall survival (OS) at 16 weeks post-RT (36 weeks post-randomization) when CT was planned to complete. Pts were excluded if they did not get RT or assigned CT, or experienced DFS events/lost to follow-up $<$ 36 wks post-randomization. Hazard ratios (HR), 95% confidence intervals (CI), and PSA-by-treatment interaction were estimated by Cox or competing-risks regression. **Results:** 333 pts were analyzed: 190 without and 143 with CT. 37% of pts had a post-RT PSA $\leq$0.2, 34% $>$ 0.2, and 29% no recorded PSA in the defined interval. CT was associated with improved DFS for pts with PSA $>$ 0.2 (HR 0.59, 0.38-0.91), but not for those with PSA $\leq$0.2 (HR 0.94, 0.60-1.46; interaction p = 0.13). This association, for those with PSA $>$ 0.2, persisted in those pts who received the full course of CT and trended in the same direction for pts receiving 1-3 cycles. CT was associated with a trend toward improved TDM in the PSA $>$ 0.2 group (HR 0.56, 0.23-1.35) and not in the PSA$\leq$0.2 group (HR 1.31, 0.36-4.70), based on 32 pts with metastases. OS did not show the same pattern (PSA $>$ 0.2: HR 0.98, 0.55-1.77; PSA$\leq$0.2: HR 0.57, 0.29-1.13). **Conclusions:** This analysis suggests that men with high-risk CaP and suboptimal response to AS+RT, as identified by post-RT PSA $>$ 0.2, may benefit from adjuvant CT. Prospective trials using contemporary CT (e.g. docetaxel) will help optimize treatment for these men. NRG-GU002, recently activated, is addressing this issue.

5079 Poster Session (Board #153), Mon, 1:15 PM-4:45 PM

Long-term results of a prospective phase II study of androgen deprivation therapy, external radiation, cs-131 brachytherapy, and adjuvant docetaxel in high-risk prostate cancer. *First Author: Stephanie Rice, University of Maryland Department of Radiation Oncology, Baltimore, MD*

Background: We report the long-term results of a prospective, Phase II study of 2 years androgen deprivation therapy (ADT), 45 Gy bone marrow sparing pelvic radiation (BMS-PR), Cs-131 brachytherapy boost (85 Gy), and 4 cycles of adjuvant docetaxel (75 mg/m2 q21d + prednisone) in high risk, localized prostate cancer. **Methods:** From2006-2014,38 patients were enrolled. Acute hematologic as well as acute and chronic gastrointestinal (GI) and genitourinary (GU) toxicities were scored based on the CTCAE v3.0 criteria. Biochemical recurrence was defined as a nadir + 2 rise in PSA. Actuarial freedom from PSA failure (bNED) and overall survival (OS) were calculated using SPSS v24. Median Gleason score was 8 (74% Gleason 8-10). Median PSA was 11.2 (range 2.8-96). **Results:** A total of 38 patients were enrolled on the trial. Median age was 62 years (range 45-82). 82% of patients completed all protocol specified treatments, while 84% completed all 4 cycles of docetaxel. After a median follow up of 44 mo (range 3.4-118), the 5-year bNED rate was 86% while 5-year OS was 80%. Acute grade $\geq$ 2 GI and GU toxicity rates were 12.5% and 21.9%, respectively. Chronic grade $\geq$ 2 GI and GU toxicity rates were 3.1% and 3.1%, respectively. 25.6% (n = 10) patients receiving docetaxel developed grade 4 hematologic toxicity. There were no grade 5 toxicities. **Conclusions:** We found this aggressive multi-modal approach to be feasible, safe, well-tolerated, and effective. It does not appear that BMS-PR decreases hematologic toxicity. Cs-131, with its 9.7 day half-life, does not appear to increase acute or late toxicity. These data build upon the ASCENDE-RT and RTOG 0521 trials that demonstrate the added benefits of brachytherapy boost and adjuvant docetaxel, respectively, in high-risk prostate cancer.

5080 Poster Session (Board #154), Mon, 1:15 PM-4:45 PM

Identification of low prostate-specific antigen, high Gleason prostate cancer as a unique hormone-resistant entity with poor survival: A contemporary analysis of 640,000 patients. *First Author: David Dewei Yang, Harvard-MIT Division of Health Sciences and Technology, Harvard Medical School, Boston, MA*

Background: The clinical implications of a low prostate-specific antigen (PSA) in high-grade prostate cancer are unclear. We examined the prognostic and predictive value of a low PSA in high-grade prostate cancer. **Methods:** We identified 642,975 patients in the National Cancer Database (n = 491,505) and Surveillance, Epidemiology, and End Results program (n = 151,470) with localized or locally advanced prostate cancer from 2004-2013. Patients were stratified by Gleason score (8-10 vs. $\leq$7) and PSA ($\leq$2.5, 2.6-4.0, 4.1-10.0, 10.1-20.0, and $>$ 20.0 ng/mL) for analyses. Multivariable Fine-Gray competing risks and Cox regressions were used to analyze prostate-cancer specific mortality (PCSM) and all-cause mortality (ACM), respectively. **Results:** 5.6% of Gleason 8-10 tumors were diagnosed with PSA $\leq$2.5 ng/mL. Among Gleason 8-10 disease using PSA 4.1-10.0 ng/mL as referent, PCSM was U-shaped with respect to PSA, with adjusted hazard ratio (AHR) of 1.75 (95% CI 1.05-2.92, P = 0.032) for PSA $\leq$2.5 ng/mL vs. 1.31, 0.88, and 1.60 for PSA 2.6-4.0, 10.1-20.0, and $>$ 20.0 ng/mL. In contrast, PCSM was linear for Gleason $\leq$7 disease with AHR of 0.32 (95% CI 0.10-1.00, P = 0.050) for PSA $\leq$2.5 ng/mL vs. 1.13, 1.69, and 3.22 for PSA 2.6-4.0, 10.1-20.0, and $>$ 20.0 ng/mL ($P_{Gleason*PSA\ interaction} < 0.001$). Gleason 8-10 disease with PSA $\leq$2.5 ng/mL had a much higher risk of PCSM than standard NCCN high-risk disease (AHR 1.92, 95% CI 1.18-3.14, P = 0.009; 47-month PCSM 14.0% vs. 10.5%). For Gleason 8-10 tumors treated with definitive radiotherapy, androgen deprivation therapy (ADT) was associated with decreased ACM for PSA $>$ 2.5 ng/mL (AHR 0.87, 95% CI 0.81-0.94, P $<$ 0.001) but trended toward increased ACM for PSA $\leq$2.5ng/mL (AHR 1.27, 95% CI 0.89-1.81, P = 0.194; $P_{ADT*PSA\ interaction} = 0.026$). **Conclusions:** Low PSA, high-grade prostate cancer appears to be a unique hormone-resistant entity with a high risk of PCSM that responds poorly to standard treatment. Further molecular classification and trials are urgently needed to develop biological insight into this entity and establish new treatment paradigms, potentially including chemotherapy or novel systemic agents.

5081 Poster Session (Board #155), Mon, 1:15 PM-4:45 PM

Investigation of mechanisms of resistance to ipilimumab therapy with a pre-surgical trial in patients with high-risk, localized prostate cancer. *First Author: Jianjun Gao, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Anti-CTLA-4 therapy ipilimumab (BMS) has led to clinical benefit in patients with metastatic melanoma. However, in multiple clinical trials in patients with prostate cancer, ipilimumab has not demonstrated significant clinical benefit. To identify potential immune inhibitory pathways responsible for resistance to ipilimumab therapy, we evaluated tumor samples from a pre-surgical clinical trial and performed correlative laboratory studies. **Methods:** We carried out a pre-surgical clinical trial with androgen deprivation therapy (ADT), (leuprolide acetate, Tap Pharmaceuticals) plus ipilimumab in patients with localized, high-risk prostate cancer. Each patient received one injection of leuprolide (22.5 mg) on week 0 and ipilimumab (10 mg/kg) on weeks 1 and 4. Patients then underwent surgery at week 8. Tumor tissues were collected at baseline and then at surgery for flow cytometry, IHC, multiplex immunofluorescence, and gene profiling analyses. In vitro studies were carried out for functional analysis. **Results:** Sixteen patients completed treatment with ipilimumab plus ADT and surgery. We observed a significant increase of immune cells including T cells and macrophages into prostate tumors after ipilimumab therapy, similar to data observed in ipilimumab-treated melanoma samples. However, compared to melanoma tumors, we found higher expression of PD-L1 and VISTA inhibitory molecules on CD68+ macrophages in prostate tumors. Interestingly, PD-L1 and VISTA were expressed on distinct subset of CD68+ macrophages, with high expression of CD163, suggesting an M2 subtype. In vitro studies demonstrated that engagement of PD-L1 and/or VISTA pathways inhibited T cell responses. Coculture with monocytes resulted in suppression of T cell function, which can be reversed with anti-VISTA blocking antibody. **Conclusions:** These data suggest that evolving compensatory inhibitory pathways including PD-L1 and VISTA may mediate resistance of prostate cancer to ipilimumab therapy. Concurrent blockade of other immune checkpoints such as PD1/PD-L1 and/or VISTA may be necessary to provide significant clinical benefits for patients with prostate cancer. Clinical trial information: NCT01194271.

5082 Poster Session (Board #156), Mon, 1:15 PM-4:45 PM

Survival impact of initial local therapy selection for men under 60 with high risk prostate cancer. *First Author: Adeel Kaiser, University of Maryland School of Medicine, Baltimore, MD*

Background: The impact of initial local therapy selection on survival for high risk prostate cancer (PCa) patients remains uncertain. We sought to assess this effect, while limiting competing causes of death, through the examination of a younger PCa patient cohort within the National Cancer Database. **Methods:** We evaluated the overall survival (OS) of men under 60 with high risk PCa receiving either radiation therapy (RT) or radical prostatectomy (RP). All men in this age group were treated between 2004 and 2013, harbored cN0M0 disease, and presented with Gleason Scores (GS) of 8 to 10. The RT group included patients who received external beam radiation (EBRT) alone or EBRT in combination with brachytherapy (BT). Overall survival and covariates were evaluated using multivariable Cox regression analysis. **Results:** A total of 16,944 patients met inclusion criteria of which 12,155 underwent RP and 4,789 received RT as initial therapy. 82.5% of RT patients received hormonal therapy, and the median dose was 77.4 Gy. In the RP group, 17.2% of patients received postoperative radiation, and 87% of these cases received a dose exceeding 64.80 Gy. The RP group had a higher proportion of cases with Charlson-Deyo comorbidity score $>$ 0 (15.2% v. 11.2%, $p < 0.000001$). At a median follow-up of 50 months (0 - 131 months), RP was associated with improved OS in comparison to RT (hazard ratio = 0.52; 95% CI (0.47, 0.58); $p < 0.000001$). The estimated 8-year OS ($\pm$1 standard error of the estimate) was 85.1$\pm$0.7% and 74.9$\pm$0.7%, after RP and RT, respectively. This benefit remained present when adjusting for age, year of treatment, race, comorbidity score, Gleason score, T stage, hormonal therapy, chemotherapy, form of radiation, PSA, or insurance status. **Conclusions:** Compared to RT, initial treatment of men under 60 with high risk PCa with RP results in a large, statistically significant improvement in overall survival that remains consistent over time and remains significant in a multivariable model adjusting for known prognostic variables. These results are limited by the retrospective nature of the database analysis, and the lack of cancer specific survival information.

5084 Poster Session (Board #158), Mon, 1:15 PM-4:45 PM

The accuracy of multiparametric magnetic resonance imaging (mpMRI) using PI-RADS v2 in disease upgrading on re-biopsy among patients with low-risk prostate cancer (PCa) on active surveillance (AS): A Brazilian perspective. *First Author: PÃoblio C. C. Viana, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil*

Background: The current selection criteria to AS is critical and it becomes even more relevant in Latin America, given the higher proportion of high risk cancers. The objective of this study is to analyze the accuracy of mpMRI using PI-RADS v2 in predicting the risk of upgrading on re-biopsy (UR) in men with low-risk PCa on AS. **Methods:** In this Institutional Review Board approved prospective study, patients with low-grade PCa selected for AS at our institution underwent mpMRI at least 6 weeks after the baseline 12-core random prostate biopsy (BSB), from March 2014 to March 2016. One blinded abdominal radiologist evaluated the exams regarding presence of dominant lesion and assigned the PI-RADS v2 score. MRI-target transrectal ultrasound-guided re-biopsies were performed in all patients within 6-12 months after the BSB. Standardized 12-core biopsy was performed and additional cores were taken from suspicious areas on mpMRI. **Results:** One hundred and nine patients were included, 93 (85.3%) patients had a dominant lesion on MRI. mpMRI were classified as PI-RADS 1, 2 or 3 in 67 (61.5%) patients, and as PI-RADS 4 or 5 in 42 (38.5%) patients. UR occurred in 42 (38.5%) patients. Out of these, 39 (92.8%) had radical prostatectomy, 6 (15.4%) T2a, 24 (61.5%) T2b, and 9 (23.1%) T3a. The diagnostic performance of mpMRI for PCa upgrading after re-biopsy was summarized in table 1. Patients assigned as PI-RADS 4 or 5 presented a significantly higher risk for UR compared with patients with PI-RADS 1, 2 or 3 (73.8% vs 16.4%, $p < 0.001$). Logistic regression analyses demonstrated that PI-RADS 4 or 5 remained a significant predictor of UR (OR: 37.366, $p < 0.0001$). **Conclusions:** We demonstrated in our population that mpMRI using PI-RADS v2 is a significant predictor for upgrading on re-biopsy in patients on AS and could be used to guide TRUS biopsy, increasing the accuracy of current clinical criteria for AS.

Sensitivity	0.761 (0.612; 0.874)
Specificity	0.889 (0.784; 0.954)
Positive predictive value	0.833 (0.686; 0.930)
Negative predictive value	0.836 (0.725; 0.915)
Accuracy	0.835 (0.752; 0.899)

5085 Poster Session (Board #159), Mon, 1:15 PM-4:45 PM

Prostate cancer (PCa) in 696 hypogonadal men with and without long-term testosterone therapy (TTh): Results from a controlled registry study. *First Author: Ahmad Haider, Bremerhaven, Germany*

Background: There is no evidence that TTh in men with hypogonadism increases PCa incidence or severity. A Canadian group recently found that long-term TTh decreased the risk of PCa diagnosis (Wallis et al., Lancet Diab Endocrinol 2016; 4:498). We assessed incidence and severity of PCa in hypogonadal men on long-term TTh (T-group) in comparison to an untreated hypogonadal control group (CTRL). **Methods:** 400 men with testosterone $\leq$350 ng/dL and symptoms received testosterone undecanoate 1000 mg every 3 months for up to 10 years. 296 hypogonadal men (57-74) opted against TTh. Median follow-up: 8 years. Total observation time covered more than 5,000 patient-years. Prostate volume (PV), PSA, weight and C-reactive protein (CRP) were measured and digital rectal examination/transrectal ultrasound performed before treatment initiation and then every 6-12 months. Biopsies were performed when indicated according to EAU guidelines. **Results:** In the T-group, PV increased slightly but significantly by 2.41 mL ($p < 0.0001$), PSA by 0.22 (NS). In CTRL, PV decreased slightly but significantly by -1.20 mL ($p < 0.005$), PSA by -0.38 ($p < 0.0001$). Weight dropped by 18.23% in the T-group and increased by 1.78% in CTRL, CRP decreased significantly in the T-group and remained unchanged in CTRL. In the T-group, 9 men (2.3%) were diagnosed with PCa. In CTRL, 15 (5.1%) were diagnosed with PCa. The incidence per 10,000 years was 29 in the T-group and 102 in CTRL. The mean baseline age of PCa patients was 65 years in the T-group and 65.5 in CTRL. Prostatectomy was performed in all men. In the T-group, all but 1 patient had a Gleason score $\leq$6, and all a predominant Gleason score of 3. Tumor grade was G2 in all 9 (100%), tumor stage T2a in 7 (78%) and T2b in 2 (22%) patients. In CTRL, Gleason score was $>$ 6 in all 15 patients. 4 men had a predominant Gleason score of 3, 10 had 4, and 1 had 5. Tumor grade was G2 in 7 (46.7%) and G3 in 8 (53.3%) patients, tumor stage T2b in 1 (6.7%), T2c in 1 (6.7%), T3a in 1 (6.7%), T3b in 7 (46.7%) and T3c in 6 (50%) patients. **Conclusions:** In hypogonadal men, TTh may decrease PCa incidence compared to CTRL. PCa was less severe in the T-group. Weight loss and reduced inflammation by TTh may have contributed to our findings.

TPS5086 Poster Session (Board #160a), Mon, 1:15 PM-4:45 PM

A randomized phase II trial of abiraterone, olaparib or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair defects. *First Author: Zachery Reichert, University of Michigan, Ann Arbor, MI*

Background: Approximately 20% of patients with metastatic castration-resistant prostate cancer (mCRPC) harbor mutations in genes encoding DNA repair proteins (e.g. ATM, BRCA1, BRCA2, PALB2, RAD51, CHEK2, FANCA). These mutations impact base excision repair and alternative end-joining, which rely on the activity of poly(ADP-ribose) polymerase (PARP). Olaparib (olap) inhibits PARP and showed activity in a post hoc analysis in mCRPC patients with DNA repair defects (DRD). In a subgroup analysis of the NCI 9012 trial evaluating abiraterone (abi) +/- veliparib (a PARP inhibitor), patients with DRD in both treatment groups had a $>$ 80% prostate-specific antigen (PSA) response rate and prolonged progression free survival (PFS) (13.8 mos vs. 7.8 mos; P = 0.01). Preclinical data suggests interactions between androgen signaling and PARP activity. These observations provide the rationale to evaluate the efficacy of olap, abi or the combination in patients with DRD. **Methods:** This is a prospective, randomized, open-label phase 2 clinical trial with a primary endpoint of objective PFS (radiographic + clinical). Secondary endpoints: objective disease and PSA response rates. Analysis of tumor specimens, circulating tumor cells/DNA will be performed. Eligible patients with progressive mCRPC, no prior mCRPC therapy with tumor loss of ATM, BRCA1 or BRCA2 (based on known germline loss, prior CLIA certified tumor analysis or new metastatic biopsy) will be stratified by germline vs. somatic mutational status and randomized 1:1:1 to abi (1000 mg daily) + prednisone (5 mg bid), olap (300 mg daily) or olap + abi + prednisone (same doses). Patients in single agent arms may cross over to opposite single agent therapy at progression. An exploratory cohort of patients with DNA repair defects besides ATM, BRCA1, BRCA2 may receive olap. Statistical analysis will provide median, 12-month, and 24-month product-limit estimates of PFS by treatment arm. The study is recruiting 60 randomized patients at sites in the US. The trial is coordinated by the Prostate Cancer Clinical Trials Consortium, LLC and funded by AstraZeneca. Clinical trial information: NCT03012321.

TPS5087 **Poster Session (Board #160b), Mon, 1:15 PM-4:45 PM**

Trial of rucaparib in prostate indications 3 (TRITON3): An international, multicenter, randomized, open-label phase 3 study of rucaparib vs physician's choice of therapy for patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination deficiency (HRD). *First Author: Charles J. Ryan, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Pts with mCRPC often initially receive androgen receptor-targeted therapy (eg, abiraterone or enzalutamide), but they almost always progress. Poly(ADP-ribose) polymerase (PARP) inhibitors (eg, olaparib) have demonstrated clinical activity in pts with mCRPC with a deleterious mutation in a homologous recombination (HR) DNA repair gene; 14 of 16 evaluable pts with mCRPC and a tumor alteration in an HR gene, including *BRCA1*, *BRCA2*, and *ATM*, responded to olaparib (Mateo et al. *N Engl J Med*. 2015;373:1697-708). The PARP inhibitor rucaparib is approved in the US for treatment of pts with ovarian carcinoma that harbors a deleterious *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have received ≥2 chemotherapies. These data support investigating rucaparib as a treatment option in pts with mCRPC with HRD. **Methods:** TRITON3 (NCT02975934)is a phase 3 study evaluating rucaparib (600 mg BID) vs physician's choice (abiraterone, enzalutamide, or docetaxel) in pts with mCRPC who have a deleterious germline or somatic mutation in *BRCA1*, *BRCA2*, or *ATM* as determined by local and/or central testing. All pts must have progressed on abiraterone or enzalutamide in the mCRPC setting; pts who received prior chemotherapy for mCRPC or PARP inhibitor treatment are excluded. Pts will be randomized 2:1 to rucaparib or physician's choice of comparator therapy; pts randomized to physician's choice may cross over to rucaparib on radiographic progression confirmed by independent radiology review (IRR). The primary endpoint is IRR-confirmed radiographic progression-free survival (modified RECIST version 1.1/PCWG3 criteria). Secondary objectives include overall survival, objective response rate, duration of response, clinical benefit rate, pt-reported outcomes, and safety. Pretreatment blood samples will be collected from all pts to enable development of a plasma-based companion diagnostic to identify pts who may benefit from rucaparib treatment. Pts (≈400) will be enrolled at > 100 sites worldwide. Clinical trial information: NCT02975934.

TPS5088 **Poster Session (Board #161a), Mon, 1:15 PM-4:45 PM**

A phase 1/1b multicenter, open-label, dose escalation and dose expansion study to evaluate the safety, pharmacokinetics, immunogenicity, and antitumor activity of MEDI3726 in patients with metastatic, castration-resistant prostate cancer who have received prior treatment with abiraterone or enzalutamide. *First Author: Mark T. Fleming, Virginia Oncology Associates, Norfolk, VA*

Background: Therapeutic advances have recently been achieved for patients with metastatic, castration-resistant prostate cancer (mCRPC) due to abiraterone acetate (ABI) and enzalutamide (ENZ). However, virtually all patients with mCRPC eventually progress in their disease, and further treatment options are limited. Prostate-specific membrane antigen (PSMA) is highly expressed in nearly all prostate cancers, and its expression is highest in mCRPC. MEDI3726 is an antibody-drug conjugate composed of anti-PSMA antibody derived from J591, site-specifically conjugated to the cytotoxic, DNA cross-linking, pyrrolobenzodiazepine dimer. MEDI3726 has demonstrated potent and specific in vitro and in vivo antitumor activity in human prostate cancer-derived preclinical models with different expression levels of PSMA. **Methods:** This is a first-in-human, phase 1/1b, multicenter, open-label, dose escalation and dose expansion study in patients who have received prior treatment with ABI or ENZ, with or without prior taxane-based chemotherapy in the mCRPC setting (NCT02991911). The primary objectives are to assess safety and tolerability, describe dose-limiting toxicities, and determine the maximum tolerated dose or maximum administered dose of MEDI3726. The secondary objectives are to evaluate MEDI3726 for its antitumor activity (based on a composite response according to RECIST Version 1.1, a reduction in prostate-specific antigen level of 50% or more compared to baseline, or a conversion in the circulating tumor cell count [defined as a reduction from ≥5 cells/7.5 mL blood to < 5 cells/7.5 mL blood]), safety and tolerability in combination with ENZ, pharmacokinetics alone and in combination with ENZ, and immunogenicity. Recruitment is ongoing for this study, which has an estimated total target enrollment of 224 patients. Clinical trial information: NCT02991911.

TPS5089 **Poster Session (Board #161b), Mon, 1:15 PM-4:45 PM**

Phase 1b/2 keynote-365 trial: Pembrolizumab (pembro) combination therapy in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Evan Y. Yu, Seattle Cancer Care Alliance, Seattle, WA*

Background: Approved treatments for mCRPC (eg, enzalutamide and docetaxel) may increase programmed death ligand 1 (PD-L1) expression and facilitate neoantigen release. In phase 1b and 1/2 trials, pembro, an anti–PD-1 antibody, has produced antitumor responses in previously treated mCRPC as monotherapy and in combination with enzalutamide. Olaparib, a PARP inhibitor, has shown activity in mCRPC with DNA-repair defects. The nonrandomized, multicohort, open-label KEYNOTE-365 study (NCT02861573) will evaluate the safety and efficacy of pembro with olaparib (cohort A), docetaxel + prednisone (cohort B), or enzalutamide (cohort C) in mCRPC. **Methods:** Cohort allocation depends upon prior treatment: cohort A requires prior docetaxel (treatment with 1 other chemotherapy and ≤2 second-generation hormonal manipulations is allowed); cohort B requires prior abiraterone acetate or enzalutamide (but not both); cohort C requires prior abiraterone acetate. Additional eligibility criteria include confirmed prostate adenocarcinoma, disease progression (PD) ≤6 months before screening, ongoing androgen deprivation (serum testosterone < 50 ng/dL), and provision of nonirradiated tumor sample. Pembro 200 mg will be given every 3 weeks (Q3W) with either olaparib 400 mg twice daily (cohort A), docetaxel 75 mg/m^2 Q3W + prednisone 5 mg twice daily (cohort B), or enzalutamide 160 mg once daily (cohort C). Pembro treatment will continue for up to 35 cycles or until PD or unacceptable adverse events (AEs). Patients in cohort B may receive a maximum of 10 cycles of docetaxel + prednisone. Patients who discontinue 1 of 2 drugs in a combination because of a treatment-related AE may continue to receive the other drug until PD. Response will be evaluated by prostate-specific antigen (PSA) levels Q3W and by imaging Q9W for the first year and Q12W thereafter. Primary end points are safety and PSA response rate (decline of ≥50% from baseline twice ≥3 weeks apart). Secondary end points include time to PSA progression, progression-free survival, overall survival, and overall response rate. Enrollment will continue until 70 patients are enrolled for each cohort. Clinical trial information: NCT02861573.

TPS5090 **Poster Session (Board #162a), Mon, 1:15 PM-4:45 PM**

A phase III trial comparing atezolizumab with enzalutamide vs enzalutamide alone in patients with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Thomas Powles, Barts Cancer Institute, London, United Kingdom*

Background: In the past decade, several therapies have been approved for patients (pts) with mCRPC, including the androgen receptor (AR) antagonist enzalutamide (enza) and the androgen synthesis inhibitor abiraterone acetate (abi). Despite these advances, most pts experience disease progression and there are inadequate data to guide the sequencing of agents to optimize outcomes. Pts with mCRPC who progress on enza have increased circulating PD-L1/PD-L2–positive dendritic cells compared with enza-naive pts or pts who are still responding to treatment (Bishop et al. *Oncotarget*. 2014). In two recent studies, PSA and radiographic responses were observed in mCRPC pts treated with a PD-L1/PD-1 pathway inhibitor with or without enza (Graff et al. *Oncotarget*. 2016; Hansen et al. *Ann Oncol*. 2016). Atezolizumab (atezo) is an anti–PD-L1 monoclonal antibody that inhibits the interaction between PD-L1 and its receptors, PD-1 and B7.1, enhancing T-cell responses and improving anti-tumor activity. Taken together, this suggests that the combination of atezo and enza may provide an effective treatment option for mCRPC pts. **Methods:** A Phase III randomized, multicenter, clinical trial (NCT03016312) is being conducted to evaluate the efficacy and safety of atezo with enza compared with enza alone in mCRPC pts who have received prior abi treatment and have progressed on, are ineligible for, or have refused a taxane regimen. Eligibility criteria include mCRPC or locally advanced, incurable CRPC and ECOG PS 0-1. Exclusion criteria include CNS metastasis, autoimmune disease, history of seizures, prior immunotherapy and prior treatment with enza or any other newer AR antagonists. Pts will be randomized 1:1 to receive atezo 1200 mg q3w and enza 160 mg qd or enza alone. The primary endpoint is OS, and secondary endpoints include PSA response rate, rPFS, ORR and safety. Exploratory biomarkers associated with responses to atezo and enza will be evaluated in tumor tissue collected at baseline and progression. Approximately 550 pts will be enrolled at 150 sites globally. Clinical trial information: NCT03016312.

TPS5091 Poster Session (Board #162b), Mon, 1:15 PM-4:45 PM

PROfound: A randomized Phase III trial evaluating olaparib in patients with metastatic castration-resistant prostate cancer and a deleterious homologous recombination DNA repair aberration. *First Author: Johann S. De Bono, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: The median overall survival for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) is short. Available agents may offer limited therapeutic benefit, but no molecularly stratified treatment has yet been approved for this heterogeneous disease. A sizable percentage of pts with mCRPC has loss of function aberrations in genes involved in homologous recombination repair (HRR) in tumor tissue, such as *BRCA1/2* and *ATM*. These aberrations can confer sensitivity to poly(ADP-ribose) polymerase (PARP) inhibition. A Phase II study indicated that the oral PARP inhibitor olaparib (Lynparza) had antitumor activity in 33% of mCRPC pts who had progressed after new hormonal agent (NHA) treatment and chemotherapy, with a strikingly higher composite response rate in pts with a deleterious HRR gene aberration (HRRa) (88%; 14/16) vs pts without a HRRa (6%; 2/33) (Mateo *et al.*2015). The PROfound study evaluates olaparib efficacy and safety versus physician's choice of either abiraterone acetate or enzalutamide, in pts with mCRPC and a HRRa (NCT02987543). **Methods:** To be eligible for this multinational, open-label, Phase III study, mCRPC pts must have progressed on prior NHA treatment and have a tumor HRRa in one of 15 genes, as confirmed by an HRR Assay (Foundation Medicine, Inc.). Cohort A (n = 240 approx) includes pts with mutations in *BRCA1*, *BRCA2* or *ATM*, while pts with a mutation in 12 other HRR genes will be assigned to Cohort B (n = 100 approx). Pts will be randomized (2:1) to olaparib tablets (300 mg orally bid) or physician's choice of either enzalutamide (160 mg orally od) or abiraterone acetate (1000 mg orally od with 5 mg bid prednisone) and treatment continued until radiographic progression (as assessed by blinded independent central review) or lack of treatment tolerability. The primary endpoint of radiographic progression-free survival (rPFS) will be assessed in Cohort A using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria. Key secondary efficacy endpoints include confirmed objective response rate, time to pain progression, overall survival (all Cohort A) and rPFS (both cohorts combined). Clinical trial information: NCT02987543.

TPS5092 Poster Session (Board #163a), Mon, 1:15 PM-4:45 PM

ARASENS phase 3 trial of ODM-201 in men with metastatic hormone-sensitive prostate cancer (mHSPC). *First Author: Matthew Raymond Smith, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: Androgen deprivation therapy (ADT) ± docetaxel is recommended first-line therapy for mHSPC, but most patients progress to castration-resistant PC (CRPC). BAY-1841788 (ODM-201) is an investigational oral androgen receptor (AR) antagonist that has a unique chemical structure designed to block the growth of cancer cells through binding to the AR with high affinity and inhibiting the receptor function. In preclinical studies, ODM-201 and its main circulating metabolite are active also in known AR mutants (eg, W742L, F877L), and have been found to have negligible blood-brain barrier penetration. In the phase 1 ARAFOR and phase 1/2 ARADES trials, ODM-201 had antitumor activity and was well tolerated in men with mCRPC (Massard et al. *Eur Urol.* 2016;69:834–840; Fizazi et al. *Lancet Oncol.* 2014;15:975–985). Given this promising activity in mCRPC, the ARASENS trial is evaluating ODM-201 plus standard ADT + docetaxel in men with metastatic disease (mHSPC). **Methods:** This international, randomized, double-blind, placebo-controlled, phase 3 trial (NCT02799602) is being conducted in 23 countries. ~1300 men with newly diagnosed mHSPC will be randomized 1:1 to either ODM-201 600 mg twice daily (2×300 mg tablets) orally with food or placebo, both with ADT + docetaxel (6 cycles after randomization), and stratified by extent of disease and alkaline phosphatase levels. Key inclusion criteria are histologically or cytologically confirmed PC with documented metastases, started ADT ± first-generation anti-androgen therapy ≤12 weeks before randomization, and Eastern Cooperative Oncology Group performance status 0 or 1. The primary objective is to show superior overall survival with ODM-201 vs placebo, both with ADT + docetaxel. Secondary end points include time to CRPC, initiation of subsequent anticancer therapy, symptomatic skeletal event-free survival (SSE-FS), time to first SSE, initiation of opioid use, pain progression, and worsening of physical symptoms, all measured at 12-week intervals. Safety will be assessed by adverse events. The trial is open for enrollment; first patient first visit was in November 2016 and > 10 sites are open for recruitment and enrolling patients. Clinical trial information: NCT02799602.

TPS5093 Poster Session (Board #163b), Mon, 1:15 PM-4:45 PM

Phase I dose-escalation study of fractionated-dose ^{177}Lu-PSMA-617 for progressive metastatic castration resistant prostate cancer (mCRPC). *First Author: Scott T. Tagawa, Sandra and Edward Meyer Cancer Center, New York, NY*

Background: PC is a radiosensitive disease. PSMA is selectively overexpressed in advanced PC with upregulation by androgen receptor (AR) pathway dysregulation; limited expression exists in other organs. A series of sequential studies of radiolabeled anti-PSMA antibody J591 revealed 1) targeting and safety [Bander 2003]; 2) safety and prelim efficacy [Milowsky 2004, Bander 2005]; 3) efficacy and initial dose-response [Tagawa 2013]; 4) dose-fractionation allows higher doses, ability to combine with docetaxel, confirmation of dose-response (PSA and overall survival) [ASCO 2010, 2014, 2016]; 5) predictable, reversible myelosuppression is dose-limiting [Tagawa 2013]. Small molecule PSMA inhibitor ligands can be successfully radiolabeled and are widely used for imaging and treatment in Europe. ^{177}Lu-PSMA-617 is the most commonly used, but experience is mostly anecdotal/retrospective and no formal dose-escalation studies have been performed. **Methods:** Men with progressive mCRPC following at least 1 potent AR-targeted agent (e.g. abi/enza) and docetaxel (or unfit/refuse chemo) without limit of # prior therapies provided adequate organ function will undergo imaging with ^{68}Ga-PSMA-HBED-CC PET/CT followed by escalating fractionated doses of ^{177}Lu-PSMA-617. Cohort 1 = 3.7 GBq x2 two weeks apart up to 11.1 GBq x2 in a 3+3 dose-escalation study. Dose-limiting toxicity (DLT) is defined as attributable grade 4 heme toxicity or grade 3/4 non-heme toxicity. Planned cohort expansion will occur at recommended phase 2 dose (RP2D) in a 2-stage design. The primary endpoint is determination of DLT and RP2D. Secondary endpoints include toxicity, PSA decline rate, RECIST response, PFS, rPFS, OS. Correlatives include baseline/follow up PSMA imaging, whole body distribution of ^{177}Lu-PSMA-617, CTC count (CellSearch) changes, tissue and circulating genomic assessment of DNA repair pathways, patient reported outcomes (FACT-P and BPI-SF). Clinical trial information: NCT03042468.

TPS5094 Poster Session (Board #164a), Mon, 1:15 PM-4:45 PM

A phase II randomized trial of observation versus stereotactic ablative radiation for oligometastatic prostate cancer (ORIOLE). *First Author: Ryan Phillips, Department of Radiation Oncology and Molecular Radiation Sciences, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: ORIOLE is a randomized, non-blinded Phase II interventional study evaluating the safety and efficacy of SBRT in biochemically recurrent, oligometastatic, hormone-sensitive prostate cancer at 3 centers in the US. Patients will be stratified by clinical characteristics and randomized 2:1 to SBRT or observation. The primary clinical endpoint is progression at 6 months defined by PSA increase, radiologic or clinical evidence, ADT initiation, or death from any cause. Secondary endpoints include local control at 6 months, SBRT-associated toxicity and quality of life, and ADT-free survival. Imaging and laboratory correlates will characterize, in isolation, the effects of SBRT on oligometastatic disease. **Methods:** Eligible patients are hormone-sensitive, have undergone prior definitive treatment and recurred with 1-3 asymptomatic bone or soft tissue metastases diagnosed within 6 months, PSA doubling time (PSADT) < 15 months, ECOG performance status ≤ 2, and normal organ and marrow function. Minimization will be used to balance assignment by primary intervention, prior ADT, and PSADT. Accrual of 54 patients provides 85% power to detect a decrease in progression rate from 80% to 40% with type I error = 0.05 using one-sided Fisher's exact test. Hazard ratios and Kaplan-Meier estimates of progression free survival, ADT free survival, and time to locoregional and distant progression will be calculated based on intention-to-treat. Local control will be assessed using RECIST 1.1 criteria. Withdrawal prior to 6 months will be counted as progression. Adverse events will be summarized and quality of life pre- and post-SBRT will be measured by Brief Pain Inventory. The investigational targeted imaging agent ^{18}F-DCFPyL will be compared to bone scan and CT for identifying oligometastases before SBRT and monitoring disease response following SBRT. Biological alterations induced by SBRT will be investigated using circulating tumor cell analysis, deep sequencing of circulating tumor DNA, and T-cell repertoire profiling. A hereditary cancer assay will inform efforts to advance personalized screening and therapy. Clinical trial information: NCT02680587.

TPS5095 Poster Session (Board #164b), Mon, 1:15 PM-4:45 PM

Abiraterone +/- cabazitaxel in defining complete response in prostatectomy (ACDC-RP) trial. *First Author: Anthony M. Joshua, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Given recent advances in the management of de novo metastatic hormone-sensitive prostate cancer with both docetaxel and abiraterone, as well as evidence of significant activity of cabazitaxel in the post-abiraterone castrate-resistant setting, we hypothesized that the addition of cabazitaxel to neoadjuvant abiraterone will improve pathological complete response rates by overcoming mechanisms of resistance in localized high-risk prostate cancer. Aim: To determine the relative efficacy of the addition of cabazitaxel to abiraterone in the neoadjuvant treatment of prostate cancer to achieve a complete response. **Methods:** Open label, randomized, 2-arm multi-centre, phase 2 clinical trial. Primary endpoint: Pathological complete response rate (pCR). Secondary endpoints: surgical outcomes (positive margins, extracapsular extension, seminal vesicle or nodal involvement), pharmacodynamic markers in residual tumour (apoptosis, androgen receptor expression, localization, and signaling), biomarkers (intra-prostatic androgen levels), and safety. Design: Study participants will be randomized in a 1:1 ratio to receive either: Arm A: Abiraterone (1000 mg/day), prednisone (5 mg b.i.d.), leuprolide (22.5 mg s.c. every 3 months), and cabazitaxel (25 mg/m^2 starting at week 2, with 6 mg pegfilgrastim 24 h following cabazitaxel) or Arm B: Abiraterone (1000 mg/day), prednisone (5 mg b.i.d.) and leuprolide (22.5 mg s.c. every 3 months). Assessments will take place biweekly for the first 12 weeks, then monthly until the prostatectomy (scheduled for 24 weeks following start of treatment). Target accrual is 88 participants within 36 months. Study is powered to detect a 15% difference with 85% power, assuming a one-sided type 1 error rate of 20%. A 6 patient safety run-in is included. As of Jan 2017, 1 site is open in Canada, with 4 additional Canadian sites and 1 site in Australia pending. To date, 4 participants are randomized and undergoing treatment. ACDC-RP is an investigator-initiated trial led by the Princess Margaret Urology Trials Group with funding from Ontario Institute for Cancer Research (OICR) and in-kind contributions from Janssen and Sanofi. Clinical trial information: NCT02543255.

TPS5096 Poster Session (Board #165a), Mon, 1:15 PM-4:45 PM

Randomised phase III trial of enzalutamide in androgen deprivation therapy (ADT) with radiation therapy for clinically localised, high risk, or node-positive prostate cancer: ENZARAD (ANZUP 1303). *First Author: Scott Williams, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Adjuvant ADT with an LHRH analog (LHRHA) given before, during and after radiotherapy (RT) is standard of care for high risk localised prostate cancer (PC). Enzalutamide is more effective in metastatic disease than conventional non-steroidal anti-androgens (NSAA). We hypothesize that addition of enzalutamide to adjuvant ADT and RT will improve outcomes. The aim is to determine the efficacy of enzalutamide compared with NSAA as part of adjuvant ADT with LHRHA in men planned for RT for localized high risk or node-positive PC. **Methods:** DESIGN: Open label, randomised, phase 3 trial including ANZ, USA, UK, Ireland and Europe. ENDPOINTS: OS (primary), cause-specific survival, PSA PFS, clinical PFS, time to subsequent hormonal therapy, time to castration-resistant disease (PCWG2 criteria), metastasis free survival, adverse events and HRQOL. Tertiary objectives: identification of prognostic/predictive biomarkers from archival tumour tissue and 4 serial fasting bloods. 800 target participants with 5.5 yrs minimum follow-up. 80% power to detect 33% reduction in the hazard of death assuming 5-year survival rate of 76% amongst controls. TREATMENT: Participants are randomised 1:1 to enzalutamide 160mg daily for 24 months versus conventional NSAA for 6 months. All participants receive LHRHA for 24 months and RT starting after week 16. RT delivered as 78Gy in 39 Fx or 46Gy in 23 Fx plus brachytherapy (nodal RT optional for N0, mandatory for N1). ASSESSMENTS: Baseline, then every 8 weeks until year 2, then 3-4 monthly until year 5, 6-monthly until year 7, then annually. CT/MRI and bone scan at baseline, PSA progression, 6 monthly until re-initiation of ADT, when PCWG2 criteria for CRPC are met and then 3 monthly until evidence of metastases. As of 1st February 2017, 55 of 67 sites open with 398 patients recruited. EORTC sites expected to open from Quarter 1 2017. ENZARAD is an investigator-initiated cooperative group trial led by ANZUP Cancer Trials Group with funds and product from Astellas. ANZUP is supported by Cancer Australia and previously CI NSW. ClinicalTrials.gov: NCT02446444, ANZCTR: ACTRN12614000126617 Clinical trial information: NCT02446444.

TPS5097 Poster Session (Board #165b), Mon, 1:15 PM-4:45 PM

A randomized study of enzalutamide in patients with localized prostate cancer undergoing active surveillance (ENACT). *First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC*

Background: Prostate cancer (PC) patients (pts) who select active surveillance (AS) are a heterogeneous population with varying risks for disease progression. Studies have estimated that approximately 31–42% of pts electing AS have experienced disease progression (pathological or therapeutic) over 1.8 and 2.3 years. There is no evidence-based pharmacological intervention which has effectively lessened this progression event. Pharmacological intervention with enzalutamide (ENZ), an androgen receptor inhibitor approved for treatment of metastatic castration-resistant PC, may lessen this progression. The aims of this study are to evaluate the efficacy of ENZ versus AS alone for delaying time to progression in pts with clinically localized PC undergoing AS. This study examines the effects of ENZ on progression in a subset of pts with low- or intermediate-risk PC who would otherwise elect an AS protocol. **Methods:** This is a multicenter, randomized, open-label study (NCT02799745). Eligibility criteria include histologically confirmed prostate adenocarcinoma within 6 months of screening, low or intermediate risk PC (T1c−T2c, prostate-specific antigen [PSA] $<$ 20, N0, M0, Gleason score $\leq$7 [3+4 pattern only]), Eastern Cooperative Oncology Group status $\leq$2 and estimated life expectancy $>$ 5 years. Exclusion criteria include any prior PC intervention. Pts will be randomized to receive open-label oral ENZ 160 mg/day once daily or to AS during the 1-year study treatment period. After the first year, all pts will be followed for one additional year with no other intervention. All pts will undergo prostate biopsy at 1 and 2 years. The primary end point is time to PC progression (pathological or therapeutic). Secondary end points include safety, incidence of negative biopsies for cancer at 1 and 2 years, percentage of cancer positive cores at 1 and 2 years, time to PSA progression, incidence of secondary rise in serum PSA, and quality-of-life questionnaires. Exploratory end points include biomarker assessment and genomic analysis. Study enrolment commenced in June 2016, with study completion expected in March 2019. Planned total enrolment is 222 pts from ~60 United States/Canadian sites. Clinical trial information: NCT02799745.

5500 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

LION: Lymphadenectomy in ovarian neoplasms—A prospective randomized AGO study group led gynecologic cancer intergroup trial. *First Author: Philipp Harter, AGO and Kliniken Essen Mitte, Essen, Germany*

Background: So far, there is no level-1 evidence regarding the role of systematic pelvic and para-aortic lymphadenectomy (LNE) in patients with advanced ovarian cancer (AOC) with macroscopic complete resection und clinically negative lymph nodes (LN). Therefore, surgical management regarding LNE worldwide is very heterogeneous. **Methods:** Prospective randomized trial including patients with newly diagnosed AOC FIGO IIB-IV with macroscopic complete resection and pre- and intra-operatively clinical negative LN were randomized intra-operatively to LNE versus no-LNE. All centers had to qualify regarding surgical skills before participation in this trial. The primary endpoint was overall survival. **Results:** 647 patients were randomized between 12/08 and 1/12 to LNE (n=323) or no-LNE (n=324). The median number of removed LN in patients randomized to LNE was 57 (pelvic 35 and para-aortic22). Post-op platinum-taxane based chemotherapy was applied in 85% of the patients in the no-LNE arm and 80% in the LNE arm. Microscopic metastases were diagnosed in 56% of the pts in the LNE arm. Median OS in the no-LNE arm was 69 months and 66 months in the LNE arm (HR 1.06, 95%CI 0.83-1.34, p=0.65) and the median PFS was 26 months in both arms (HR 1.11, 95%CI 0.92-1.34 p=0.30). Surgery in the LNE arm was 64 minutes longer (means: 352 vs 288 min), resulted in a higher median blood loss (650 vs 500 ml), and a higher transfusion rate (67% vs 59%). Furthermore, serious post-operative complications occurred more frequently in the LNE arm (e.g. rate of re-laparotomies 12.1% vs 5.9% [p=0.006], hospital re-admittance rate 8.0% vs 3.1% [p=0.006] and deaths within 60 days after surgery 3.1 vs 0.9% [p=0.049]). **Conclusions:** Systematic pelvic and para-aortic LNE in patients with AOC with both intra-abdominal complete resection and clinically negative LN neither improve overall nor progression-free survival despite detecting (and removing) sub-clinical retroperitoneal lymph node metastases in 56% of the patients. Our data indicate that systematic LNE of clinical negative LN in patients with AOC and complete resection should be omitted to reduce post-operative morbidity and mortality. Clinical trial information: NCT00712218.

5501 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20. *First Author: Andreas Du Bois, AGO and Kliniken Essen Mitte, Essen, Germany*

Background: The role of secondary cytoreductive surgery in recurrent ovarian cancer (OC) has not been defined by level-1 evidence. **Methods:** Pts with OC and 1st relapse after 6+ mos platin-free interval (TFIp) were eligible if they presented with a positive AGO-score (PS ECOG 0, ascites ≤500 ml, and complete resection at initial surgery) and were randomized to 2^{nd}-line chemotherapy alone vs cytoreductive surgery followed by chemo. Chemo regimens were selected according to the institutional standard. We report here results of the predetermined interim analysis. **Results:** 407pts were randomized 2010-2014. The TFIp exceeded 12 mos in 75% and 76% pts in both arms. 8.9% of 203 pts were operated despite of randomization to the no-surgery arm, whereas 6.9% of 204 pts in the surgery arm did not undergo operation. Complete resection was achieved in 67% of pts; 87% and 88% received a platinum-containing 2^{nd}-line therapy. Median PFS was 14 mos without and 19.6 mos with surgery (HR: 0.66, 95%CI 0.52-0.83, p<0.001). Median time to start of first subsequent therapy (TFST) was 21 vs 13.9 mos in favor of the surgery arm (HR 0.61, 95%CI 0.48-0.77, p=p<0.001). PFS-2 between 1^{st} and 2nd relapse equaled or even exceeded PFS-1 before 1^{st}relapse in 26% after surgery and only 16% without-surgery. Analysis of the primary endpoint OS is kept blinded due to immaturity and will be evaluated after extended follow-up (the observed pooled unblinded 2-YSR was 83% instead of the initially in the protocol assumed 55-66%). 60d mortality rates were 0 and 0.5% in the surgery and no-surgery arm. Re-laparatomies were performed in 7 pts (3.5%) in the surgery arm.With the exception of myelosuppression which occurred more frequently in the no-surgery arm no further significant differences were observed with respect to grade 3+ acute adverse events. **Conclusions:** Surgery in pts with 1st relapse of OC after a TFIp of 6+ mos and selected by a positive AGO-Score resulted in a clinically meaningful increase of PFS and TFST with acceptable treatment burden. Until final OS data will definitively define the role of secondary cytoreductive surgery it should at least be considered as valuable option in pts with a positive AGO-Score. Clinical trial information: NCT01166737.

5502 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

Final results of the international randomized PORTEC-3 trial of adjuvant chemotherapy and radiation therapy (RT) versus RT alone for women with high-risk endometrial cancer. *First Author: Stephanie M. De Boer, Department of Radiation Oncology, Leiden University Medical Center, Leiden, Netherlands*

Background: Women with high-risk endometrial cancer (HREC) are at increased risk of distant metastasis and endometrial cancer-related death. The randomized PORTEC-3 intergroup trial was initiated to investigate the benefit of adjuvant chemotherapy during and after radiotherapy (CTRT) versus pelvic radiotherapy (RT) alone for women with HREC. **Methods:** Women with HREC (FIGO stage I grade 3 with deep myometrial invasion and/or LVSI; stage II or III; or serous/clear cell histology) were randomly allocated (1:1) to RT (48.6 Gy in 1.8 Gy fractions) or CTRT (two cycles of cisplatin 50 mg/m² in week 1 and 4 of RT, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m² at 3-week intervals) with stratification for participating center, lymphadenectomy, stage, and histological type. The co-primary endpoints were overall survival (OS) and failure-free survival (FFS). The Kaplan-Meier method, log-rank test and Cox regression analysis were used for final analysis according to intention-to-treat. PORTEC-3 is registered with ISRCTN (ISRCTN14387080) and ClinicalTrials.gov (NCT00411138). **Results:** 686 women were included between 2006 and 2013. 13 patients with early informed consent withdrawal and 13 ineligible patients were excluded, leaving 660 patients in the analysis with a median follow up time of 60.2 months (IQR 47.1 – 72.9): 330 CTRT and 330 RT. Three- and five-year overall survival rates for CTRT vs. RT were 84.7% versus 83.7%, and 81.9% versus 76.6%, HR 0.78 [0.55-1.10], p = 0.16. Three- and five-year FFS rates were 83.5% (CTRT) versus 74.6% (RT) and 79.5% versus 70.8%, HR 0.68 [0.50-0.92], p = 0.014. Patients with stage III EC had lower 5-year FFS (69.6% vs 79.5% for stage I-II, p = 0.00124) and greatest absolute benefit of CTRT: 5-year FFS for stage III was 75.4% for CTRT vs 63.4% for RT, p = 0.0292. **Conclusions:** Adjuvant chemotherapy given during and after pelvic radiotherapy for treatment of HREC significantly improved 5-year FFS, with absolute and relative risk reductions of 9% and 30%, respectively, compared with RT alone. There was a non-significant 5% higher 5-year OS with CTRT; follow-up will continue to evaluate long-term OS. Clinical trial information: NCT00411138.

5503 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

A randomized phase III trial of docetaxel plus cisplatin or paclitaxel plus carboplatin compared with doxorubicin plus cisplatin as adjuvant chemotherapy for endometrial cancer at high risk of recurrence: Japanese Gynecologic Oncology Group study (JGOG2043). *First Author: Hiroyuki Nomura, Keio University School of Medicine, Tokyo, Japan*

Background: The superiority of chemotherapy regimens employing a taxane plus a platinum agent over standard therapy with doxorubicin plus cisplatin (AP) was recently demonstrated for advanced or recurrent endometrial cancer. This multicenter phase III trial evaluated the clinical benefit of taxane plus platinum agent regimens as adjuvant chemotherapy compared with AP for endometrial cancer patients at high risk of recurrence after surgery. **Methods:** Endometrial cancer patients having a high risk of recurrence and postoperative residual disease < 2 cm were randomly assigned (1:1:1) with stratification by FIGO stage and histologic grade to receive 6 cycles of doxorubicin (60 mg/m^2) plus cisplatin (50 mg/m^2) on day 1 (AP), docetaxel (70 mg/m^2) plus cisplatin (60 mg/m^2) on day 1 (DP) or paclitaxel (180 mg/m^2) plus carboplatin (AUC 6.0 mg/mL x minute) on day 1 (TC) every 3 weeks as adjuvant chemotherapy. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), adverse events, and tolerability. **Results:** From November 2006 to January 2011, 788 patients were enrolled from 118 institutions in Japan and were eligible for evaluation. The proportion of patients receiving 6 cycles was 80% for AP, 83% for DP, and 76% for TC, and tolerability of the regimens showed no significant difference. After a median follow-up period of 7.0 years, there was no statistical difference of PFS (P=0.1246) or OS (P=0.6734) among the 3 groups. The 5-year PFS rate was 74.9% for AP, 80.9% for DP, and 74.7% for TC, while the 5-year OS rates were 84.3%, 89.3%, and 88.4%, respectively. **Conclusions:** There was no significant difference of survival among patients receiving AP, DP, or TC as adjuvant chemotherapy for endometrial cancer. Since each regimen showed adequate tolerability, taxane plus platinum agent regimens may be a reasonable alternative to AP. Clinical trial information: UMIN000000522.

5504 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. *First Author: Antoine Hollebecque, Gustave Roussy Cancer Institute, Villejuif, France*

Background: Treatment options for cervical, vaginal, and vulvar (GYN) cancers are limited after first-line therapy. Human papillomavirus (HPV) infection is associated with squamous cell carcinomas of the cervix (≥90%) and vulva/vagina (40–70%), and may elicit an immune reaction. Programmed death (PD)-1 and its major ligand PD-L1 are expressed in GYN cancers and inhibit immune responses. Nivolumab disrupts PD-1–mediated signaling, restoring antitumor immunity. **Methods:** In CheckMate 358 (NCT02488759), an ongoing multicohort study of 5 virus-associated cancers, PD-L1–unselected adults with R/M GYN cancers, ECOG PS 0–1, and ≤2 prior systemic therapies for R/M disease were eligible to receive nivolumab 240 mg every 2 weeks until progression or unacceptable toxicity. Primary endpoints were objective response rate (ORR) and safety; secondary endpoints were duration of response (DoR), progression-free survival (PFS), and overall survival (OS). **Results:** Of 24 treated patients (pts), 19 had cervical and 5 had vaginal or vulvar cancer; median age was 51 y. At a median follow-up of 31 wks (range: 6–38), ORR was 20.8% (Table), and disease control rate (ORR + SD) was 70.8%. All responses were in pts with cervical cancer (ORR, 26.3%) and were observed regardless of PD-L1 or HPV status or number of prior R/M therapies. Median PFS was 5.5 mo (95% CI: 3.5, NR); median OS was NR. **Conclusions:** Nivolumab demonstrated encouraging clinical activity in pts with cervical cancer and a manageable safety profile in virus-associated GYN cancers, supporting further evaluation in these pts. Updated clinical and biomarker data to be presented. Clinical trial information: NCT02488759.

Response and safety.

		Prior systemic R/M therapies	
	Response-evaluable pts (N = 24)	0 (n = 7)	≥1 (n = 17)
Best overall response, n (%)			
Complete response	1 (4.2)	0	1 (5.9)
Partial response	4 (16.7)	2 (28.6)	2 (11.8)
Stable disease (SD)	12 (50.0)	3 (42.9)	9 (52.9)
Progressive disease	7 (29.2)	2 (28.6)	5 (29.4)
ORR, % (95% CI)	20.8 (7, 42)	28.6 (4, 71)	17.6 (4, 43)
Time to response, median (range), mo	5.3 (1.9, 7.1)		
DoR, median, mo	NR		
Treatment-related adverse events, %			
Any grade	70.8		
Grade 3–4	12.5		

NR = not reached.

5505 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. *First Author: Daniela Matei, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Patients with stage III/IVA uterine cancer (UC) carry high risk of systemic and local recurrence. Chemotherapy was shown to reduce systemic recurrence, however the risk of local failure remains high. **Methods:** The primary endpoint of this open label, randomized phase III trial was to determine if treatment with cisplatin and volume-directed radiation followed by carboplatin and paclitaxel for 4 cycles (C-RT, experimental arm) reduces the rate of recurrence or death (i.e., increases recurrence-free survival, RFS) when compared to carboplatin and paclitaxel for 6 cycles (CT, control arm) in patients with stages III-IVA (<2 cm residual disease) or FIGO 2009 stage I/II serous or clear cell UC and positive cytology. Secondary objectives were assessment of overall survival (OS), acute and late toxicities, and quality of life. A 28.5% reduction in the rate of recurrence or death was considered significant. Treatment randomization and analysis were stratified by gross residual tumor and age. **Results:** Between 6/2009 and 7/2014, 813 patients were enrolled and randomized (407 C-RT and 406-CT). Of those, 733 were eligible (344 C-RT and 360 CT), and 680 received the trial intervention (333 C-RT and 347 CT). Median follow up is 47 months. Patients characteristics were balanced between arms. There were 201 (58%) > grd 3 toxicity events in the C-RT arm and 227 (63%) in the CT arm. The most common > grd 3 events were myelosupression (40% vs. 52%), gastrointestinal (13% vs. 4%), metabolic (15% vs. 19%), neurological (7% vs. 6%), infectious (4% vs. 5%). Treatment hazard ratio for RFS was 0.9 (C-RT vs. CT; CI 0.74 to 1.10). C-RT reduced the incidence of vaginal (3% vs. 7%, HR = 0.36, CI 0.16 to 0.82), pelvic and paraaortic recurrences (10% vs. 21%, HR=0.43, CI 02.8 to 0.66) compared to CT, but distant recurrences were more common with C-RT vs. CT (28% vs. 21%, HR 1.36, CI 1 to 1.86). The analysis is premature for OS comparison. **Conclusions:** Although C-RT reduced the rate of local recurrence compared to CT; the combined modality regimen did not increase RFS in optimally debulked, stage III/IVA UC. Clinical trial information: NCT00942357.

5506 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Overall survival results of ICON6: A trial of chemotherapy and cediranib in relapsed ovarian cancer. *First Author: Jonathan A. Ledermann, University College London Cancer Institute, London, United Kingdom*

Background: ICON6 is a three-arm double-blind, placebo-controlled phase 3 trial of cediranib in platinum-sensitive relapsed ovarian cancer (NCT00532194). The primary analysis (Ledermann et al Lancet 2016) showed a significant ($p < 0.0001$), 2.3 month extension in progression-free survival (PFS) using cediranib with chemotherapy and as maintenance compared to chemotherapy and placebo. We present the final overall survival (OS) results. **Methods:** The trial was originally designed to recruit 2000 patients with OS as the primary endpoint. AstraZeneca discontinued cediranib development in Sep 2011, leading to an unplanned redesign prior to analysis. The sample size was reduced and primary outcome became PFS, comparing two arms, placebo (A) to cediranib given with chemotherapy and as maintenance (C). In arm B cediranib was given with chemotherapy followed by placebo maintenance. Analysis of PFS was performed on a sample size of 456 patients receiving a 20mg dose of cediranib. At the primary analysis, 52% patients had died; this mature OS analysis was performed after 85% patients died. **Results:** The OS analysis was performed at a median 25.6 months follow up; 102/118 (86%) died in A and 140/164 (85%) in C. In A the median survival was 19.9 months (95% CI: 17.4, 26.5) and in C 27.3 months (24.8, 33.0). Using the logrank test the Hazard Ratio estimate was 0.85 (0.66, 1.10) in favour of cediranib ($p = 0.21$). Evidence of non-proportionality of the survival curves was observed ($p = 0.0029$), so we measured the Restricted Mean Survival Time as an alternative to the median. Over 6 years, there was a 4.8 month (-0.1, 9.8) increase in time to death in C compared to A, from 29.4 to 34.2 months. The mean for arm B (32.0 months) was consistent with a benefit of increased use of cediranib. **Conclusions:** Cediranib has demonstrated a significant effect in increasing PFS. The mature survival analysis (85%) shows an improvement in median OS of 7.4 months, and an incremental benefit with increased cediranib use. The previously published significant PFS benefit coupled with the increase in OS highlights the potential value of cediranib in platinum-sensitive recurrent ovarian cancer. Further exploration of cediranib in this setting is underway. Clinical trial information: NCT00532194.

5507 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Health-related quality of life (HRQOL) and patient-centered outcomes with maintenance olaparib compared with placebo following chemotherapy in patients with germline (g) BRCA-mutated (m) platinum-sensitive relapsed serous ovarian cancer (PSR SOC): SOLO2 phase III trial. *First Author: Michael Friedlander, UNSW Clinical School, Prince of Wales Hospital, Randwick, Australia*

Background: The median PFS after chemotherapy in PSR SOC is less than 6 months in many patients. In SOLO2 (ENGOT Ov-21; NCT01874353), maintenance olaparib (O) given after response to chemotherapy resulted in a significant improvement in PFS vs placebo (P) in patients with g*BRCA*m PSR SOC (hazard ratio [HR] 0.30, 95% CI 0.22, 0.41; $P<0.0001$; median 19.1 vs 5.5 months; 63% data maturity; Pujade-Lauraine *et al*. SGO 2017). Our *a priori* hypothesis was that maintenance therapy with O would not negatively impact HRQOL compared with P and would be associated with additional patient-centered benefits to support the prolongation of PFS, the primary endpoint of SOLO2. **Methods:** HRQOL was evaluated by the Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index (FACT-O TOI) in all 295 patients. This measures functional and physical well-being and symptoms, including adverse events. Change from baseline in FACT-O TOI score during the first 12 months was the primary HRQOL analysis (mixed model repeated measures). Secondary planned analyses included duration of 'good quality of life' by time without symptoms of disease or toxicity (TWiST) and quality-adjusted PFS (QAPFS; a single measure of PFS and HRQOL outcomes). **Results:** There was no significant detrimental effect of O vs P on HRQOL analyzed by change from baseline in TOI score (–3.1 vs –2.9, respectively, difference (O minus P) –0.2; 95% CI –2.4, 2.1; $P=0.88$). There was a significant improvement for patients on maintenance O in TWiST (13.5 vs 7.2 months, difference 6.3; 95% CI 2.9, 8.6; $P<0.001$) and QAPFS (mean 14.0 vs 7.3 months for O and P, respectively, difference 6.7; 95% CI 5.0, 8.5; $P<0.0001$). **Conclusions:** Maintenance O did not detrimentally impact HRQOL relative to P. The significant improvement in PFS with O was associated with additional patient-centered benefits, including a longer duration without symptoms of disease or treatment toxicity and longer QAPFS. Clinical trial information: NCT01874353.

5508 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Phase II randomized trial of neoadjuvant (NA) chemotherapy (CT) with or without bevacizumab (Bev) in advanced epithelial ovarian cancer (EOC)þ (GEICO 1205/NOVA TRIAL). *First Author: Yolanda Garcia Garcia, Hospital Parc Tauli Sabadell, Sabadell, Spain*

Background: First line carboplatin(C)-paclitaxel(P) and Bev has proved to be an active combination after primary debulking surgery and improve overall survival in sub-optimal resected advanced EOC patients (pts). However, the role of Bev in the NA setting has not been well defined yet. **Methods:** We performed a phase II randomized open label multicentric study in pts with high grade serous or endometrioid EOC, FIGO stage III-IV, ECOG 0-2, considered unresectable in whom NA CT and interval debulking surgery (IDS) were planned. Main exclusion criteria were intestinal occlusion and contraindication for Bev. Pts were randomized to 4 courses of triweekly C AUC 6 and P 175 mg/m2 iv alone or with at least 3 courses of Bev 15 mg/kg i.v. every 3w in experimental arm. The primary endpoint was complete macroscopic response (CMR) rate at IDS. Secondary objectives were safety, surgical feasibility, optimal surgery rate (OSR), RECIST 1.1 and CA-125 GCIG response rate. Sample collection for translational research was taken at diagnosis and IDS. After surgery pts in both arms completed 3 additional cycles of CT and Bev, followed by maintenance Bev up to 15 mo. **Results:** Sixty-eight out of seventy-one evaluable pts. Clinical pts characteristics were well balanced, median age 60.0 y.o and a 33.8% stage IV. No differences in CMR were found at IDS (2/33 Control and 2/35 Bev). Bev arm was favoured in rate of surgical feasibility (66.7 vs 88.6%, p = 0.029), while no differences were found in OSR (63.6 vs 65.7%, p = 0.858) and in number of pts considered unresectable at time of IDS (2 vs 0). Median time from IDS to restarting Bev was 7.1 w. Median PFS was 20.3 mo in both arms, 20.13 mo in control arm and 20.36 mo in Bev arm, HR: 1.14 (IC 95%, 0.656 - 1.994). There were lower rates of serious adverse events (grade 3-4) in Bev arm (69.7 vs 42.9%, p = 0.026). 8 pts presented AE of special interest in Bev arm (3G2 proteinuria, 1G2/1G3 hypertension, 1G3 entero-vaginal fistulae, 1G3 entero-cutaneous fistulae, 1G3 deep venous thrombosis, 1G2 bleeding, 1G1 surgical dehiscence). **Conclusions:** NACT with Bevacizumab was feasible and improved the surgical outcomes at IDS in pts initially considered unresectable. Clinical trial information: 2012-003883-31.

5509 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM

A novel genomic rearrangement signature to predict poor survival among women with high grade serous ovarian cancer. *First Author: Robert Tyler Hillman, MD Anderson Cancer Center, Houston, TX*

Background: Resistance to platinum-based chemotherapy is a major cause of disease progression and mortality among women with high grade serous ovarian cancer (HGSOC). It is not known whether patterns of genomic rearrangement are predictive of clinical outcome in HGSOC. **Methods:** This was a retrospective cohort analysis of whole genome sequences from 80 HGSOC tumors. Genomic rearrangements were identified and categorized by size and type (inversion, duplication, deletion, or translocation). Non-negative matrix factorization was then used to extract rearrangement signatures. Wilcoxon rank-sum test was used for comparison of continuous variables. Univariate and multivariate analyses were performed using Cox proportional hazards models. **Results:** A rearrangement signature characterized by 10 kilobase to 10 megabase duplications and deletions was identified. The median overall survival (OS) was 22.5 months (95% CI, 20.1 to 33.5 months) in the Sig-High group versus 46.0 months (95% CI, 27.7 to 80.6 months) in the Sig-Low group (hazard ratio, 2.13; 95% CI, 1.27 to 3.55; P=0.004). Exploration of clinical variables showed a significantly higher median signature contribution in platinum-resistant disease than platinum-sensitive disease (20.0% vs 9.1%, p=0.007). Multivariate analysis showed a hazard ratio for death of 2.1 associated with the Sig-High group (Table). Validation of this signature was performed using HGSOC copy number data from the Cancer Genome Atlas. In this cohort, the median OS was 38.8 months (95% CI, 36.7 to 44.5 months) in the Sig-High group versus 49.5 months (95% CI, 45.2 to 56.3 months) in the Sig-Low group (hazard ratio, 1.44; 95% CI, 1.14 to 1.82; P=0.024). **Conclusions:** A genomic rearrangement signature is associated with chemoresistance and poor prognosis in HGSOC. Prediction of poor survival outcomes could allow early identification of women who may be candidates for clinical trials.

Multivariate model of OS.

	Hazard Ratio	95% Confidence Interval	p value
Age at Diagnosis	1.01	0.98-1.04	0.53
Initial Stage	0.55	0.25-1.24	0.15
Optimal Tumor Debulking	0.87	0.49-1.53	0.62
Germline BRCA1/2 Mutation	0.80	0.37-1.72	0.57
Rearrangement Signature Group	2.10	1.19-3.70	0.01

5510 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM

Is the mesenchymal transition subtype more responsive to dose dense taxane chemotherapy combined with carboplatin (ddTC) than to conventional taxane and carboplatin chemotherapy (TC) in high grade serous ovarian carcinoma? A survey of Japanese Gynecology Oncology Group study (JGOG3016A1). *First Author: Ryusuke Murakami, Department of Gynecology and Obstetrics, Graduate School of Medicine, Kyoto University, Kyoto, Japan*

Background: High-grade serous ovarian cancer (HSOC) was divided into four transcriptome subtypes (i.e. Mesenchymal, Immunoreactive, Proliferative, and Differentiated). We established a new pathological classification based on these transcriptome subtypes: Mesenchymal Transition (MT) type, Immune Reactive (IR) type, Solid and Proliferative (SP) type and Papillo-Glandular (PG) type (PMID: 26993207). The MT type has the worst prognosis. We discovered the Mesenchymal transcriptome subtype might be sensitive to taxane chemotherapy. Therefore, we hypothesized that the MT type, which represents the Mesenchymal transcriptome subtype, may respond better to dose dense taxane combined with carboplatin (ddTC) rather than to conventional taxane and carboplatin (TC). **Methods:** We collected 207 HSOC slides registered in the Japanese Gynecology Oncology Group 3016 (JGOG3016) study. Two of the authors, R.M. and I.K., classified the samples into the four pathological subtypes (n=201). We categorized the patients into two groups based on the treatment they received: ddTC (n=95) or TC (n=106). Progression free survival (PFS) was compared between the two groups for each pathological subtype. **Results:** Among the MT patients, the ddTC group had a significantly better PFS than the TC group (n= 30 vs 42, median survival: 1.8 vs 1.2 years, p=0.01). Among the SP patients, the ddTC group had better PFS than the TC group, even though the difference was not statistically significant (n=22 vs 27, median survival: 3.2 vs 1.4 years, p=0.08). In contrast, among the IR patients, the two groups showed no significant difference in PFS (n=16 vs 16, median survival: 5.2 vs 5.8 years, p=0.64). The PG patients also showed no significant difference in PFS between the two groups (n=27 vs 21, median survival: 1.5 and 1.7 years, p=0.64). **Conclusions:** The HSOC of MT type is more responsive to ddTC than to TC. This new pathological classification reflecting HSOC transcriptome subtypes leads to individualization of chemotherapy treatments.

5511 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM

Evaluation of BRCA1/2 and homologous recombination defects in ovarian cancer and impact on clinical outcomes. *First Author: Melinda S. Yates, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Recent studies show that germline or somatic BRCA1/2 mutations and homologous recombination (HR) defects can be used to predict response to PARP inhibitors in recurrent ovarian cancer. However, the impact of defects in BRCA1/2 and HR genes on overall clinical outcomes are not yet defined for patients undergoing neoadjuvant chemotherapy (NACT) versus upfront surgical debulking (USD). **Methods:** Previously untreated ovarian cancer patients were prospectively enrolled under approved IRB protocol. Germline and tumor BRCA1/2 mutation testing and methylation were analyzed when sufficient tumor and blood was available. Mutation in 21 additional hereditary cancer genes (including HR genes) was also evaluated. Tumor HR defects were scored on LOH, telomeric allelic imbalance, and large-scale state transitions (as previously described). Presence of germline or somatic BRCA1/2 mutations, BRCA1 methylation, HR score $\geq$42, or germline mutation in other HR genes were defined together as HRD positive. **Results:** Of 299 enrolled patients, 129 (43%) received USD and 170 (57%) received NACT. Patients receiving USD had better outcomes compared to NACT, including overall survival (OS, 65.8 vs 45.2 months, p = 0.0003) and event free survival (EFS, 24.8 vs 15.6 months, $p < 0.0001$). In the overall cohort, EFS was significantly longer for HRD positive patients vs HRD negative (20.5 vs 16.3 months, p = 0.0268). Patients with somatic and germline BRCA1/2 mutations had longer OS vs BRCA1/2 negative (65.3 vs 46.1 months, p = 0.0403). Overall outcomes were worse in NACT compared to USD, but impact of BRCA1/2 mutations and HR defects was stronger in this group. NACT patients with any HR defect had longer EFS (19.7 vs 14.5 months, p = 0.0247). NACT patients with BRCA1/2 germline mutations had longer OS (65.3 vs 38.3 months, p = 0.0230). NACT patients with BRCA1/2 germline mutation had longer EFS (22.6 vs 14.6 months, p = 0.0047). OS and EFS in USD patients were significantly changed based on only debulking status; mutation or HR status did not have a statistically significant effect. **Conclusions:** While HR defects and BRCA1/2 mutations influence overall outcomes for ovarian cancer patients, the impact is stronger in NACT compared to USD.

5512 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM

Comprehensive genomic profiling (CGP) with loss of heterozygosity (LOH) to identify therapeutically relevant subsets of ovarian cancer (OC). *First Author: Julia Andrea Elvin, Foudation Medicine, Inc., Cambridge, MA*

Background: Defective homologous recombination DNA repair (HRD) is associated with high grade serous (OC-S) histology, longer survival, and platinum (Pt) or PARP inhibitor (PARPi) sensitivity. HRD causes LOH, a pattern of allelic imbalance detectable by CGP. *BRCA*wt OC-S can have LOH and respond to PARPi, while non-serous (OC-NS) or difficult to classify (OC-NOS) OC are often less responsive to Pt-based therapy. Integrating multiple genomic features derived from CGP may define other therapeutically relevant subsets. **Methods:** DNA from FFPE tumor tissue obtained during clinical care for 4114 advanced OC was analyzed for all classes of genomic alterations (GA) by hybrid-capture, next-generation sequencing of up to 315 genes. Tumor subtype counts were OC-S, n = 2770; OC-NOS, n = 807; OC-NS, n = 537 (mucinous, clear cell, endometrioid, neuroendocrine, carcinosarcomas, and low grade serous). Algorithms evaluated microsatellite instability (MSI), tumor mutation burden (TMB; TMB-H $\geq$ 10 muts/Mb), and LOH (LOH-H $\geq$ 14, LOH-L $<$ 14). **Results:** 706/4114 (17.2%) OC had $\geq$1 deleterious *BRCA* GA, OC-S (18.7%) more so than OC-NS (4.4%). Median LOH score for OC-S was significantly higher than OC-NS (12.8 vs. 5.8, $p < 0.05$). *BRCAmut* OC-S and OC-NS were similarly LOH-H (86% and 75%), unlike *BRCAwt* OC-S (38.4%) or OC-NS (18%). Regardless of LOH, similar co-occurrence of *MYC* (26.9%) and/or NF1 (19%) GA was seen in *BRCAmut* OC. *BRCAwt* LOH-L OC commonly had *CCNE1* (19.7%), *KRAS* (19%), *PIK3CA* (16.2%), *AKT2* (7.4%), *ERBB2* (4.7%), or *BRAF*(3.3%) GA. Frequency of TMB-H was 2.5% and MSI-H 1%. Correlation of GA with treatment, clinical histories and outcomes for some patients will be presented. **Conclusions:** *BRCAmut* or OC-S are commonly LOH-H; ~1 in 5 *BRCAwt* OC-NS, including carcinosarcomas and mucinous, are also LOH-H. Genes co-mutated in late stage LOH-H OC may be linked to treatment resistance. CGP of this large OC cohort reveals molecular, rather than histologic, patient subsets that may benefit from PARPi (46.2% *BRCA*mut or LOH-H), targeted therapy ($>$ 50% *BRCA*wt LOH-L, excluding *TP53*) or immunotherapy (3.5% TMB-H or MSI-H), providing more support for insurance coverage and integration into OC clinical trials.

5513 Poster Discussion Session; Displayed in Poster Session (Board #335), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Pembrolizumab in patients (pts) with PD-L1–positive (PD-L1$^+$) advanced ovarian cancer: Updated analysis of KEYNOTE-028. *First Author: Andrea Varga, Institut Gustave Roussy, Villejuif, France*

Background: Overexpression of the PD-1 ligand PD-L1 has been demonstrated in ovarian cancer and may hinder an effective antitumor immune response. A preliminary analysis of the ovarian cancer cohort of the KEYNOTE-028 study (NCT02054806) suggested that the PD-1 inhibitor pembrolizumab has promising antitumor activity in pts with PD-L1$^+$advanced ovarian cancer. An updated analysis of the ovarian cancer cohort based on 15.5 months of follow-up is presented. **Methods:** Key eligibility criteria for the ovarian cohort of this nonrandomized, multicohort phase Ib trial were advanced ovarian epithelial, fallopian tube, or primary peritoneal carcinoma; failure of prior therapy; PD-L1 positivity defined as membranous staining on $\geq$1% of tumor and associated inflammatory cells or positive staining in stroma; and ECOG PS 0/1. Pembrolizumab (10 mg/kg every 2 wk) was given for $\leq$2 y or until confirmed progression/unacceptable toxicity. Response was assessed per RECIST v1.1 by investigators every 8 wk for the first 6 mo and every 12 wk thereafter. Primary end points were safety, tolerability, and confirmed ORR. **Results:** 26 pts (median age, 57.5 y) were enrolled; 61.5% were white, 38.5% received $\geq$5 therapies for recurrent/metastatic disease, and 53.8% received prior neoadjuvant/adjuvant therapies. As of the October 10, 2016, data cutoff, the median follow-up duration was 15.5 mo (range, 2.4-30.8 mo). 1 pt had a complete response and 2 had partial responses; 6 pts had stable disease as best response. ORR was 11.5% (95% CI, 2.4%-30.2%). Tumor reduction was observed in 6/26 (23.1%); all 3 patients who responded completed 2 years of treatment. Median duration of response was not reached (range, 24.9+ to 26.5+ mo). Median (95% CI) PFS and OS were 1.9 mo (1.8-3.2 mo) and 13.1 mo (6.7-17.5 mo) respectively. Treatment-related AEs occurred in 73.1% of pts, and the most common were arthralgia (19.2%), nausea (15.4%), pruritus (15.4%), rash (11.5%), and diarrhea (11.5%). 1 patient had a grade 3 drug-related adverse event (transaminase increased). **Conclusions:** With 15.5 mo of follow-up, pembrolizumab continued to be well tolerated and demonstrated durable antitumor activity in pts with advanced ovarian cancer. Clinical trial information: NCT02054806.

5514 Poster Discussion Session; Displayed in Poster Session (Board #336), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Pembrolizumab for previously treated advanced cervical squamous cell cancer: Preliminary results from the phase 2 KEYNOTE-158 study. *First Author: Jan H.M. Schellens, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: In the phase 1b KEYNOTE-028 study, pembrolizumab showed promising activity as monotherapy in patients with advanced cervical cancers that expressed PD-L1. As part of the ongoing, multicohort, phase 2 KEYNOTE-158 study (NCT02628067), we assessed the antitumor activity of pembrolizumab in a larger cohort of patients with previously treated, advanced cervical squamous cell cancer who were enrolled without regard to tumor PD-L1 or other tumor biomarker expression. **Methods:** Key eligibility criteria for this cohort included age $\geq$18 years, histologically or cytologically confirmed advanced cervical squamous cell cancer, progression on or intolerance to $\geq$1 line of standard therapy, ECOG PS 0 or 1, and provision of a tumor sample for biomarker analysis. Patients received pembrolizumab 200 mg Q3W for 2 years or until progression, intolerable toxicity, or physician or patient decision. Clinically stable patients with progression could remain on treatment until progression was confirmed on subsequent assessment. Tumor imaging was performed every 9 weeks for the first 12 months and every 12 weeks thereafter. PD-L1 positivity was evaluated retrospectively by IHC and was defined as a combined positive score $\geq$1%. Primary end point was ORR assessed per RECIST v1.1 by independent central radiologic review. Planned enrollment is ~100 patients. This efficacy analysis includes patients who had $\geq$18 weeks of follow-up as of Oct 19, 2016. **Results:** Among the first 47 patients with advanced cervical cancer who enrolled, ORR was 17% (95% CI, 8%-31%), with 3 confirmed and 5 unconfirmed responses. 41 (87%) patients had PD-L1–positive tumors, and ORR was independent of PD-L1 status. Among the 15 patients who had $\geq$27 weeks of follow-up, ORR was 27% (95% CI 8%-55%), with 3 confirmed responses and 1 unconfirmed response. Safety and updated efficacy data for 83 patients with $\geq$27 weeks of follow-up will be available for presentation. **Conclusions:** Preliminary data from KEYNOTE-158 suggest that pembrolizumab has promising antitumor activity in patients with previously treated advanced cervical squamous cell cancer. The observed ORR with pembrolizumab appears to increase with longer follow-up. Clinical trial information: NCT02628067.

5515 Poster Discussion Session; Displayed in Poster Session (Board #337), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Aromatase inhibitor maintenance therapy in high grade advanced ovarian cancer to delay first recurrence. *First Author: Alexandra Maria Knipprath-Mészáros, Gynecological Cancer Centre, University Hospital Basel, Basel, Switzerland*

Background: Ovarian cancer (OC) is mostly diagnosed as G3 serous advanced stage disease with survival of only 20% in 5 years. Maintenance therapy after 1st line chemotherapy is increasingly used, particularly with Bevacizumab or PARP inhibitors. However, the effect of antihormonal treatment in breast cancer but also in relapsed gynecological cancers has been shown. Also in low grade OC, data are highly supportive of antihormonal treatment. In a previous study of ours, also high grade serous cancers express high amounts of estrogen receptor (ER). The aim of this study was to analyze whether a maintenance antihormonal therapy in advanced OC adds a benefit in relation to the time of recurrence. **Methods:** All newly diagnosed G3 FIGO III/IV OC cases at our Hospital were assessed prospectively for ER expression. Patients with positive ER status ($>$ 10%) were treated as maintenance therapy with Letrozol 2.5mg 1x/d or not. Progression free survival was recorded and analyzed according to Kaplan-Meier. Patients with macroscopic residual disease post surgery receiving Bevacizumab maintenance treatment were also included. **Results:** We identified 51 patients with G3 serous OC FIGO III/IV expressing ER. Hereby, 24 patients received and 27 patients did not receive Letrozol after adjuvant chemotherapy. Time to progression ranged from 4 to 121 months. The use of Letrozol was associated with a significant prolonged progression free interval. After 12 months, only 65% of women in the control group vs 84% in the Letrozol group were progression-free. After 24 months, the effect was even stronger (46% in the control group vs 74% with Letrozol ($p = 0.02$)). Within the subgroup of patients with residual disease treated with Bevacizumab a similar effect was seen with 41% of patients progression free after 12 months vs 89% when taking Letrozol in addition to Bevacizumab. **Conclusions:** The use of Letrozol as a maintenance therapy after the 1st line treatment in G3 advanced stage serous OC patients was associated with a longer recurrence free interval in our cohort. These findings warrant a randomized controlled trial comparing all existing maintenance regimen as this might have a major influence on cost development in OC treatment.

5516 Poster Discussion Session; Displayed in Poster Session (Board #338), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Evaluating the cost-effectiveness of current FDA-approved PARP inhibitors for the treatment of recurrent ovarian cancer. *First Author: Juliet Elizabeth Wolford, University of California, Irvine, Orange, CA*

Background: Unlike approved IV administered therapies, Medicare is under no obligation to cover prescription medicines. We sought to evaluate the cost-effectiveness of the two FDA-approved orally administered PARP inhibitors (PARPi), olaparib and rucaparib. **Methods:** A Markov model was created in TreeAge Pro 2015 with nodes in the chain allowing patients to transition through response, hematological complications, non-hematological complications, progression, and death. Separately, the PARP inhibitors were compared with IV administered drugs approved for recurrent ovarian cancers including platinum-based, non-platinum, and bevacizumab-based regimens. Toxicity and mean PFS rates for the different agents were obtained from registration trial data. Costs of IV chemotherapy, managing toxicities, infusions, and supportive care were estimated using 2015 Medicare data. Incremental cost-effectiveness ratios (ICER) were calculated and survival was reported in quality adjusted life months. **Results:** Platinum-based combinations were the most cost-effective at $1,672/PFS mo as compared to non-platinum agents ($6,688/mo), bevacizumab-containing regimens ($12,482/mo), olaparib ($13,3731/mo), and rucaparib ($14,034/mo). Considering a cost of $114,478 for olaparib and $137,068 for rucaparib prior to progression, costs associated with PARPi were 7.1 to 8.3X more than platinum combinations. To better compare the registration trial data to PARPi data, probability was adjusted to 2nd line for rucaparib, revealing it's ICERs' of per month of life added to be $26,997 for bevacizumab, $17,757 for non-platinum, and $79,585 for platinums. Using the adjusted-to-2nd-line probabilities for olaparib, exhibited ICERs were $16,549 for bevacizumab, $25,637 for non-platinums and $72,083 for platinums. **Conclusions:** The high costs of PARPi were not balanced by costs of infusion and managing toxicities of IV drugs typically associated with lower response rates and shorter PFS in the recurrent space. Balancing incremental clinical benefit with novel therapies remains problematic and could widen disparities among those with limited access to care.

5517 Poster Discussion Session; Displayed in Poster Session (Board #339), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Efficacy of niraparib on progression-free survival (PFS) in patients (pts) with recurrent ovarian cancer (OC) with partial response (PR) to the last platinum-based chemotherapy. *First Author: Mansoor Raza Mirza, Nordic Society of Gynecologic Oncology (NSGO) and Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark*

Background: Therapeutic paradigms for recurrent OC vary by geography. Maintenance following response to platinum-based chemotherapy (Plat) is standard in Europe, whereas in the US maintenance is considered following complete response (CR) vs treatment for partial response (PR). Niraparib is a highly selective PARP 1/2 inhibitor (PARPi). In preclinical studies it concentrates in the tumor relative to plasma, delivering > 90% durable PARP inhibition and antitumor effects. Niraparib demonstrated significantly longer PFS vs placebo (P) in pts with recurrent OC following a CR or PR to Plat in the randomized, controlled, double-blind phase 3 ENGOT-OV16/NOVA trial. **Methods:** Pts with recurrent OC, no prior PARPi use, ≥2 prior courses of Plat, and response to most recent Plat were eligible. Pts were assigned to 1 of 2 cohorts on the basis of g*BRCA* testing (g*BRCA*mut or non-g*BRCA*mut) and randomized 2:1 within each cohort to niraparib 300 mg or P qd until progressive disease (PD). Randomization occurred up to 8 weeks after last dose of the most recent Plat. Pts were stratified by time to progression after penultimate Plat (6 to < 12 months or ≥12 months), prior use of bevacizumab (yes/no), and response to most recent Plat (CR or PR). PFS was measured from time of randomization to death or earliest PD as assessed by independent review committee. **Results:** 49% of pts (niraparib: 67/138; P: 32/65) in the g*BRCA*mut and ~49% of pts (niraparib: 117/234 [50%]; P: 56/116 [48%]) in the non-g*BRCA*mut cohorts entered NOVA with a PR following their most recent Plat. At time of unblinding, 30 (45%) niraparib and 23 (72%) P pts in the g*BRCA*mut and 65 (56%) niraparib and 45 (80%) P pts in the non-g*BRCA*mut cohorts had PFS events. PFS hazard ratios (95% CI) were 0.24 (0.131–0.441) in g*BRCA*mut and 0.35 (0.230–0.532) in non-g*BRCA*mut cohorts for pts who had a PR to their most recent platinum regimen. This compared favorably to the overall NOVA study results, where PFS hazard ratios (95% CI) were 0.27 (0.173–0.410) in g*BRCA*mut and 0.45 (0.338–0.607) in non-g*BRCA*mut cohorts. **Conclusions:** Niraparib treatment provided significant benefit to pts with recurrent OC who achieved a PR following Plat. Clinical trial information: NCT01847274.

5518 Poster Discussion Session; Displayed in Poster Session (Board #340), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Adverse events (AEs) with maintenance olaparib tablets in patients (pts) with *BRCA*-mutated (*BRCA*m) platinum-sensitive relapsed serous ovarian cancer (PSR SOC): Phase III SOLO2 trial. *First Author: Jonathan A. Ledermann, University College London Cancer Institute, London, United Kingdom*

Background: In the SOLO2 trial (ENGOT Ov-21; NCT01874353), maintenance therapy with the PARP inhibitor olaparib significantly improved PFS vs placebo (PBO) in *BRCA*m PSR SOC pts (HR 0.30, 95% CI 0.22–0.41, *P*<0.0001; median 19.1 vs 5.5 months) and was well tolerated (Pujade-Lauraine *et al*, SGO 2017). We analyzed AEs in SOLO2, the first study in PSR SOC to use the olaparib tablet formulation. **Methods:** Pts with *BRCA*m PSR SOC, who were in response to platinum chemotherapy, were treated with olaparib (300 mg bid; tablets; n=195) or PBO (n=99) until progression. AEs were graded by CTCAE v4.0. **Results:** The most common AEs with olaparib – nausea, fatigue/asthenia, anemia, and vomiting – were largely grade 1–2, though anemia was the most common grade ≥3 AE. AEs of fatigue/asthenia, vomiting and nausea generally improved as treatment continued, though fatigue/asthenia and anemia could last for several months (table). Most AEs were manageable by supportive treatment, dose interruptions (olaparib, 45%; PBO, 18%) and dose reductions (olaparib, 25%; PBO, 3%). Discontinuation of olaparib due to AEs was minimal (11%); anemia and neutropenia were the only AEs leading to discontinuation of olaparib in >one pt. **Conclusions:** Most AEs experienced by pts receiving olaparib tablets in SOLO2 were low grade and manageable. Initial nausea, vomiting and fatigue generally improved with ongoing treatment. The majority of AEs first occurred within the first three months of treatment. AEs causing treatment discontinuation were rare and mainly hematological. Clinical trial information: NCT01874353.

	Nausea		Vomiting		Fatigue/asthenia		Anemia		Neutropenia	
	O	P	O	P	O	P	O	P	O	P
Pts with AE	148 (80)	33 (33)	73 (37)	19 (19)	128 (66)	39 (39)	85 (44)	8 (8)	38 (20)	6 (6)
Grade 3–4	5 (3)	0	5 (3)	1 (1)	8 (4)	2 (2)	38 (19)	2 (2)	10 (5)	4 (4)
First onset in 0-3 months	138 (71)	27 (27)	48 (25)	10 (10)	106 (54)	26 (26)	58 (30)	5 (5)	20 (10)	5 (5)
Median duration of first event, months*	1.72	0.43	0.07	0.07	5.78	2.04	2.79	2.60	0.95	0.69
Supportive treatment	79 (41)	9 (9)	17 (9)	7 (7)	7 (4)	1 (1)	34 (17)	1 (1)	5 (3)	2 (2)
Discontinuation	1 (1)	0	0	0	0	0	6 (3)	0	3 (2)	0

Values are n (%) unless otherwise stated; *Only uses AEs with a resolution date, n<total sample size; O, olaparib; P, PBO

5519 Poster Discussion Session; Displayed in Poster Session (Board #341), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase 3 trial of hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer. *First Author: Willemien Van Driel, Center for Gynecologic Oncology, Amsterdam, Netherlands*

Background: Cytoreductive surgery and systemic therapy are essential for newly diagnosed ovarian cancer. We conducted a multicenter phase 3 trial to study whether the addition of intraperitoneal chemotherapy under hyperthermic conditions (HIPEC) to interval cytoreductive surgery would improve outcome among patients receiving neo-adjuvant chemotherapy for stage III epithelial ovarian cancer. **Methods:** We randomly assigned patients who showed at least stable disease after three cycles of carboplatin (area under the curve 6) and paclitaxel (175 mg/m^2) to receive interval cytoreductive surgery with or without HIPEC using cisplatin (100 mg/m^2). Randomization was performed per-operatively and eligible patients had no residual mass greater than 2.5 mm. Three additional cycles of carboplatin and paclitaxel were given post-operatively. The primary endpoint was recurrence-free survival. Overall survival, toxicity, and quality-of-life were key secondary endpoints. **Results:** A total of 245 patients were randomly assigned to one of the two treatment strategies. In an intention-to-treat analysis, interval cytoreductive surgery with HIPEC was associated with longer recurrence-free survival than interval cytoreductive surgery alone (15 vs. 11 months, respectively; hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.49 to 0.86; P=0.003). At the time of analysis, 49% of patients were alive, with a significant improvement in overall survival favoring HIPEC (48 vs. 34 months; HR, 0.64; 95% CI, 0.45 to 0.91, P=0.01). The number of patients with grade 3-4 adverse events was similar in both treatment arms (28% vs. 24%, p=0.61). Quality-of-life analysis will follow. **Conclusions:** The addition of HIPEC to interval cytoreductive surgery is well tolerated and improves recurrence free and overall survival in patients with stage III epithelial ovarian cancer. Clinical trial information: NCT00426257.

5520 Poster Discussion Session; Displayed in Poster Session (Board #342), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer. *First Author: Myong Cheol Lim, National Cancer Center, Seoul, Republic of Korea*

Background: Cytoreductive surgery followed by taxane and platinum-based chemotherapy is standard treatment for advanced ovarian cancer. We compared results of randomly allocated HIPEC in primary advanced epithelial ovarian cancer who have optimal cytoreductive surgery in this prospective randomized multicenter trial. The study endpoint is to evaluate progression free survival (PFS) and overall survival (OS). **Methods:** 184 patients staged III and IV were randomly allocated to trial arm (HIPEC, cisplatin 75 mg/m^2, 90 min) or control arm (no HIPEC), intraoperatively based on residual tumor (size $<$1cm) from July 2010 to January 2016. The groups were well balanced according to the age, body mass index, performance status, stage, histology, serum CA125 level, and use of neoadjuvant chemotherapy (NAC) at study entry. **Results:** 184 pts (HIPEC, 92; control, 92) were included in this preplanned analysis. No mortality after surgery $\pm$ HIPEC was identified in both groups. Postoperative outcomes including extent of surgery, estimated blood loss, residual tumor, and hospitalization day were not different between both group, except operation time (487 vs. 404 min, $p<0.001$) due to HIPEC procedure. The most common adverse event was anemia: 67.4% in HIPEC and 50% in control group (p=0.025). The other toxicity common in HIPEC group is the elevation of creatinine (15.2% vs. 4.3%, p=0.026). There were no differences between both groups for transfusion (35.9 vs. 29.3, p=0.432), neutropenia (19.6 vs. 10.9%, p=0.151), and thrombocytopenia (9.8 vs. 3.3%, p=0.136). Two-year PFS was 43.2% and 43.5% and 5-year PFS was 20.9% and 16.0% in HIPEC and control group, respectively (p=0.569). Five-year OS was 51.0% and 49.4% in HIPEC and control group, respectively (p=0.574). In women who received NAC, the median PFS for HIPEC and control group were 20 and 19 months, respectively (log-rank test, p = 0.137) and the median OS for HIPEC and control group were 54 and 51 months, respectively (log-rank test, p = 0.407). In the subgroup with NAC, 2-year PFS was 37.2% in HIPEC group and 29.5% in control group and 5-year OS was 47.9% in HIPEC group and 27.7% in control group. After 20 months in PFS and 30 months in OS, two survival curves in women who received NAC showed the trend of gradual distinction, favoring HIPEC group. **Conclusions:** No mortality was identified and postoperative morbidities were not statistically different between two groups except anemia and creatinine elevation in HIPEC group. The survival analysis did not show the statistical superiority of the HIPEC arm. More follow-up is required to confirm the impact of HIPEC on long-term survival outcome in ovarian cancer, especially in NAC group. Clinical trial information: NCT01091636.

5521 Poster Discussion Session; Displayed in Poster Session (Board #343), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

The prognostic value of tumor residuals indicated by surgeon, by radiology or an integrated approach by surgeons' assessment and pre-chemotherapy CT-scan in patients with advanced ovarian cancer: An exploratory analysis of the AGO Study led Intergroup trial AGO-OVAR 12. *First Author: Florian Heitz, Department of Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany*

Background: Post-OP TR is a strong prognostic factor in AOC; the best prognosis is observed after complete resection (TR0). TR assessment is performed at the end of the surgery and may be exposed to personal bias. Pre-Chemo CT may improve post-OP assessment, however, it may also be prone to findings by post-OP tumor re-growth, tissue repair or scarring. **Methods:** Pts with FIGO IIB-IV AOC recruited into the double-blind randomized frontline AGO-OVAR12 trial were scheduled for baseline CT before the 1st chemo cycle. SA and RA of TR were compared. Additionally, a measurement of TR integrating both approaches were assessed (IA). For this IA information of surgical and path reports were reviewed by two of the authors. **Results:** 1355 pts had complete data for all 3 assessment methods. Of 689 pts with TR0 in SA, 497 (72%) and 539 (78%) had also TR0 pre-Chemo (RA and IA), but showed TR$>$0 in 192 (28%) and 150 pts (22%), respectively. Pts with SA defined TR0 had a similar median PFS of 27.6 mos compared to TR0 defined by RA (27.8 mos) and IA (28.9 mos). Pts with concordant TR0 (SA/ IA and SA/ RA) had a median PFS of 28.9 mos. In contrast, pts with discordant SA TR0 - RA TR$>$0 or SA TR0 - IA TR$>$0 showed inferior median PFS of 19.2 mos (HR: 1.89, 95%CI: 1.48-2.40; $p<0.0001$) and 16.9 mos (HR: 2.02, 95% CI: 1.57- 2.59; $p<0.0001$), respectively. Pts with concordant TR$>$0 had an even lower median PFS of 13.5 (SA and IA) and 12.9 mos (SA and RA). PFS of the experimental therapy or placebo dependent if SA, RA or IA were used, will be presented. **Conclusions:** Pre-Chemo CT provides information separating the group of pts with post-OP TR0 in pts with TR0 and pts with TR$>$ 0 pre-Chemo. The latter group showed PFS values in between those with surgically assessed post-OP TR0 and those with post-OP TR$>$ 0, forming a third prognostic group. Detailed analysis should evaluate to what extend tumor biology, surgical bias, or imperfect imaging contribute to the discrepancies. Integrating all this may lead to better definition of prognostic groups and the need for specific treatment strategies.

5522 Poster Discussion Session; Displayed in Poster Session (Board #344), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase II clinical and molecular trial of oral ENMD-2076 in clear cell ovarian cancer (CCOC): A study of the Princess Margaret phase II consortium. *First Author: Stephanie Lheureux, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: CCOC is a rare chemoresistant subtype of OC. ENMD-2076 is an oral multi-target kinase inhibitor with antiangiogenic/antiproliferative profile; selective activity against the mitotic kinase Aurora A and VEGFRs, FGFRs. **Methods:** This is a multi-center Phase II study of ENMD-2076 in pts with recurrent CCOC and prior platinum. Primary endpoints were ORR and 6-m PFS rate. Correlative analyses include ARID1A, PTEN expression by IHC and genome sequencing by custom capture library of 555 genes. **Results:** Completed study enrolled 40 pts – 37 evaluable, median age of 54 (39-78). 12 pts (31%) received prior radiation and 24 (62%), 11 (28%), 4 (10%) had 1, 2 or 3 lines of chemotherapy. Archival tissue was available for 36/37 pts. Best response was PR for 2 pts (1 unconfirmed), SD for 25 (68%) and PD for 10 (26%) pts. Median PFS was 3.7 months (m) (95%CI: 3.4-4.4). ENMD was well tolerated with main related AE: hypertension (21 pts - 8 G3), nausea (18 pts -1 G3) and diarrhea (17 pts - 4 G3). By IHC, median PFS (95%CI) in ARID1A loss (19 pts) was 4.1m (3.5-10.3) vs 3.6m (1.7-3.9) in ARID1A positive (17 pts) (p = 0.024). Whilst, by IHC, PTEN was loss in 20 pts; intact in 10 and heterogeneous in 6 pts; no difference in PFS was observed. By PI3KCA mutation status, median PFS (95% CI) in wild-type (WT) (12 pts) was 5m (3.4-19.3) vs 3.7m (167-4.4) in mutated group (20 pts) (p = 0.038). Molecular profiling showed variants in PI3KCA (27%), ARID1A (26%), TP53 (7%), BRIP1 (7%), ATM (11%), BRCA1 (5%), BRCA2 (3%), RAD50 (3%), PABL2 (1%), RAD51C (1%), FANCA (1%), CTNNB1 (3%).The patient with the longest treatment duration (22m) was PTEN WT, diploid PTEN, putative bi-allelic inactivation of ARID1A. **Conclusions:** The PFS at 6 months was 20% for the evaluable patients, 31% in ARID1A loss and 12% in ARID1A positive patients. Loss of ARID1A, a known negative prognostic factor, was correlated with better PFS on ENMD-2076. Additional molecular profiling of the baseline biopsy material is underway. Clinical trial information: NCT01914510.

5523 Poster Discussion Session; Displayed in Poster Session (Board #345), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Stage I ovarian immature teratomas: Is there a role for chemotherapy? *First Author: John K. Chan, Palo Alto Medical Foundation, San Francisco, CA*

Background: To determine the impact of chemotherapy on survival of patients with stage I ovarian immature teratomas. **Methods:** Data obtained from the National Cancer Database from 2004-2013. Kaplan-Meier methods and multivariate Cox regression models were used for statistical analyses. **Results:** Of 888 patients (median age 24 years), 76%, 7%, 15%, 3% were stages I, II, III, and IV, respectively. 27%, 28%, 38%, and 8% had grades 1, 2, 3 and 4. The predominant racial group was White (50%) and remainder Black (19%), Hispanic (16%), Asian (6%) and other (9%). 64% had fertility sparing surgery and 55% received chemotherapy. For all patients, 5 year survival was over 90%. Chemotherapy did not change the 5 year survival for stage I or stage II disease (p = 0.35 and p = 0.69, respectively). However, chemotherapy improved 5 year survival from 59% to 76% in stages III-IV ($p < 0.01$). When controlling for other factors, older age (HR 3.2, $p < 0.01$), stages II and III-IV (HR 6.0, $p < 0.01$; HR 10.6, $p < 0.01$) and grades 3-4 (HR 15.3, $p < 0.01$) had worse survival. In a subset analysis of stage I patients chemotherapy did not improve 5 year survival of those with stage I grade 1 (p = 0.75) but chemotherapy did improved the survival of those with stage I grade 2 disease from 85% to 99% (p = 0.04). **Conclusions:** The overall survival of patients with immature teratomas is excellent. In patients with stage I grade 2 or higher disease chemotherapy was associated with an improved overall survival.

5524 Poster Discussion Session; Displayed in Poster Session (Board #346), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase II study of cabozantinib (cabo) in patients (pts) with recurrent/metastatic endometrial cancer (EC): A study of the Princess Margaret, Chicago, and California phase II consortia. *First Author: Neesha C. Dhani, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Recurrent/metastatic EC has a poor prognosis with no standard 2ndline therapy. Cabo is a multi-targeted kinase inhibitor of MET, VEGFR, TIE2, AXL & KIT, relevant in epithelial-stromal cross-talk. The role of MET/HGF in aggressive EC biology, where transient benefit of VEGF-targeting is due to MET/HGF, TIE2 & AXL, provides rationale for MET targeting in EC. **Methods:** PHL86 (NCI#9322/NCT01935934) is a multi-centre, phase II trial of cabo (60mg oral daily dose) in pts with EC recurring within a year of adjuvant chemotherapy (ctx), or with progression after 1 line of ctx for metastatic disease. Experimental (E) cohort was stratified by histology (serous (SER) vs endometroid (END)) in a Simon two-stage design for co-primary endpoints of response rate ($>$ 30%) & 12-week progression-free-survival (PFS) ($>$ 55%). Activity was defined as $>$ 7 partial responses (PRs) or $>$ 15 instances of 12 wk-PFS in 36 pts. Pts with rare histology EC were treated in a parallel exploratory (Ex) cohort. **Results:** From May 2013 to Nov 2016, 102 pts (E: 71; Ex: 31) have been treated with cabo after prior radiation (59) and/or ctx (no. lines: 1 (77); 2(22)). Cabo was well tolerated with common toxicities of fatigue, nausea, diarrhea & hand-foot syndrome. Most frequent Grade 3/4 toxicity was hypertension (32/101 pts). Fistula/perforation occurred in 4 of 71 SER/END pts & 4 of 31 Ex pts; no risk factors were identified. In 33 END pts, 6 PRs & 24 instances of $>$ 12-wk PFS were observed; median PFS is 4.8 mths (95% CI: 4.4 – 6.4) with estimated 6-mth PFS of 43% (95% CI: 27 to 59%). In 34 SER pts, 4 PRs & 20 instances of $>$ 12-wk PFS were observed; median PFS is 4.0 mths (95% CI: 2.7 – 4.7) with estimated 6-mth PFS of 30% (95% CI: 15 to 46%). 4 pts have had PFS $>$ 12 mths, 1 SER pt remains on study after 25mths. Mutational analysis demonstrated presence of KRAS with PTEN or PIK3CA mutations in 9 (SER/END) pts, of whom 8/9 pts met 12-wk PFS endpoint, with a median PFS 5.9 mth (4.1 to 15.4). **Conclusions:** Cabo has single agent activity in END and SER EC with durable disease control. Concurrent mutation in KRAS/PTEN/PIK3CA may enrich for response. The current data support further evaluation of cabo in EC. Clinical trial information: NCT01935934.

5525 Poster Session (Board #347), Sat, 1:15 PM-4:45 PM

Association of T cell responses after vaccination with HPV16 long peptides for late stage cervical cancer with prolonged survival. *First Author: Winald R. Gerritsen, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands*

Background: Therapeutic vaccination with HPV type 16 synthetic long peptides (HPV16-SLP) results in T cell–mediated regression of HPV16-induced premalignant lesions but fails to install effective immunity in patients with advanced HPV16-positive cervical cancer. We showed that HPV16-SLP vaccination in mice and in patients with advanced cervical cancer patients fosters robust HPV16-specific T cell responses, when combined with chemotherapy (Welters et al. Sci. Transl. Med., 2016). **Methods:** We have now completed a chemo-immunotherapy study in 70 patients with late stage HPV16+ cervical cancer (clinical trials.gov NCT02128126). Three HPV16-SLP vaccine doses were given 2 weeks after the second, third and fourth cycle of standard chemotherapy (carboplatin, AUC 6; paclitaxel 175 mg/ m^2). Cohorts of 12 patients each were vaccinated with each of 4 dose levels (20, 40, 100 and 300 μg/ per peptide) of 13 overlapping HPV16 synthetic long peptides (HPV16-SLP) together covering the length of the 2 E6 and E7 proteins. Two additional cohorts of 6 patients each were vaccinated with the most promising doses of 40 and 100 μg/ peptide. **Results:** Robust vaccine-induced HPV16-specific T cell responses as assessed by interferon-γ Elispot were observed and were sustained until at least 30 days after the 6th cycle of chemotherapy. In addition the chemotherapy augmented recall responses to microbial antigens. Such robust T cell responses were not noted in previous trials when similar patients were vaccinated without timing of vaccination during chemotherapy. A marked and significant positive correlation was observed between the strength of the vaccine-induced immune response and overall survival. No such correlation was observed between the strength of the T cell response against common recall antigens and survival. In addition a remarkably high proportion of patients survived beyond 2 years after the start of therapy. **Conclusions:** The results suggest that survival duration is directly related to the strength of the vaccine-induced HPV16-specific T cell response and is not due to generally better immuno-competence. Clinical trial information: NCT 02128126.

5526 Poster Session (Board #348), Sat, 1:15 PM-4:45 PM

A phase I study of sequential ipilimumab in the definitive treatment of node positive cervical cancer: GOG 9929. *First Author: Jyoti Mayadev, University of California, Davis, Sacramento, CA*

Background: The outcome of lymph node positive (LN) cervical cancer (CC) with chemoradiation (CRT) is dismal, especially with involved para-aortic nodes (PAN). The anti-CTLA-4 immune checkpoint inhibitor ipilimumab (ipi) holds promise. We report the safety, tolerability, and efficacy in this GOG phase I study examining sequential ipi after CRT for CC. **Methods:** Patients (pts) with LN CC were treated with 6 weekly doses of cisplatin (40 mg/m2) and extended field radiation (RT). 2-6 weeks after RT, if there was no progression of disease, sequential ipi was given at the following dose levels: dose level 1: 3mg/kg, level 2: 10mg/kg, and an expansion cohort of 10mg/kg. The primary endpoints (endpts) were the maximum tolerated dose (MTD), and dose-limiting toxicities (DLT) of adjuvant ipi. Secondary endpt included the 1-yr disease free survival (DFS). Translational endpts included the effect of CRT on enumeration and subsets of T-cells, and CTLA4, PD-1 and ICOS expression. **Results:** 34 pts were enrolled, and 19 pts are evaluable for the endpts: 14 pts went off study to reasons unrelated to the study drug, 1 pt continues in her DLT evaluable period. Of the evaluable pts, all had pelvic LN, with 25% PAN. All pts completed CRT, 90% had 4 cycles of ipi, and the other 10% had 2 cycles of ipi. The ipi MTD was 10 mg/kg. There were 3 pts (16%) with acute grade 3 toxicity (lipase, ↓ANC, rash) which self-resolved. Most of the acute toxicities were grade 1-2 GI distress, rash, endocrinopathies. There were no minor or major RT quality deviations. With a median follow up of 12 months, there were no major late toxicities reported, with a 1-year DFS of 74%. There was no difference in CD4$^+$- and CD8$^+$- T cell levels nor CTLA-4 expression with sequential ipi. CRT itself increased ICOS and PD-1 expression. **Conclusions:** This study is the first to describe the safety of immunotherapy sequencing with definitive CRT in CC. Our data suggests that immunotherapy is tolerable and shows possible activity in this population with a historical dismal prognosis with standard therapy. CRT increased ICOS and PD-1 expression which was sustained with ipi, illustrative of immune modulation targets for future clinical trials and radio-immunotherapy combinations. Clinical trial information: NCT01711515.

5527 Poster Session (Board #349), Sat, 1:15 PM-4:45 PM

A randomized phase III trial of cisplatin with or without S-1 in patients with FIGO IVB, recurrent, or persistent cervical cancer: An Asian study. *First Author: Soyi Lim, Department of Obstetrics and Gynecology, Gachonuniversity Gil Medical Center, Incheon, Republic of Korea*

Background: A combination of S-1, an oral fluoropyrimidine, plus cisplatin has been used for advanced gastric cancer in Asia and EU, and lung cancer in Japan. It also evaluated in advanced or recurrent cervical cancer in a phase II setting. We conducted a randomized phase III trial to compare the efficacy and safety of S-1 plus cisplatin with those of cisplatin alone in recurrent or persistent after treatment and FIGO IVB cervical cancer patients. **Methods:** Stage IVB, recurrent or persistent cervical cancer patients aged ≥ 20 years, ECOG PS 0–1 and adequate organ function were randomly assigned (1:1) to receive S-1 (80–120 mg daily, according to BSA, day 1–14) plus cisplatin (50 mg/m^2 on day 1) (study group) or cisplatin alone (50 mg/m^2 on day 1) (control group) every 3 weeks. Treatment was continued until disease progression. In all, 360 patients (at least 296 events) with a hazard ratio (HR) for death of 0.72 were required for a two-sided alpha of 5% and power of 80% under 2 years of recruitment and 1.5 years of follow-up. Stratification factors included recurrence in previously irradiated field, previous platinum-based therapy, and institution. Primary endpoint was OS based on intent-to-treat principle, and secondary endpoints were PFS, overall response rate (ORR), and safety. **Results:** In all, 375 patients were assigned to the study (n = 189) and control (n = 186) groups. Rate of previous platinum-based therapy was 64%. The median survival time was 21.9 and 19.5 months (95% CI, 18.6–25.8 and 17.0–24.3) with the use of unstratified log-rank test in the study and control groups, respectively (log-rank P = 0.125; HR, 0.84; 95% CI, 0.67–1.05). Significant increases in median PFS (7.3 vs. 4.9 months; log-rank P $<$ 0.001; HR, 0.62) and ORR (43.8 vs. 20.1%, P $<$ 0.001) were observed in the study group. Adverse events (grade≥3) were frequent in the study group (80.9 vs. 41.7%) with neutropenia (52.7%), anemia (34.6%), and leukopenia (32.4%) being the most common events. **Conclusions:** Compared with cisplatin alone, S-1 plus cisplatin did not significantly improve OS but increased ORR, prolonged PFS, and had tolerable safety of patients with stage IVB, recurrent or persistent cervical cancer. Clinical trial information: NCT00770874.

5528 Poster Session (Board #350), Sat, 1:15 PM-4:45 PM

The neoantigen landscape and immune regulators in cervical cancer. *First Author: Jason Roszik, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Human papillomaviruses (HPVs) play a major role in development of cervical cancer, and HPV oncoproteins are being targeted by immunotherapies. Although these treatments show promising results in the clinic, many patients do not benefit or the durability is limited. **Methods:** To explore the landscape of neoantigens in cervix cancer, we predicted all possible mutated neopeptides using exome and RNA sequencing data of a large number of tumors in two independent data sets (n = 194 and 79), and analyzed whether mutation and neoantigen load correlate with expression of genes involved in antigen presentation, infiltrating immune cell type markers, and HPV oncoprotein-associated genes. Normal tissue expression analyses were also performed using data from the Genotype-Tissue Expression project (n = 8,555). **Results:** We found that potentially immunogenic and targetable neoantigens can be predicted for almost all cervix tumors, including recurrent neoantigens from mutations of known oncogenic driver genes (KRAS G12D, MAPK1 E322K, PIK3CA E545K, PIK3CA E542K, ERBB2 S310F, and ERBB3 V104M). Furthermore, we found that expression of HPV-associated "master regulator" genes is associated with mutation, neoantigen, and HPV load, and also with expression of several important markers in the immune microenvironment. Notably, the OVOL1 master regulator positively correlated with mutation and neoantigen load, and also with PD-L1 and TGFB1 expressions. Furthermore, ENO1 overexpression in cervical cancer was associated with high HPV load, and ENO1 level also positively correlated with PD-L1 and TGFB1 expressions, suggesting that it may be a potential target in cervical cancer. **Conclusions:** For most of the cervix tumors we report predicted neoantigens, and we also identified recurrent neopeptides derived from mutations in known oncogenes. We have also identified statistically significant associations between neoantigen availability, antigen presentation, cytotoxic T-cell function, suppressive mechanisms, and expression of HPV master regulators to help guide immunotherapies of cervical cancer.

5529 Poster Session (Board #351), Sat, 1:15 PM-4:45 PM

Functional and oncologic outcomes of radical trachelectomy in early-stage cervical cancer: A prospective multicentric cohort of 61 patients. *First Author: Vincent Balaya, Hopital Européen Georges Pompidou, Paris, France*

Background: The aim of this study was to assess the post-operative morbidity of patients who have undergone a radical trachelectomy for early-stage cervical cancer and the oncologic outcomes. **Methods:** We retrospectively analyzed the data of two prospective trials on sentinel node biopsy for cervical cancer (SENTICOL I & II). Patients underwent a radical trachelectomy for early-stage cervical cancer between January 2005 and March 2012 from 8 French oncologic centers. **Results:** A total of 61 patients have undergone a radical trachelectomy: 41 patients by laparoscopic-assisted vaginal way, 7 patients by total laparoscopic way, 11 patients by total vaginal way and 2 patients by laparotomy. The median age was 33 years (range = 22-68 years). 88.5 % of patients had a stage IB1 disease. There were 63.9% of epidermoid carcinoma and 34.4 % of adenocarcinoma. Eighteen patients (29.5%) had only a sentinel lymph node biopsy and 43 patients (70.5%) had an additional pelvic lymphadenectomy. The median follow-up was 46 months (range = 0-85 months). Twenty patients (32.8%) had a urinary complication. There were 12 cases of urinary infections (19.6%), 6 cases of dysuria (9.8%), 3 cases of urinary incontinence (4.9%), and one case of ureteral fistula (1.6%). Nine patients had a major neurologic complication (14.7%): the genito-femoral nerve was injured in 4 cases (6.5%) and the obturator nerve was injured in 5 cases (8.2%). Sixteen patients (26.2%) presented a lymphovascular complication. There were 12 cases of limb lymphedema (19.7%) and 5 cases of pelvic lymphocyst (8.2%). During the follow-up, 3 patients (4.9%) had a local recurrence and two patients died : one from a breast cancer and one from a liver metastasis. **Conclusions:** The radical trachelectomy is a feasible and safe alternative option for young patient with a early-stage cervical cancer in order to preserve their fertility. See table.

Post-operative complications.

Postoperative complications	
Clavien I	19 (31,1%)
Clavien II	16 (26,2%)
Clavien III	3 (4,9%)
Urinary	
Urinary infections	12 (19,6%)
Dysuria	6 (9,8%)
Lymphovascular	
Limb lymphedema	12 (19,6%)
Lymphocyst	5 (8,2%)
Neurologic	
Obturator nerve	5 (8,2%)
Genito-femoral nerve	4 (6,5%)

5530 Poster Session (Board #352), Sat, 1:15 PM-4:45 PM

3D HDR intracavitary brachytherapy combined with complementary applicator-guided external beam radiotherapy for 338 patients with stage IIB-IIIB uterine cervical cancer: A single-center phase II prospective study with long-term follow-up. *First Author: Jin Yi Lang, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*

Background: For uterine cervical cancer (UCC) patients with asymmetric parametric lesions, 3D HDR-intracavitary brachytherapy (HDR-ICBT) could not cover all the lesions, resulting in residual lesion and treatment failure. To settle this problem, a novel treatment modal of 3D HDR-ICBT combined with complementary applicator-guided external beam radiotherapy (EBRT) was used for UCC patients with stage IIB-IIIB in present study. **Methods:** Between June 2010 and June 2015, 338 patients with locally advanced cervical cancer (International Federation of Gynecology and Obstetrics stage IIB-IIIB) were treated with concurrent chemoradiotherapy. Imaged guided IMRT was used for external beam radiotherapy, 45Gy/25f. The chemotherapy was weekly cisplatin (40mg/m2). Four fractions of 3D HDR-ICBT combined with complementary applicator-guided external beam radiotherapy were used. The prescribed dose for HR-CTV and IR-CTV was 7Gy (D90) and 5Gy (D90). Dose constraints for organs at risk were D2cc $<$70 Gy for rectum, and D2cc$<$90 Gy for bladder in terms of equivalent total dose in 2 Gy fractions as GEC-ESTRO recommendations. **Results:** Median follow-up was 64 months (11–71 months). The D_{90} of GTV, HR-CTV, and IR-CTV in all cases were 93.4 (85.1-107.8) Gy, 86.4 (79.9-91.3) Gy and 72.3 (70.8-75.2) Gy, respectively. The $D2_{CC}$ of bladder, rectum and sigmoid were 74.3Gy、65.5Gy and 64.1Gy, respectively. 5-year LRC, DFS, and OS was 90.8%, 84.1% and 80.8%, respectively. Treatment was well tolerated. The grade $\geq$3 genitourinary and gastrointestinal acute and late toxicities were 2.1% and 5.2%, respectively. **Conclusions:** The combination of HDR-ICBT with an applicator-guided IMRT is feasible for uterine cervical cancer patients with asymmetric parametric lesions. Further study is needed to determine whether this treatment modal could be used to replace the invasive interstitial brachytherapy (ISBT) in the cases of locally advanced cervical cancer where HR-CTV coverage cannot be obtained with ICBT.

5531 Poster Session (Board #353), Sat, 1:15 PM-4:45 PM

Treatment and outcomes of small cell neuroendocrine carcinoma of the cervix (SCCC). *First Author: Brooke Schlappe, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Extrapulmonary small cell carcinoma is rare. SCCC represent 2% of cervical cancers and can portend a poor prognosis. Treatment standardization is challenging given its rarity. We describe management of limited stage (LS; disease could be encompassed within one radiation port) at a large tertiary referral center and the characteristics and outcomes in a cohort of patients (pts) with LS and extensive stage (ES) SCCC. **Methods:** Pts with SCCC diagnosed from 1/1990-1/2016 were identified following IRB approval. Clinicopathologic, treatment, and follow-up data were recorded. Descriptive statistics were provided. Median PFS/OS or PFS/OS rate were estimated using Kaplan-Meier method. **Results:** 39 pts were identified, 29 with LS. Select characteristics are shown in table. Tumor molecular profiling revealed *MYC* amplifications, *TP53* mutations, *PIK3CA* mutation among the small subset of pts who had this performed. LS SCCC was treated with whole pelvic radiation therapy (RT) (4500-5040cGy) and concurrent IV cisplatin ($60mg/m^2$) on day 1 and etoposide ($120mg/m^2$) on days 1, 3, and 5 during RT and days 1-3 post RT to complete a total of 4 cycles. 26 pts, all had LS, underwent initial surgical management. No pt had prophylactic cranial RT. 3 pts (8%), all had LS, developed brain metastases. Median follow-up was 59.5 months (1.9-234.1). Median PFS (95%CI) for LS pts was 39.2 months (15.1-not estimable) vs 2.9 months (0.9-4.6) for ES. Median OS(95%CI) was 31.8 months (16.3-56.0) for the whole cohort, 52.8 months (31.8-not estimable) for LS and 5.9 months(1.8-16.3) for ES. **Conclusions:** In the LS SCCC cohort treated with concurrent cisplatin/etoposide chemo/RT and outback cis/etoposide +/- post initial radical hysterectomy the 5-year PFS (95%CI) was 37.5% (19.2-55.9%). Clinicopathologic characteristics and risk factors for SCCC appear distinct to cervical cancers and lung small cell cancers. Further investigation of molecular alterations and treatment of this rare tumor is needed to improve pt outcomes.

Characteristics	Median (range) or n (%)
Age (years)	39 (24-85)
Smoking history	11 (28%)
Lymphovascular invasion +	20 (80%)
Stage	
I	18 (46%)
II/III	13 (33%)
IV	8 (21%)

5532 Poster Session (Board #354), Sat, 1:15 PM-4:45 PM

A randomized phase II evaluation of weekly gemcitabine plus pazopanib versus weekly gemictabine alone in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. *First Author: Linda R. Duska, University of Virginia Health System, Charlottesville, VA*

Background: Inhibition of angiogenesis is a valuable treatment strategy for ovarian cancer. Pazopanib (paz) is a potent angiogenic small molecular inhibitor of the tyrosine kinases VEGRF-1, -2, -3, PDGFR, c-kit and has shown activity as a single agent in ovarian cancer. We designed a trial to assess the benefit of adding paz to gemcitabine (gem) in patients with recurrent, advanced ovarian cancer. **Methods:** An open-label, randomized, multi-site, phase 2 trial was conducted (NCT01610206) including patients with platinum resistant or sensitive ovarian cancer with up to 3 prior lines of chemotherapy, and measurable or evaluable disease. Patients were randomly assigned (1:1) to receive weekly gem 1000 mg/m^2 with or without paz 800 mg QD and stratified according to platinum sensitivity and number of prior lines (1 vs 2 or 3). The primary endpoint was PFS. Intent-to-treat was defined as all eligible patients who receive any protocol treatment with analysis based on randomized arm. **Results:** As of 3/2017, we randomized 148 and treated 146 patients (target sample size 148 eligible patients who receive any protocol treatment). 75 (46 platinum resistant, 61%) were randomly assigned to receive gem/paz and 71 (41 platinum resistant, 58%) to receive gem only. 110 patients (75%) had received 2 or 3 prior lines. There were no unexpected toxicities or deaths. Adverse events were more common in the gem/paz group. The most common grade 3–4 AEs (gem/paz vs gem) were: neutropenia (25 [33%] vs 15 [21%]), fatigue (7 [10%] vs 1 [2%]), hypertension (11 [15%] vs 1 [1%]), elevated alanine aminotransferase (8 [11%] vs 0), thrombocytopenia (9 [12%] vs 12[3%]) and anemia (7 [9%] vs 2 [3%]). There were 2 GI perforations in the paz arm. Median time on therapy was 12 weeks (range 1-55 weeks). Of the 138 patients off study to date, 30 (22%) were for AE's (23 on gem/paz arm). **Conclusions:** The gem/paz combination is tolerable in this population, with patients tolerating multiple cycles with manageable toxicity. Median follow-up and PFS data will be presented after 122 events (progression or death) have occurred per protocol (currently 117 events). Clinical trial information: NCT01610206.

5533 Poster Session (Board #355), Sat, 1:15 PM-4:45 PM

Clinically significant long-term maintenance treatment with olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). *First Author: Charlie Gourley, University of Edinburgh Cancer Research UK Centre, MRC IGMM, Edinburgh, United Kingdom*

Background: In Study 19 (NCT00753545), a RCT in 265 pts with PSR SOC, the oral PARP inhibitor olaparib significantly improved progression-free survival (PFS) vs placebo (PBO), with the greatest benefit seen in pts with a *BRCA1/2* mutation (*BRCA*m); an interim overall survival (OS) analysis suggested an advantage for olaparib-treated pts (DCO: Sep 30, 2015; Ledermann *et al*, 2016). We report a planned final analysis of the long-term benefit of olaparib in pts with PSR SOC in Study 19. **Methods:** Pts who had received ≥2 prior regimens of platinum-based chemotherapy and were in response to their most recent regimen received olaparib (400 mg bid; capsules) or PBO until disease progression. Retrospective germline or tumor testing resulted in a known *BRCA*m status for 254/265 pts (96%). **Results:** At final DCO (May 9, 2016) median OS follow-up was 78.0 months. A long-term treatment benefit and the final hazard ratio (HR) for OS vs PBO (unadjusted for crossover: 13% of PBO pts – full analysis set [FAS]; 23% of PBO pts – *BRCA*m subgroup) is shown (Table). Details of *BRCA*wt pts on treatment for ≥6 years will be presented. No new safety signals or changes in olaparib tolerability profile were seen. **Conclusions:** The Study 19 final analysis shows that olaparib provides clinically significant, long-term treatment benefit in pts with PSR SOC. A durable benefit was seen in ≥10% of *BRCA*m and *BRCA*wt pts, who continued to receive and benefit from olaparib for ≥6 years–unprecedented in the relapsed ovarian cancer setting. Olaparib is well tolerated in this pt population and the analysis suggests olaparib confers an OS benefit in *BRCA*m pts. Clinical trial information: NCT00753545.

OS maturity, %	FAS 79		*BRCA*m 73		*BRCA*wt 86	
N	Olaparib 136	PBO 129	Olaparib 74	PBO 62	Olaparib 57	PBO 61
Pts on treatment at final DCO, n (%)	14 (10.3)	1 (0.8)	7 (9.5)	1 (1.6)	7 (12.3)	0
Pts on treatment for ≥6 years, n (%)	15 (11.0)	1 (0.8)	8 (10.8)	1 (1.6)	7 (12.3)	0
OS events, n (%)	98 (72.1)	112 (86.8)	49 (66.2)	50 (80.6)	45 (78.9)	57 (93.4)
Median OS, months	29.8	27.8	34.9	30.2	24.5	26.6
HR (95% CI)	0.73 (0.55–0.95)		0.62 (0.42–0.93)		0.84 (0.57–1.25)	
Nominal *P* value*	0.021		0.021		0.397	

* *P* value not considered statistically significant due to multiple testing.

5534 Poster Session (Board #356), Sat, 1:15 PM-4:45 PM

Long-term benefit of niraparib treatment of recurrent ovarian cancer (OC). *First Author: Ursula A. Matulonis, Dana-Farber Cancer Institute, Boston, MA*

Background: Current therapies for recurrent OC include chemotherapy (C) or bevacizumab (B) in combination with C followed by continuous B, which showed improved progression-free survival (PFS) compared with C followed by placebo (P) over 3.4 months (GOG-0213) or 4.0 months (OCEANS). Potential impact of B on effectiveness of subsequent therapies has not been described. Niraparib (N) is a highly selective PARP 1/2 inhibitor (PARPi). In preclinical studies, N concentrates in the tumor; N showed significantly longer PFS vs P in patients (pts) with recurrent OC following complete/partial response (CR/PR) to platinum based chemotherapy (Plat) in the randomized, controlled, double-blind phase 3 ENGOT-OV16/NOVA trial. We report the long term effect of treatment with N and its impact on subsequent therapy. **Methods:** Eligibility for NOVA included recurrent OC, fallopian tube or peritoneal cancer, no prior PARPi use, and completion of ≥2 prior courses of Plat, with a CR or PR following the most recent Plat. Pts were enrolled into g*BRCA*mut or non-g*BRCA*mut cohorts based on BRCA mutation test results and randomized 2:1 to receive N 300 mg qd or P until progression of disease or death (PD). Tumors were tested for homologous recombination deficiency (HRD). Estimated probability of PD in each cohort at 12, 18 and 24 months post randomization, representing ~18, 24 and 30 months post chemotherapy initiation, was determined; the difference between PFS2 and PFS (PFS2-PFS) was evaluated in all randomized pts. **Results:** 203 pts were randomized in the g*BRCA*mut cohort. Of 350 pts randomized in the non-g*BRCA*mut cohort, 162 had HRD+ and 134 HRD− tumors. Estimated probability (product-limit method) of PFS at 12, 18 and 24 months was greater in the niraparib arm than in the placebo arm in each cohort and subgroup at each time interval. Probabilities (95% CI) at 24 months for niraparib vs control were 0.42 (0.30, 0.55) vs 0.16 (0.07, 0.28) (gBRCAmut) and 0.27 (0.19, 0.35) vs 0.12 (0.06, 0.21) (non-gBRCAmut). PFS2-PFS was similar in the 2 treatment arms in the combined cohorts (HR 1.02, 95% CI 0.765, 1.349). **Conclusions:** Niraparib provided long term benefit in pts with recurrent OC irrespective of g*BRCA*mut or HRD status, and no decrement in the benefit of subsequent therapy was observed. Clinical trial information: NCT01847274.

5535 Poster Session (Board #357), Sat, 1:15 PM-4:45 PM

Overall survival and updated progression-free survival results from a randomized phase 2 trial comparing the combination of olaparib and cediranib against olaparib alone in recurrent platinum-sensitive ovarian cancer. *First Author: Joyce F. Liu, Dana-Farber Cancer Institute, Boston, MA*

Background: We previously reported that the combination of cediranib (ced) and olaparib (olap) improved progression-free survival (PFS) and overall response rates (ORR) in women with recurrent platinum-sensitive (plat-sens) high-grade serous (HGS) or BRCA-related ovarian cancer (OvCa) (NCT 01116648). We conducted an updated PFS and overall survival (OS) analysis. **Methods:** Patients (pts) across 9 centers were randomized 1:1 in this Ph 2 open label study to Olap (olap 400 mg capsules BID) or Ced/Olap (olap 200 mg capsules BID; ced 30 mg daily), stratified by BRCA status and prior anti-angiogenic therapy. Eligibility included pts with recurrent plat-sens HGS or BRCA-related OvCa. Pts had measurable disease by RECIST 1.1, PS 0 or 1, and the ability to take POs. No prior anti-angiogenics in the recurrent setting or prior PARP inhibitor was allowed. PFS was defined as time from randomization to radiographic progression or death. OS was defined as time from randomization to death. **Results:** Pts were enrolled from Oct 2011 to Jun 2013: 46 to Olap, 44 to Ced/Olap. 48 pts were known BRCA carriers (25 Olap; 23 Ced/Olap). As of Dec 21, 2016, 67 pts had a PFS event, and 52 pts had an OS event. Updated median PFS was 8.2 mos for Olap and 16.5 mos for Ced/Olap (HR 0.50, 95% CI 0.30-0.83, p=0.007). Median OS was 33.3 mos for Olap and 44.2 mos for Ced/Olap (HR 0.64, 95% CI 0.36-1.11, p=0.11). Within known germline BRCA mut carriers, updated PFS was 16.5 vs 16.4 mos (HR 0.75, p=0.42), and OS was 40.1 vs 44.2 mos (HR 0.79, p=0.55) for Olap and Ced/Olap, respectively. In pts without known germline BRCA mut, updated PFS was 5.7 vs 23.7 mos (HR 0.32, p=0.002), and OS was 23.0 vs 37.8 mos (HR 0.48, p=0.074). **Conclusions:** Updated PFS results consistently demonstrated that Ced/Olap significantly extended PFS compared to Olap in the overall population of women with plat-sens OvCa. In this Phase 2 study not powered to detect OS diferences, there was a trend towards OS improvement with Ced/Olap, particularly in pts without a known germline BRCA mutation. Results from ongoing studies of this oral combination in OvCa are of clinical interest. Clinical trial information: NCT 01116648.

5536 Poster Session (Board #358), Sat, 1:15 PM-4:45 PM

A randomized phase II study assessing an optimized schedule of oregovomab (O) anti-CA125 vaccination with carboplatin paclitaxel (CP) relative to CP alone in front-line treatment of optimally cytoreduced stage III/IV ovarian cancer (EOC). *First Author: Gabriella Ferrandina, Catholic University of Rome, Rome, Italy*

Background: In a phase II study of vaccination schedule in front-line combinatorial treatment of EOC (Braly JIT 2009), simultaneous day infusion dramatically enhanced the magnitude of induced immunity relative to a one week delayed schedule & other schedules historically evaluated. The current study is exploring the clinical & biological effects of the optimized 4 vaccine schedule relative to CP alone. **Methods:** Stage III/IV EOC patients (pts) optimally debulked to <1cm residual disease with CA125 >2x ULN were randomized to CP+O (cycle 1,3,5, & C5 +12 weeks) vs CP and followed for clinical outcomes and immune reponse. A total of at least 80 evaluable pts were required for 80% power to detect a difference of 45% vs 15% for a primary comparative analysis of induced CA125 specific T cell immunity using an IFN-γ ELISpot. Clinical evaluations and safety were considered secondary endpoints. **Results:** 97 pts (47 OV+SOC & 50 SOC) were accrued at 13 centers in US & Italy. Analysis of immune markers and long term clinical outcomes is ongoing. The median duration of follow up at time of this analysis was 26 months (m). There was no difference in safety outcomes between the treatment groups. Grade 3-4 toxicity was observed in 24 (52%) CP+O vs 28 (58%) C-P pts. Toxicities were typical of standard IV C-P chemotherapy. K-M Analysis of recurrence free survival (RFS) showed median RFS not estimable for CP+O [95% CI: 21.3, NE] vs 15.4 m [10.9,19.3] for CP (p=0.0009 log rank). In the interim analysis of survival (OS), 4 deaths have been observed in CP+O vs 16 in CP (log rank p=0.0025). Cox proportional hazard analysis finds consistent results across centers, and no imbalance in identified risk factors explanatory for the emerging outcome **Conclusions:** This study suggests simultaneous day vaccination with O on alternate cycles of front line CP leverages CP associated temporal change in the tumor microenvironment permitting an immune treatment effect to enhance the outcomes achievable with CP alone. This observation will be further characterized in ongoing translational studies and confirmed in a future phase III study. Clinical trial information: NCT01616303.

5537 Poster Session (Board #359), Sat, 1:15 PM-4:45 PM

Effect of adoption of neoadjuvant chemotherapy for advanced ovarian cancer on all-cause mortality. *First Author: Alexander Melamed, Massachusetts General Hospital, Boston, MA*

Background: Use of neoadjuvant chemotherapy followed by surgery for advanced epithelial ovarian cancer is controversial in the United States. **Methods:** Use of neoadjuvant chemotherapy for stage IIIC and IV ovarian cancer has increased gradually in the United States since 2007, but rates of adoption vary by region. Between 2011 and 2012, use of neoadjuvant chemotherapy increased by 27% in the New England and East South Central regions, but remained unchanged in three control regions (South Atlantic, West North Central, and East North Central regions). Employing prospectively collected data from Commission on Cancer-accredited cancer programs in the United States, we used this discontinuity in treatment approach to assess the causal impact of neoadjuvant chemotherapy on all-cause mortality in a quasi-experimental fuzzy regression discontinuity design. Kaplan-Meier curves and proportional hazard models were estimated to compare mortality differences between rapidly-adopting regions and controls. We also conducted a cross-sectional analysis of the relationship between regional use of neoadjuvant chemotherapy and survival. **Results:** We identified 1,156 women treated for advanced epithelial ovarian cancer during 2011 and 2012 in the two rapidly-adopting regions and 4,878 women in the three control regions. In the rapidly-adopting regions, patients treated in 2012 compared with 2011 had a mortality hazard ratio (HR) of 0.81 (95%CI=0.71-0.94) after adjusting for mortality time trends, while no difference was observed in control regions (HR=1.02, 95%CI=0.93-1.12). Compared with control regions, we observed larger declines in 90-day surgical mortality (7.0% to 4.0% versus 5.0 to 4.3%, p=0.01) and in the proportion of women not receiving surgery and chemotherapy (20.0% to 17.4% versus 19.0 to 19.5%, p=0.04) in rapidly adopting regions. Cross-sectional analysis confirmed that treatment in regions with greater use of neoadjuvant chemotherapy was associated was lower mortality (p=0.001). **Conclusions:** Adoption of neoadjuvant chemotherapy for advanced epithelial ovarian cancer in New England and East South Central regions led to a sizable reduction in mortality within three years after diagnosis.

5538 Poster Session (Board #360), Sat, 1:15 PM-4:45 PM

Efficacy and long-term safety with bevacizumab included in neoadjuvant and adjuvant therapies in patients with advanced ovarian cancer: Results of the ANTHALYA trial. *First Author: Florence Joly, GINECO and Regional Centre Control Against Cancer Francois Baclesse, Caen, France*

Background: ANTHALYA showed that neoadjuvant Bevacizumab (B) added to Carboplatin and Paclitaxel (CP) was well tolerated and achieved encouraging complete resection rates at IDS (58.6%) in unresectable FIGO stage IIIC/IV ovarian, tubal or peritoneal adenocarcinoma (EJC 2017;70: 133–42). We report response rates, PFS and long-term safety. **Methods:** Patients (pts) in ANTHALYA were randomized 2:1 to 4 cycles (c) of neoadjuvant CP ±3 c of B (15 mg/kg), IDS for eligible patients, then 1 c of CP + 3 c CPB + 21 c of B. Response and progression were evaluated by RECIST 1.1 using CT scan and CA-125. Circulating tumor cell counts (CTC) were evaluated at baseline, c2 and IDS. **Results:** 95 pts were treated in CP (n=37) or BCP (n=58) groups (mean study duration were 16.1 months [mo] and 16.9 mo, respectively). 80 pts (CP: 81% / BCP: 88%) had a CA-125 response (50% reduction in CA-125 level) before IDS. Objective response rates were 65% (62% CP / 67% BCP) before IDS (28 days after c4), 46% at c8 (46% CP/ 47% BCP) and 19% at c26 (19% CP/ 19% BCP). 24 (64.9%) CP pts and 26 (44.8%) BCP pts progressed during follow up (median PFS 21.2 mo [95%CI: 14.5, 26.7] and 23.5 mo [18.5, 30.6], respectively). Median PFS was respectively: 25.8 mo (21.0, 30.0) and 17.1 mo (13.5, 22.2) for pts with/without complete resection at IDS; 21.0 mo (15.0, 25.4) and 25.8 mo (18.5, 27.2) for pts with/without baseline CTCs (n=29 / 59); 21.8 mo (17.5, 27.1) and 22.2 mo (15.3, 38.0) for pts with FIGO IIIC and IV tumors. 36 pts did not receive adjuvant therapy within the study (21 were unresectable for IDS), 59 pts (57% CP / 66% BCP) received it. Of those, 34 pts (52% CP / 61% BCP) had Grade ≥3 adverse events including neutropenia (29% CP / 34% BCP), HBP (10% CP / 8% BCP), proteinuria (10% CP / 0% BCP), deep venous thrombosis (5% CP / 3% BCP), pulmonary embolism (0% CP / 8% BCP). **Conclusions:** Neoadjuvant BCP followed by IDS and adjuvant BCP achieves high response rates and extended PFS with an acceptable toxicity in this specific population of pts with FIGO stage IIIC/IV ovarian, tubal or peritoneal adenocarcinoma not eligible for primary debulking surgery. IDS outcome and CTC counts should be further explored as long term prognostic factors. Clinical trial information: NCT01739218.

5540 Poster Session (Board #362), Sat, 1:15 PM-4:45 PM

Trends in the receipt of guideline care and survival for women with ovarian cancer. *First Author: Joan Warren, National Cancer Institute, Bethesda, MD*

Background: Guideline care has been found to improve survival for women with ovarian cancer, yet many women do not receive appropriate care. We assessed trends in the receipt of guideline care and 2-year cause-specific survival for women diagnosed with ovarian cancer. **Methods:** This retrospective cohort analysis used National Cancer Institute's Patterns of Care studies data for women diagnosed with primary ovarian cancer in 2002 and 2011 (weighted n=6867). Data included patient characteristics, type of treatment, and provider characteristics. We used logistic regression to evaluate the association of year of diagnosis with receipt of guideline surgery, multiagent chemotherapy, or both. Two-year cause-specific survival, 2002-2013, was assessed using SEER data. **Results:** Forty-six percent of women received stage-appropriate surgery, unchanged from 2002 to 2011. The percent of women seeing a gynecologic oncologist (GO) 2002 to 2011 increased from 43% to 77%, 53.6% of women who saw a GO received stage-appropriate surgery. The percent of women with Stages IC-IV cancer who received both stage-appropriate surgery and multiagent chemotherapy increased significantly from 31% in 2002 to 38% in 2011. From 2002 to 2011, 2-year cause-specific ovarian cancer survival did not improve for Stages I/II cancers, with slight improvement for Stages III/IV cancers. **Conclusions:** There has been modest improvement in the receipt of guideline care for women with ovarian cancer, 2002-2011. However, current treatment falls far short of clinical recommendations and may explain limited improvement in 2-year cause-specific survival. There has been a marked increase in the percent of women consulting a GO and seeing a GO increased the chances of receiving guideline care. However many women who consulted a GO did not receive guideline care. There needs to be a better understanding of the decision-making process about treatment during the consultation with GOs and other factors precluding receipt of guideline care.

5541 Poster Session (Board #363), Sat, 1:15 PM-4:45 PM

A multicenter phase II study of the efficacy and safety of quisinostat (an HDAC inhibitor) in combination with paclitaxel and carboplatin chemotherapy (CT) in patients (pts) with recurrent platinum resistant high grade serous epithelial ovarian, primarily peritoneal or fallopian tube carcinoma cancer (OC). *First Author: Sergei Tjulandin, N. N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia*

Background: Quisinostat is an orally bioavailable potent pan-histone deacetylase inhibitor. Combinations of HDAC inhibitors with paclitaxel or cisplatin demonstrate promising results in preclinical models with cisplatin and paclitaxel resistant OC. In phase Ib study the dosage of Quisinostat in combination of paclitaxel and carboplatin recommended for the phase II study was 12 mg. We report results of the phase II study of Quisinostat in combination with paclitaxel and carboplatin in pts with recurrent platinum resistantOC. **Methods:** the main inclusion criteria was tumor progression observed not less than 1 month and no more than 6 months after completion of the planned number of cycles of 1st line platinum/paclitaxel based CT. Quisinostat was administered at dose 12 mg p.o. each 3 week cycle on Days 1, 3, 5, 7, 9, 11 with of paclitaxel (175 mg/m^2) and carboplatin (AUC5) on Day 7 of each cycle, for 2nd line. Pts received up to 6 cycles. The primary efficacy endpoint is the objective response rate (ORR) verified by the ICR. The secondary endpoints include safety, progression free survival (PFS) and overall survival. The study design implies the use of the two-stage Simon model: 29 patients who underwent treatment would provide 80% power for hypothesis testing in order to frequency of the ORR 30% (α = 0.05). **Results:** 31 pts were enrolled (30 pts evaluated). Median age was 57 years. Twenty one pts (67.7%) received all 6 cycles of therapy. ORR was 50.0% (15 pts). Median duration of response was 5 months (4.2-5.7). Median PFS - 6 months (95%CI 4.4-7.6). Any SAE were seen in 16.1% pts, AE of grade 3 and 4 – in 71% and 48.4% pts temporarily discontinued therapy due to AE. Dose reduction of CT due to AE was performed in 22.6% pts. The most common adverse events were neutropenia – 67,7%, nausea – 61.3%, weakness – 29%, thrombocytopenia – 22.6%, neuropathy – 19.4%, vomiting – 19.4%. **Conclusions:** Quisinostat in combination with paclitaxel and carboplatin in pts with recurrent platinum resistant ovarian cancer showed high efficacy and good tolerability Clinical trial information: NCT02948075.

5543 Poster Session (Board #365), Sat, 1:15 PM-4:45 PM

CD8$^+$ TILs in early stage epithelial ovarian cancer: A GEICO study. *First Author: Ignacio Romero, Clinical Area of Gynecologic Oncology, Instituto Valenciano de Oncología (IVO), Valencia, Spain*

Background: The extent of tumor infiltrating lymphocytes (TILs) has emerged as a potential clinical useful biomarker in epithelial ovarian cancer (OC); however differences in TILs among OC histological types have not been extensively analysed. **Methods:** From a prospective early stage (I-II) GEICO registry of 1151 cases, 573 were sent for central pathology review. Complete analysis for classification of OC correctly identified 488 cases. Histological typing was performed according to morphological features and the expression of WT1, p53, p16, estrogen receptor (ER), progesterone receptor, and napsin A. The expression of mismatch repair (MMR) proteins MLH1, PMS2, MSH2 and MSH6 was performed in all tumors. The absolute number of stromal and intraepithelial CD8$^+$ TILs per 0.6 mm^2 TMA core was quantified and correlated with pathological features. **Results:** The series included 127 high-grade serous carcinomas (HGSC) (26%), 22 low-grade serous carcinomas (LGSOC) (4.5%), 165 endometrioid carcinomas (EC) (33.8%), 124 clear cell carcinomas (CCC) (2.4%), and 50 mucinous carcinomas (MC) (10.2%). The mean of intraepithelial CD8$^+$ TILs was higher in HGSG (48.7) than in all other histological types (LGSG: 16.3; EC: 27.1; MC: 7.0; and CCC 10.3; $p<0.0001$). In the stromal component, the mean of CD8$^+$TILs was also higher in HGSG (31.1) than in EC, MC and CCC (15.8, 8.0 and 12.7, respectively; $p<0.0001$). The mean of intraepithelial CD8$^+$ TILs was significantly higher in RE-positive (71.9) than in RE-negative (34.8) HGSC (p=0.002). In the complete series, 33 (6.6%) OCs showed absent expression of at least 1 MMR protein, and the mean of intraepithelial CD8$^+$ TILs was significantly higher in these OCs (57.0) than in those with preserved expression of all MMR proteins (23.6; p=0.0035). MMR protein deficiency was observed in 27 (16%) ECs, and these tumours had significantly higher mean of both intraepithelial (60.4 vs. 20.7 p=0.003) and stromal CD8+ TILs (26.6 *vs.* 13.8, p= 0.046). No significant differences in TILs were observed among EC of different histological grades. **Conclusions:** The extent of CD8$^+$TILs significantly correlates with the histological type and MMR status in OCs, being HGSCs and EC with MMR deficiency those OCs with higher CD8$^+$TILs.

5544 Poster Session (Board #366), Sat, 1:15 PM-4:45 PM

Management of platinum-sensitive recurrent ovarian cancer (PSROC) in the era of biologics: Can ASCO's net health benefits (NHB) inform our decisions? *First Author: Jonathan Foote, Division of Gynecologic Oncology, Duke Cancer Institute, Duke University Medical Center, Durham, NC*

Background: The ASCO value framework allows assessment of novel cancer therapies based on NHB. We assessed novel biologic therapies in the management of PSROC. **Methods:** ASCO's revised value framework NHBs were constructed for key therapies based on randomized clinical trials for PSROC. BRCA-germline and HRD status were included. Additionally, patient-centered NHB calculations were weighted based on results from a prospective patient preferences study (n=54) and compared to ASCO-based NHB. **Results:** ASCO-centered NHB calculations were: platinum + taxane-based chemotherapy (ICON4) = 35; carboplatin + liposomal doxorubicin (CALYPSO) = 22; platinum-based chemotherapy + bevacizumab (OCEANS = 35; GOG 213 = 26). NHB scores based on germline-BRCA alterations were maintenance niraparib (NOVA) = 50 and maintenance olaparib (Study 19) = 62; wild-type BRCA, maintenance niraparib = 36 and maintenance olaparib = 33; and HRD-positive status, maintenance niraparib = 42. Patients valued clinical benefit as the most important component of NHB. Patients valued OS as the most important component of clinical benefit, followed by response rate (RR), then PFS. Patient-weighted NHB were significantly lower than ASCO-weighted scores (mean NHB 37.8 versus 23.5; p=0.009) due to decreased preference for PFS compared to other clinical benefit measures (Table). **Conclusions:** NHB scores for treatment of PSROC were highest in women with germline-BRCA and HRD tumor alterations who were treated with maintenance PARPi. Our data suggest that a patient-centered NHBs can be used to inform treatment decisions.

NHB of platinum-sensitive treatment options in the era of biologics.

Regimens		ASCO NHB	Patient-weighted NHB	P value
Platinum-based chemotherapy + taxane (ICON4)		35	27	0.009
Carbo + liposomal doxorubicin (CALYPSO)		22	17	
Platinum-based chemotherapy + bevacizumab	*OCEANS*	35	20	
	GOG 213	26	15	
Maintenance olaparib	*gBRCA*	62	38	
(Study 19)	*wBRCA*	33	20	
Maintenance niraparib	*gBRCA*	50	30	
(NOVA)	*wBRCA*	36	21	
	wBRCA HRD+	42	24	

NHB = Net Health Benefit (based on PFS); gBRCA = germline BRCA alteration; wBRCA = wild-type germline BRCA; HRD = homologous recombination deficiency

5545 Poster Session (Board #367), Sat, 1:15 PM-4:45 PM

Somatic mutations in homologous recombination pathway genes in ovarian cancer. *First Author: Carol Aghajanian, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: 15% of patients with OC have a germline *BRCA 1 / 2* mut & 6% of OC have a somatic *BRCA 1/2* mut. Inhibitors of poly ADP ribose polymerase (PARPi) are approved in this setting. Data is evolving as to activity of PARPi in *BRCA* wild type OC with somatic homologous recombination (HR) gene deficiency. We sought to determine the prevalence of somatic alterations in HR genes in an unselected cohort of epithelial OC of any histologic type. **Methods:** From 03/2014-10/2016 patients consented to an IRB approved protocol for tumor-normal sequencing, via a custom next-generation sequencing panel (MSK-IMPACT) with return of results for tumor mut only. Muts in 14 HR genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, MRE11, NBN, PALB2, PTEN, RAD51D, RAD51C)* and *p53*were assessed. Statistics were analyzed using GraphPad Prism v. 6. **Results:** 260 tumors were sequenced; 156 (60%) high grade serous (HGS), 34 (13%) low grade serous (LGS), 34 (13%) clear cell, 10 (4%) mucinous, 8 (3%) endometrioid, 18 (7%) mixed/other histology. 151 (97%) of HGS and 24 (23%) of the remaining tumors harbored *p53* mut. 48 (18%) somatic HR mut were identified. (Table 1) 26 HGS (17%) tumors and 22 (21%) of the remaining tumors harbored a HR gene mut (HGS vs other histology, p=0.4). Notably, 8 (24%) of clear cell cancers demonstrated HR gene muts (vs HGS, p=0.3). 18 (38%) of the identified muts in the overall cohort were in *BRCA 1/2*. There were no somatic HR gene muts identified in the mucinous OC, which were characterized by frequent *p53* (90%) and *KRAS*(60%) muts. **Conclusions:** In this cohort of OC, 17% of tumors harbor somatic HR gene muts. The prevalence of HR somatic muts was similar in HGS vs other histologies, with the exception of mucinous OC. *BRCA1/2* muts predominated, however 60% of identified muts were in other genes. Accrual is ongoing to increase histologic cohort sizes. Broad HR gene somatic mutational profiling may identify a wider cohort of OC patients with potential to benefit from PARPi therapy.

N	HGS 156	LGS 34	clear cell 34	mucinous 10	endometrioid 8	mixed/other 18
ATM	3	0	2	0	0	0
BARD1	2	1	0	0	0	0
BRCA1	6	0	0	0	0	5
BRCA2	6	0	0	0	1	0
BRIP1	1	0	0	0	0	0
CHEK1	1	0	0	0	0	0
CHEK2	1	0	0	0	0	0
FANCA	0	0	1	0	1	0
MRE11	3	0	1	0	0	0
NBN	0	0	0	0	0	0
PALB2	0	0	0	0	0	0
PTEN	3	0	4	0	5	1
RAD51D	0	0	0	0	0	0
RAD51C	0	0	0	0	0	0
Total	26	1	8	0	7	6

5546 Poster Session (Board #368), Sat, 1:15 PM-4:45 PM

***BRCA*-like classification in ovarian cancer: Results from the AGO-TR1-trial.** *First Author: Lisa Katharina Richters, Center for Hereditary Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Medical Faculty, University Hospital Cologne, Cologne, Germany*

Background: *BRCA* associated cancers show a distinct pattern of genomic gains and losses that is associated with impaired repair of DNA double-strand breaks via homologous recombination (HR). We investigated whether *BRCA1*- and *BRCA2*-like classifiers could predict *BRCA1* and *BRCA2* mutation status in ovarian cancer. In addition, we explored whether promoter hypermethylation or mutations in other genes involved in DNA repair associate with a *BRCA*-like profile in ovarian cancer. **Methods:** The AGO-TR1 cohort study (NCT02222883) enrolled 525 consecutive patients with primary (PR) and platinum sensitive relapsed (RE) ovarian cancer to perform paired mutational analysis of germline and tumor tissue. We performed mutation panel sequencing, *BRCA1* promoter hypermethylation and low-coverage whole genome sequencing to classify samples as *BRCA1*-like or *BRCA2*-like in 298 ovarian cancer samples (PR: n = 159, RE: n = 139). **Results:** A *BRCA*-like profile was observed in 58.1% of the samples without germline or somatic mutation in *BRCA1/2* (n = 179; *BRCA1*-like: n = 26, *BRCA2*-like: n = 23, *BRCA1*- and *2*-like: n = 55). There was no significant difference between PR- and RE-cases (54.5% vs 61.3%). 64 of 70 *BRCA1* germline mutation carriers could be identified by the *BRCA1*-like classifier (sensitivity: 0.91). The *BRCA2*-like classifier identified *BRCA2* germline mutation carrier with a sensitivity of 0.71 (17 of 24). The complementary use of both classifiers led to the detection of 22 of 25 somatic mutations in *BRCA1* (16/16) or *-2* (6/9). Remarkably, 12 of 13 tumor samples from germline *RAD51C* mutation carriers were recognized by the *BRCA1*-like classifier (sensitivity: 0.92). No correlation of *PALB2* mutation status (n = 7) with *BRCA*-like profile was observed. Of 28 tumor samples with a *BRCA1* promoter hypermethylation 26 had a *BRCA1*-like profile (sensitivity: 0.93). **Conclusions:** A high number of ovarian cancer cases display a *BRCA*-like profile. Mutations (germline and somatic) in *BRCA1, BRCA2, RAD51C* as well as *BRCA1* hypermethylation strongly associate with a *BRCA*-like profile and can explain 146 of 212 cases. Future studies will investigate whether the classifiers identify patients who benefit from HR-deficiency directed approaches beyond the *BRCA* mutation status. Clinical trial information: NCT02222883.

5547 Poster Session (Board #369), Sat, 1:15 PM-4:45 PM

Mirvetuximab soravtansine (IMGN853), a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in platinum-resistant epithelial ovarian cancer (EOC) patients (pts): Activity and safety analyses in phase I pooled expansion cohorts. *First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: The early clinical evaluation of mirvetuximab soravtansine (IMGN853), an ADC that comprises a FRα-binding antibody linked to the tubulin-disrupting maytansinoid DM4, has revealed encouraging signs of activity in pts with ovarian cancer. A pooled analysis of safety and efficacy was performed including individuals with platinum-resistant EOC, enrolled across three expansion cohorts of an ongoing phase I trial (NCT01609556), who met the eligibility criteria for the pivotal phase III study of IMGN853 (FORWARD I; NCT02631876). **Methods:** Pts were administered IMGN853 intravenously once every 3 weeks at 6 mg/kg using adjusted ideal body weight dosing. Responses were assessed according to RECIST 1.1 and adverse events (AEs) evaluated by CTCAE v4.0. **Results:** A total of 37 EOC pts treated as part of the three phase I expansion cohorts (pooled population; n = 113) met the FORWARD I enrollment criteria of moderate to high tumor FRα levels (≥ 50% of cells with ≥ 2+ FRα expression) and 1-3 prior lines of therapy. In this group of pts with platinum-resistant disease, confirmed objective tumor responses were observed in 17 individuals (1 complete response [CR] and 16 partial responses [PR]) for an overall response rate (ORR) of 46% (95% CI, 29.5, 63.1) and a median PFS of 6.7 months (95% CI, 4.1, 9.0). The safety profile of the pooled population was consistent with that previously reported (ASCO Annual Meeting, 2016) with the most common AEs being diarrhea, fatigue, nausea, and blurred vision; these were low grade and readily managed. **Conclusions:** IMGN853 continues to be characterized by favorable tolerability and encouraging activity in pts with platinum-resistant EOC. In particular, both the ORR (46%) and PFS (6.7 months) achieved in this group of pts are superior to outcomes typically seen with established single-agent chemotherapy within the setting of primary platinum resistance. Overall, these analyses provide continued, robust support for the patient eligibility strategy employed in the phase III evaluation of IMGN853. Clinical trial information: NCT01609556.

5548 Poster Session (Board #370), Sat, 1:15 PM-4:45 PM

A phase 1b/2 study of napabucasin with weekly paclitaxel in advanced, previously treated platinum resistant ovarian cancer. *First Author: Carlos Becerra, Texas Oncology, Dallas, TX*

Background: Napabucasin is a first-in-class cancer stemness inhibitor, identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells (Li et al PNAS 112 (6):1839, 2015). Napabucasin has shown potent synergistic preclinical anti-tumor activity with paclitaxel (PTX). In a phase Ib dose escalation study in patients (pts) with advanced solid tumors, napabucasin plus weekly PTX was well tolerated. A phase II expansion cohort was opened for patients with platinum resistant ovarian cancer. **Methods:** Pts with advanced ovarian cancer who had disease progression either during or in the 6 months following platinum-based systemic therapy were enrolled. napabucasin was administered orally at a starting dose of 240, 480, or 500 mg twice daily with PTX 80 mg/m2 IV weekly on 3 of every 4 weeks. AEs were evaluated using CTCAE v4.03 and objective assessments were performed per RECIST 1.1 every 8 weeks. **Results:** A total of 98 pts were enrolled. The average number of prior lines of systemic treatment was 3.5, including prior taxane-based therapy in 100% of patients. Treatment was well tolerated. Related grade 3 adverse events occurring ≥ 5% of pts included diarrhea (12.2%) and vomiting (5.1%). Among pts who received RECIST evaluation (n = 76), the disease control rate (DCR, proportion with SD at 8 weeks + PR + CR) was 65%, and the objective response rate (ORR, PR+CR) was 20%, with complete response in 3 pts (4%). In all patients (ITT, n = 98), the median progression-free survival (mPFS) was 3.0 months and median overall survival (mOS) was 9.3 months. **Conclusions:** Clinical safety and encouraging signs of anti-cancer activity, including three complete responses, were observed in pts with pre-treated platinum resistant ovarian cancer who received treatment with napabucasin plus weekly PTX. Further clinical evaluation in controlled trials is warranted. Clinical trial information: NCT01325441.

5549 Poster Session (Board #371), Sat, 1:15 PM-4:45 PM

Shared decision-making in ovarian cancer. *First Author: Lari B. Wenzel, University of California, Irvine, Irvine, CA*

Background: The value of shared decision-making in ovarian cancer is relatively unexplored. The goal of this study was to test a new decision aid, Patient Centered Outcome Aid (PCOA), that facilitates shared decision-making and helps ovarian cancer patients assimilate information and identify quality of life (QOL), toxicity and survival trade-offs between IP/IV therapy and IV therapy alone, based on their preferences and personal clinical characteristics. **Methods:** Participants were randomized to either PCOA (N=64) or usual care (N=59). Patient characteristics, QOL and shared decision-making data were collected at baseline and treatment initiation. Primary outcomes included satisfaction with treatment decision and decisional regret. Comparisons were made using t-tests and multivariate methods, adjusting for patient covariates. Multivariate linear models were used to investigate predictors of the primary outcomes. **Results:** Although satisfaction and decisional regret did not differ significantly by arm at any time point, the majority of PCOA patients indicated that the aid helped them understand treatment options and side effects. Notably, low shared decision-making and low QOL, were significant predictors of low satisfaction at treatment initiation (multiple r=0.76), six months (multiple r=0.48) and nine months (r=0.58). They were also significant predictors of decisional regret (multiple r=0.48 and 0.36 at 6 and 9 months). Patient covariates including age, stage, treatment and neoadjuvant status were not associated with differences in satisfaction or decisional regret. **Conclusions:** There were no clinically meaningful differences in satisfaction with the treatment decision, or decisional regret between the study arms. The absence of a difference may reflect the high degree of shared decision-making in both arms and greater disease severity in PCOA patients, who were more likely to report low baseline QOL and declining QOL over time. Both shared decision-making and quality of life were robust, independent predictors of satisfaction with the treatment decision over time. This implies that women who perceive themselves as less engaged in the decision process, and report poor QOL may benefit from a decision aid, in addition to physician counseling. Clinical trial information: NCT02259699.

5550 Poster Session (Board #372), Sat, 1:15 PM-4:45 PM

Bevacizumab, eribulin, and oxaliplatin in patients with platinum-resistant ovarian carcinomas: A phase II study with biomarker analysis. *First Author: Masashi Takano, Department of Obstetrics and Gynecology, National Defense Medical College Hospital, Tokorozawa, Japan*

Background: Eribulin is a candidate for paclitaxel-refractory breast cancers, and Bevacizumab (B) is known to enhance efficacy of anti-cancer agents in ovarian cancers. A phase II study to evaluate weekly administration of B with eribulin and oxaliplatin (EriOX) in patients with platinum-resistant and refractory ovarian carcinomas (PR-ROC) was performed. **Methods:** Eligible patients were as follows: (a) ECOG PS = 0~2 (b) histologically confirmed epithelial ovarian cancer (c) diagnosed as platinum-resistant ovarian cancer (d) written informed consent. Patients were treated with weekly-B-EriOX consisting of B (2mg/kg), eribulin (1mg/m^2) and oxaliplatin (30mg/m^2), three weeks on and on week off, q4weeks. The study was conducted using two-stage design of Simon (type I error = 0.05, power = 0.9, true response rate = 25%). Biomarker analyses including serum VEGF, BNP, p53, IL-6, and Her-2 were also conducted. **Results:** A total of 34 patients were enrolled in the present study: 13 cases in the first-stage, and additional 21 cases in the second-stage. There were 3 responders ($\geqq$2) in the first-stage, and the protocol was proceeded to the second-stage. Median age of the patient was 58.5 years (range: 35-76), and median number of previous regimen was 4 (range: 2-9). Overall, two patients (6%) had a complete response (CR), 8 patients (24%) had a partial remission (PR) and 16 patients (47%) had a stable disease (SD). The response rate and clinical benefit rate (CR+PR+SD) were 29% and 76%, respectively. Median progression-free survival was 4 months (range: 1-27+). Hematological adverse effects (AE) with grade 3/4 were observed in 4 patients (11%). Non-hematological AE greater than grade2 was observed in one case: hypo albuminemia and edema, which were manageable and tolerable. As there were 10 responders ($\geqq$6), the protocol was considered for additional investigation. The Patients with elevated serum mutated p53 / IL-6 showed lower response and worse prognoses. **Conclusions:** Weekly B and EriOX administration was considered for additional investigation for patients with PR-ROC. Serum mutated p53 protein and/or IL-6 could be biomarkers in PR-ROC patients treated with weekly B and EriOX.

5551 Poster Session (Board #373), Sat, 1:15 PM-4:45 PM

***BRCA1/2* reversion mutations revealed in breast and gynecologic cancers sequenced during routine clinical care using tissue or liquid biopsy.** *First Author: Paul Mayor, Roswell Park Cancer Institute, Buffalo, NY*

Background: Tumors with genomic alteration (GA) of *BRCA1* or *BRCA2* (*BRCA*) may be more sensitive to platinum (Pt) therapies and PARP inhibitors (PARPi). However, secondary reversion mutations (revGA) can arise that may restore *BRCA* function and underlie reduced sensitivity to Pt compounds or PARPi. **Methods:** DNA extracted from FFPE tumor tissue or blood samples obtained during routine clinical care for patients with predominantly relapsed, refractory or metastatic breast cancer (10967) or ovarian/peritoneal cancer (8352) was analyzed by hybrid-capture, next-generation sequencing for all classes of GA: base substitutions, indels, rearrangements, and copy number changes. RevGA were any GA that could restore the reading frame if in cis with a nonsense or frameshift (fs) GA. **Results:** 1900/19329 (9.8% $\pm$ 0.4%) tumors had $\geq$1 deleterious *BRCA* GA. 38 samples harbored potential revGA in *BRCA1* (16) or *BRCA2* (22): breast carcinoma (Ca) (21), ovarian or peritoneal serous Ca (10), ovarian or peritoneal adenocarcinoma (3), and ovarian epithelial Ca NOS (4). 35/38 sequenced samples were metastases. All potential revGA were somatic and fell into 3 classes: overlapping indel (21), compensatory fs (6), and missense mutation (11). One case harbored both an overlapping indel and a missense mutation with potential to revert a nonsense alteration. For 6 patients, testing of multiple tissue samples reveals the acquisition of revGA over time. RevGA are generally observed at allele frequencies lower than the deleterious GA they may revert. Clinical histories for patients with reversion mutations will be presented. **Conclusions:** Genomic profiling of breast and gynecological carcinomas, using either tissue or liquid biopsies, reveals potential revGA that may restore some level of *BRCA* function. RevGA, although rare, can be acquired during the course of treatment. We identified potentially compensatory missense, fs and indel mutations with CGP. Comparison of allele frequencies suggests that revGA often arise as subclones. The acquisition of a revGA over time can be observed through testing of multiple samples, either tissue or liquid biopsy.

5552 Poster Session (Board #374), Sat, 1:15 PM-4:45 PM

Prognostic impact of neo-adjuvant vs adjuvant vs neo-adjuvant plus adjuvant chemotherapy in advanced ovarian cancer: Analysis of National Cancer Database. *First Author: Suresh Mukkamala, Easton Hospital, Easton, PA*

Background: Patients (Pts) with advanced ovarian cancer (OvCa) are usually treated with primary debulking (deb) surgery (Sx) followed by adjuvant (adj) chemotherapy (CRx). Recently neo-adjuvant (neo-adj) CRx is increasingly being used to reduce the bulk of the tumor. Hence, we analyzed for any prognostic impact of neo-adj vs adj vs neo-adj plus adj CRx along with deb Sx in the management of advanced OvCa. **Methods:** Only Stage III and IV Pts in National Cancer Data Base (NCDB) from 2006-2014, who underwent deb Sx without bowel resection (1), with bowel resection (2) and with bowel and bladder resection (3) were analyzed. Group (gp) A Pts had neo-adj CRx, gp B had adj CRx and gp C Pts had neo-adj plus adj CRx. The Pearson Chi square testing was used to evaluate the survival between gp A vs B vs C. **Results:** A total of 20910 Pts in stage III and 7483 Pts in stage 4 were included. Stage III Pts had a better 5 year (yr) survival in gp B compared to gp A and C, in all Pts who underwent Sx 1, 2 and 3 (Table 1). Stage IV Pts had a better 5 yr survival in gp C compared to gp A and B who underwent Sx 1 and 2, and gp B had a better 5 yr survival in Pts who underwent Sx 3 (Table 1). Overall survival was worse for all stages in Pts with neo-adj (gp A) than gp Band C. **Conclusions:** Deb Sx followed by adj CRx had better survival than in gp A or C. This may be secondary to less bulkier disease in the beginning in gp B than those in gp A or C requiring neo-adj CRx for the later. Pts survival also improved after addition of adj CRx following deb Sx compared to no adj CRx. A prospective multicenter randomized trial between each group may further validate the true benefits of neo-adj CRx in advanced OvCa.

1- 5 yr survival for gp A (neo-adj) vs gp B (adj) vs gp C (neo-adj plus adj) based on type of deb Sx.

		5 yr survival in % for gp A vs gp B vs gp C			
Type of deb Sx	No. of Pts	gp A(neo-adj)	gp B (adj)	gp C (neo-adj plus adj)	P value
			Stage III		
Sx 1	11,666	41.6 %	52.7 %	47.8 %	<0.001
Sx 2	8523	43.4 %	51.4 %	46.4 %	<0.001
Sx 3	721	41.7 %	53.5 %	52.4 %	0.383
			Stage IV		
Sx 1	3973	39.2 %	38.6 %	46.1 %	0.001
Sx 2	3178	36.4 %	39.8 %	42.6 %	0.186
Sx 3	332	26.5 %	47.3 %	41.2 %	0.064

Sx 1- deb Sx without bowel resection, Sx 2- deb Sx with bowel resection, Sx 3- deb Sx with bowel and bladder resection.

5553 Poster Session (Board #375), Sat, 1:15 PM-4:45 PM

Safety findings from FORWARD II: A Phase 1b study evaluating the folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC) mirvetuximab soravtansine (IMGN853) in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin (PLD), or pembrolizumab in patients (pts) with ovarian cancer. *First Author: David M. O'Malley, The Ohio State University College of Medicine, Columbus, OH*

Background: FORWARD II is a phase 1b study of the FRα-targeting ADC, mirvetuximab soravtansine (IMGN853), in combination with bevacizumab (BEV), carboplatin, PLD, or pembrolizumab in adults with FRα-positive EOC, primary peritoneal, or fallopian tube tumors (NCT02606305). **Methods:** The escalation stage of this trial evaluated the safety and tolerability of IMGN853 as part of 4 combination regimens: IMGN853 + BEV; + carboplatin; + PLD; and + pembrolizumab. IMGN853 was administered in combination on Day 1 of a 21 (BEV or carboplatin) or 28-day cycle (PLD). Pembrolizumab escalation is continuing. The starting dose of IMGN853 was 5 mg/kg (adjusted ideal body weight, AIBW), one level lower than the recommended single agent phase 2 dose (RP2D; 6 mg/kg AIBW) defined in a first-in-human study (NCT01609556). Adverse events (AEs) were evaluated by CTCAE v4.0. **Results:** 46 pts enrolled in the first 3 cohorts. IMGN853 was escalated from 5 to 6 mg/kg. Carboplatin and PLD dosing were escalated from AUC4 to AUC5 and 30 to 40 mg/m^2, respectively; BEV dosing remained constant at 15 mg/kg. Diarrhea, nausea, and fatigue were common across cohorts (all grades; 33-57%) and mostly low grade (i.e. $\leq$ 2), consistent with the IMGN853 safety profile from the earlier phase I monotherapy study. AEs of interest related to the combination agents were seen in each arm. For example, grade 1/2 proteinuria (36%) and grade 3 hypertension (21%) were only observed in the BEV combination. Thrombocytopenia (44%) and neutropenia (39%), grades 1-3, occurred most frequently in the carboplatin arm. Grade 3 anemia and vomiting (each 14%), as well as low grade ($\leq$ 2) constipation (43%), were seen in the PLD cohort. **Conclusions:** The RP2D dose of IMGN853 was readily combined with the highest doses (as per protocol) of BEV, carboplatin, and PLD. The AE profiles for these combinations were manageable and as expected based on known profiles of each agent; importantly, no new safety signals were identified. Updated data from all 4 combination regimens will be presented. Clinical trial information: NCT02606305.

5554 Poster Session (Board #376), Sat, 1:15 PM-4:45 PM

Two prognostic populations of ovarian cancer patients defined by CA125 modeled kinetic parameter KELIM (AGO-OVAR 7 & 9; ICON 7 AGO/GINECO/MRC CTU/GCIG trials). *First Author: Benoit You, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), CITOHL, Lyon, France*

Background: Longitudinal CA125 kinetics during treatment can be assessed by mathematical models. The modeled CA125 elimination parameter KELIM (with 3-4 timepoints) was an early prognostic factor in CALYPSO (Gynecol Oncol 2013). Validating the prognostic value of KELIM in phase 3 trial datasets with different 1st line treatments was warranted. **Methods:** Data from AGO-OVAR 9 (training set: carboplatin-paclitaxel (CP) +/- gemcitabine; n=1742); AGO-OVAR 7 (validation set: CP +/- topotecan; n=1308); and ICON 7 trials (validation set: CP +/- bevacizumab; n=1528) were analyzed. CA125 profiles were fit to nonlinear mixed effect equations, and KELIM estimated in all patients at 100 days. KELIM prognostic value was tested regarding PFS and OS against other prognostic factors (stage; pathology; grade; arms; GCIG CA125 criteria; Oza groups in ICON 7) using univariate/multivariate tests. **Results:** KELIM (≤ or > median 0.0598) had reproducible independent prognostic value for PFS (AGO 9: HR = 0.60 [0.53-0.69]; AGO 7: HR = 0.58 [0.40-0.83]; ICON-7: HR=0.65 [0.44-0.96]) and for OS (AGO 9: HR = 0.55 [0.47-0.64]; AGO 7: HR = 0.55 [0.35-0.86]; ICON-7: HR=0.49 [0.41-0.57]) by multivariate tests. Other significant factors for PFS & OS: stage IV in AGO7 & 9 (HR=6.0 to 8.3) and ICON 7 poor progn group (PFS HR=2.24 PFS; OS HR=2.22 [1.9-2.6]). KELIM prognostic value was independent on regimen arms (Table), maintained within ICON7 progn groups (best OS gain with bevac if poor progn & unfav KELIM), and better than GCIG CA125 (inconsistent progn value). **Conclusions:** The reproducible & independent early prognostic value of KELIM regarding PFS and OS is validated. Easily calculable online, it early discriminates 2 ovarian cancer populations for PFS & OS whatever treatments, and is a new reference prognostic factor.

		PFS (months)		OS (months)	
	Treatment	Favorable KELIM > 0.059	Unfavorable KELIM ≤ 0.059	Favorable KELIM > 0.059	Unfavorable KELIM ≤ 0.059
AGO/OVAR 9	CP	25.6	11.4	59.5	36.6
	CP + Gemcitabine	21.9	11.2	NR, >70	38.7
AGO/OVAR 7	CP	28.3	12.8	NR, > 60	45.5
	CP + topotecan	19.5	10.2	NR, > 60	31.6
ICON 7	CP	25.2	8.8	NR, > 60	36.2
	CP + bevacizumab	20.7	13.9	65.0	38.7

NR: not reached

5555 Poster Session (Board #377), Sat, 1:15 PM-4:45 PM

Cell-free tumor DNA in peri-operative blood samples from advanced high-grade serous ovarian cancer patients with and without complete resection. *First Author: Florian Heitz, Department of Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany*

Background: Surgical outcome is an important prognostic factor in advanced high-grade serous ovarian cancer (HGOC). Intra-operative determination of residual disease may be prone to subjective bias. **Methods:** We prospectively collected and analyzed tumor tissue and plasma from 21 pts with FIGO IIIC-IV HGOC. All tumor specimen showed loss of TP53 in immunohistochemistry. Tumor DNA from tissue and peri-operative cell-free DNA at baseline (BL) and at d(ays) 1, d4 and d10 were subjected to comprehensive hybrid-capture based next-generation sequencing (NEO New Oncology GmbH, Cologne, Germany). **Results:** The initial cohort comprised 10 pts without (TR>0) and 11 pts with complete resection TR0, with a total of 43 somatic genomic alterations. *TP53* was mutated in 20/21 (95.2%) of tissue samples and in 15/21 (71.4%) corresponding plasma samples at BL. Therefore, *TP53* mutations were used as a molecular marker of circulating tumor DNA levels post-surgery. In the remaining 5 BL cases the *TP53* mutations were either not present in plasma (N= 3) or rested below the detection limit (N= 2). In d1, d4 and d10 post-surgical samples, the sample specific *TP53* mutations were detected in 12 out of 15, 10 out of 14 and in 7 out of 13 cases, respectively. *TP53*variant allele frequency (VAF) did not differ among TR0 and TR>0 at BL (mean= 1.91 versus 1.73, Mann-Whitney test p = 0.86) whereas it was significantly lower for TR0 at d1 (mean= 0.06 versus 2,06; p value= 0.002), d4 (mean= 0.07 versus 1.8; p= 0.04) and d10 (mean VAF= 0 versus 1.04; p= 0.008). Five out of 9 TR>0 cases showed at least one increase in VAF between d0 and any additional time-point. In 8 out of 9 mutations remained detectable at d10 (VAF: 0.076 – 3.26). By contrast, TR0 cases showed consistent reduction in VAF throughout the follow-up period which maximized at d10. **Conclusions:** Liquid biopsycan efficiently detect somatic mutations in the cfDNA of pts with HGOC following debulking surgery. Variation of the *TP53* VAF in sequential post-surgical samples appears to be restricted to TR>0 cases, whereas in TR0 pts VAF progressively decreases. Liquid biopsy may hold promise as a tool for the objective determination of residual disease after debulking surgery.

5556 Poster Session (Board #378), Sat, 1:15 PM-4:45 PM

A phase II clinical trial of metformin as a cancer stem cell targeting agent in stage IIc/III/IV ovarian, fallopian tube, and primary peritoneal cancer. *First Author: Ronald J. Buckanovich, Department of Internal Medicine, University of Michigan, Ann Arbor, MI*

Background: Epidemiologic and preclinical studies suggest that Metformin has antitumor effects which may be due to an impact on cancer stem-like cells (CSC). We present a phase II trial of metformin administered in combination with chemotherapy for patients with advanced stage epithelial ovarian cancer (EOC). Primary endpoints were 18 month progression free survival (PFS) and CSC number in Metformin treated tumors. **Methods:** Thirty-eight patients with confirmed stage IIC(n=1)/III(n=25)/IV(n=12) EOC were treated with either neoadjuvant metformin followed primary debulking surgery and adjuvant Metformin+chemotherapy, or neo-adjuvant metformin+chemotherapy, followed by interval debulking and adjuvant chemotherapy+Metformin. Patients were evaluated for side effects, PFS and overall survival (OS). Metformin treated tumors were evaluated for the presence of CSC via FACS and sphere assays. **Results:** Thirty-two patients (84%) completed at least six cycles of metformin+chemotherapy. Metformin was well tolerated with only one grade III/IV treatment-related adverse event (3%) noted. Common adverse effects were diarrhea (18%) and nausea (16%). Eighteen month PFS was 65.4% (95% confidence interval 47.9-78.3), Median PFS was 21.7 months (CI-17-26.7). Estimated three year OS was 73.5% (CI-54.7-84.3) with median OS not reached after a media follow-up of 33 months. Finally, tumors treated with metformin were noted to have a 3-fold decrease in ALDH+ CSC at baseline, increased sensitivity to Cisplatin in vitro, and a reduced ability to amplify ALDH+ CSC with passage in vitro. **Conclusions:** This is the first prospective study of Metformin in EOC patients. Translational studies confirm an impact of metformin on CSC. Metformin was well tolerated and outcome results were favorable, supporting the use of Metformin in phase-III studies. Clinical trial information: NCT01579812.

5557 Poster Session (Board #379), Sat, 1:15 PM-4:45 PM

Comparison of patient reported symptom burden in patients with ovarian cancer undergoing primary vs. interval tumor reductive surgery. *First Author: Larissa Meyer, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patient-reported outcomes (PROs) are important in comparative effectiveness research. We compared symptom burden and functional recovery in pts undergoing primary cytoreductive surgery (PCS) or neo-adjuvant chemotherapy (NACT) and interval cytoreductive surgery (ICS) within an enhanced recovery after surgery program (ERAS). **Methods:** Perioperative PROs were measured for women with ovarian cancer undergoing PCS or ICS using the MD Anderson Symptom Inventory- Ovarian Cancer, a 27-item validated tool which was administered preoperatively, daily in hospital, and at least weekly for 8 weeks post-op. Mixed-effect modeling was performed. **Results:** 108 pts (45 PCS, 63 ICS) participated. There was no difference in median age, Charlson comorbidity index, ASA status, history of chronic opioid use, length of stay or readmission rate. At pre-op baseline assessment, the mean pain score was higher in the PCS group (3.8 vs. 1.8, p = .0005). ICS pts had a lower median surgical complexity score (4.0 vs. 2.0, p = .03), and shorter median surgical time (260 min vs. 223 min, p = .05). During hospitalization, pts undergoing PCS reported significantly more bloating, urinary urgency, distress, sadness and mood disturbance. Women who received NACT had a significantly higher symptom burden of neuropathy, leg cramps and memory disturbances. There was no difference in pain, fatigue, drowsiness, nausea, or emesis within the first 5 days postoperatively. While there was no significant differences in the physical interference composite score, (walking, work, activity), those who underwent ICS had improved affective interference scores (mood, relations, enjoyment of life). **Conclusions:** Within an ERAS program, there were few significant differences in surgery related symptoms related to physical recovery between pts undergoing PCS or ICS. The differences in overall symptom burden suggest that disease related symptoms (pain, bloating, urinary urgency) and emotional symptoms may be related to recent diagnosis and higher tumor burden in pts undergoing PCS while the increased numbness, leg cramps and memory issues reflect chemo-related effects in the ICS cohort.

5558 Poster Session (Board #380), Sat, 1:15 PM-4:45 PM

Panitumumab in platinum-sensitive epithelial ovarian cancer patients with KRAS wild-type: The PROVE-study, a phase II randomized multicenter study of the North-Eastern German Society of Gynaecologic Oncology. *First Author: Radoslav Chekerov, NOGGO and Department of Gynecology, Campus Virchow-Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany*

Background: For ovarian cancer (OC) patients with platinum-sensitive recurrence the addition of new biologic agents to chemotherapy may improve survival. Panitumumab is a fully human monoclonal antibody specific to the epidermal growth factor receptor (EGFR). The purpose of this trial was to investigate the therapeutic efficacy of panitumumab in the combination with carboplatin-based chemotherapy in relation to the respective standard combination in patients with a KRAS wildtype with platinum-sensitive recurrent ovarian cancer (NCT01388621). **Methods:** Major eligibility criteria were pretreated platinum-sensitive epithelial ovarian/ fallopian/ peritoneal cancer and no more than 2 prior treatments for this disease. Only patients with measurable disease or elevated CA125 and with KRAS wild type were eligible. Patients were treated with Carboplatin AUC4/Gemcitabine 1000 mg/m^2 or Carboplatin AUC5/PLD 40 mg/m^2 and randomized to panitumumab 6 mg/kg day 1 and day 15, every 3 or 4 weeks. Tumor assessment was performed at baseline and at every third cycle according to CT-scan and CA-125 criteria. **Results:** In this multi-institutional phase II trial 102 patients were randomized and 96 enrolled for the final analysis. Progression-free survival in the intention-to-treat population (N=96) was 9.5 vs. 10.7 months (HR 0.829, 95%CI of 8.5-11.6 months vs 8.5-13.1 months) for the experimental vs. standard arm, p=0.45. Data of overall survival are not jet evaluable. The most common treatment related grade 3+ toxicities included hematologic toxicity (54%), skin reactions (18%) and gastrointestinal events (16%). **Conclusions:** The addition of panitumumab to platinum-based chemotherapy for recurrent ovarian cancer does not influence efficacy and progression-free survival in platinum sensitive patients, while no new additional toxicity aspects for panitumumab were evaluated. Clinical trial information: NCT01388621.

5559 Poster Session (Board #381), Sat, 1:15 PM-4:45 PM

ENGAGE: Evaluation of a streamlined oncologist-led *BRCA* mutation (*BRCA*m) testing and counselling model for patients with ovarian cancer. *First Author: Nicoletta Colombo, University of Milano-Bicocca and Istituto Europeo di Oncologia, Milan, Italy*

Background: Short *BRCA*m testing turnaround times (TAT) are crucial to making timely treatment decisions for patients (pts) with ovarian cancer. ENGAGE (NCT02406235; D0816R00006) evaluated a streamlined, oncologist-led germline *BRCA*m testing model, piloted by the Institute of Cancer Research and the Royal Marsden Hospital, London, UK. Results presented are from the final analysis (data cut-off: 30 Sep 2016). **Methods:** This prospective, observational study enrolled pts with ovarian cancer across sites in the US (n = 11), Italy (n = 8) and Spain (n = 7). Oncologists and nurses at participating sites were trained on genetic counselling techniques relating to *BRCA*m testing. Primary endpoints were *BRCA*m testing TAT (time from initial counselling to the provision of test results or post-*BRCA*m test counselling [whichever occurred latest]); pts' satisfaction with the oncogenetic testing model, evaluated using pre- and post-*BRCA*m testing surveys; and clinicians' opinion on the value of this new testing pathway, evaluated using a post-*BRCA*m testing survey. **Results:** For the 700 evaluable pts enrolled (US = 317; EU = 383), pre-*BRCA*m testing counselling was carried out by either an oncologist (40.7%) or clinical staff (nurse or research coordinator; 59.3%) in the US, and only by oncologists in the EU. The median overall TAT was 9.1 weeks (all pts), with 12.0 weeks in Spain, 20.4 weeks in Italy (17.4 weeks EU median) and 4.1 weeks in the US. The differences were mainly due to the time from *BRCA*m testing to obtaining the test results. Satisfaction with the overall counselling was high amongst pts, with a mean dimension score rating of 3.8/4 (where 4.0 = highest satisfaction). 93.6% of pts were happy to have received genetic testing as part of an existing oncologist appointment, and more than 80% of oncologists were satisfied with the screening process, agreeing that it was an efficient use of their time. **Conclusions:** The ENGAGE study results show that a streamlined oncologist-led *BRCA*m testing model can offer reduced TAT and high levels of satisfaction amongst pts and clinicians. The success of this model is enhanced by access to a *BRCA*m testing facility, from which results can be obtained quickly. Clinical trial information: NCT02406235; D0816R00006.

5560 Poster Session (Board #382), Sat, 1:15 PM-4:45 PM

The successful phase 3 niraparib ENGOT-OV16/NOVA trial included a substantial number of patients with platinum resistant ovarian cancer (OC). *First Author: Jose Maria Del Campo, Grupo Español de Investigación en Cáncer de Ovario (GEICO) and Vall d'Hebrón University Hospital, Barcelona, Spain*

Background: Niraparib is a highly selective poly (ADP-ribose) polymerase (PARP) 1/2 inhibitor (PARPi); in preclinical studies, it concentrates in the tumor relative to plasma to deliver durable, near complete PARP inhibition and persistent antitumor effects.Niraparib demonstrated significantly longer progression free survival (PFS) vs placebo in patients (pts) with recurrent OC who were randomized following a complete response (CR) or partial response (PR) to platinum based chemotherapy in the controlled, double-blind phase 3 ENGOT-OV16/NOVA trial. To more fully characterize the NOVA trial population, we assessed platinum resistance status, defined as a duration of response to platinum $<$ 6 months to the most recent (ultimate) platinum regimen. Analysis was limited to pts in the placebo arm, as inclusion of pts receiving active treatment (niraparib) would have confounded the ability to determine duration of response to platinum alone. **Methods:** Pts with recurrent OC, no prior PARPi use, $\geq$2 prior courses of platinum based chemotherapy, and CR or PR to the most recent platinum based chemotherapy were eligible. Pts were assigned to one of two cohorts based on g*BRCA* testing (g*BRCA*mut or non-g*BRCA*mut) and randomized 2:1 within each cohort to niraparib 300 mg or placebo qd until progressive disease (PD). Randomization occurred up to 8 weeks following the last dose of the most recent platinum based chemotherapy. PFS was measured from time of randomization to death or earliest PD as assessed by independent review committee. Estimated probability of pts having disease progression in each cohort and pooled across cohorts 6 months after the last dose of their most recent platinum therapy was calculated using the Kaplan-Meier methodology. **Results:** 181 pts were randomized to placebo (65 g*BRCA*mut and 116 non-g*BRCA*mut). Platinum resistance rate estimates for the g*BRCA*mut, non-g*BRCA*mut, and pooled cohorts were 42%, 53%, and 49%, respectively. **Conclusions:** Approximately half of the pts in the NOVA study, where niraparib treatment met its primary endpoint of prolonging PFS following a response to platinum, had developed platinum resistance to their last line of chemotherapy. Clinical trial information: NCT01847274.

5561 Poster Session (Board #383), Sat, 1:15 PM-4:45 PM

A platinum-resistant subtype of high-grade serous ovarian cancer identified by a network of somatic mutations. *First Author: John P. Shen, University of California San Diego Moores Cancer Center San Diego School of Medicine, La Jolla, CA*

Background: High-grade serous ovarian carcinoma (HGS-OvCa) is a heterogeneous entity with a widely variable clinical course even among patients of the same stage and histological subtype. Although most patients will achieve remission with platinum-based chemotherapy, ~20% will display primary platinum resistance. Currently no biomarker exists to identify these platinum resistant patients. **Methods:** We have recently developed a method called Network-based Stratification (NBS), which combines genome-scale somatic mutation profiles with genetic interaction networks and performs unsupervised clustering of patients into subtypes. **Results:** Using NBS HGSOC patients were stratified into subtype, in both TCGA (n = 330) and the ICGC (n = 92) a high-risk (HR) subtype consisting of ~20% of the patients was identified (see table). Propagated mutation scores of the HR tumors from TCGA and ICGC cohorts we remarkably correlated (Pearson r^2 = 0.94, $p < 0.001$), relative to the correlation between HR and standard risk subtypes within TGCA cohort (r^2 = 0.18). We then identified molecularly matched cell line models for *in vitro* study, finding that HR cell lines (Kuramochi, Ovkate, OAW28, 59M) were significantly more resistant to cisplatin relative standard risk cell lines (COV318, TYK-NU, OVCAR4), (IC_{50} 14.4 vs. 3.3 μM, $p < 0.0001$). There was no significant difference in sensitivity to paclitaxel. A genome-wide knockout screen using CRISPR-Cas9 has identified several candidate genes mediating this observed platinum resistance. **Conclusions:** NBS can be used to identify a molecularly distinct subtype of HGSOC characterized by poor patient survival and primary platinum resistance.

TCGA Cohort (Nature 2011).

subtype	median OS (months)	HR vs. SR I	n (% of cohort)
High-Risk (HR)	32	2.17	64 (19%)
Standard Risk I	55	–	231 (70%)
Standard Risk II	60	0.66	14 (4.2%)
Standard Risk III	not-yet-reached	0.4 log rank p = 1.6 e-5	21 (6.4%)

ICGC Cohort (Nature 2015)

subtype	OS (months)	HR vs. SR I	n (% of cohort)
High-Risk (HR)	25.2	2.15 *	20 (22%)
Standard Risk I	45.6	–	63 (68%)
Standard Risk II	not-yet-reached	0.98 log rank p = 2.0 e-4	10 (11%)

5562 Poster Session (Board #384), Sat, 1:15 PM-4:45 PM

Ki67 as a prognostic factor in low grade serous ovarian cancer (LGSOC): A retrospective analysis of the Tumor Bank Ovarian Cancer (TOC). *First Author: Jalid Sehouli, AGO and Charité Campus Virchow-Klinikum, Berlin, Germany*

Background: LGSOC is a rare and distinct entity characterized by younger age, lower response to chemotherapy and better clinical outcome. Aim of this study was to evaluate the impact of Ki67, estrogen and progesterone receptors (ER and PR) on platinum response and survival in primary LGSOC patients. **Methods:** 80 primary LGSOC patients with available FFPEs were identified within TOC. The histology was confirmed at a second histological evaluation. For Ki67 analysis conventional immunohistochemical staining was performed with the Mib-1 clone on Ventana. Slides were explored with a light microscope camera. A representative field for Ki-67 evaluation was selected, in case of heterogeneous staining a hot spot was chosen. The software classified detected cells into non-tumor, negative and positive cells. When necessary, a correction of tumor and non-tumor areas was performed by an experienced pathologist. The counted cells ranged between 175 and 2398. Overall the method allows a precise, continuous and standardized means to quantify Ki-67. ER and PR status was determined on scanned IHC TMA slides. ER and PR positive tumors were defined if the percentage of stained tumor cells was at least 10%. Statistical analysis was performed using IBM SPSS Statistics. **Results:** Median age at diagnosis was 56 years (range: 20-81), 81.3% of patients presented in advanced stage and 96.3% received platinum based chemotherapy. Ki67 median value was 5.09 (IQR: 1.56-10.5). 93.1% and 47.9% of the patients showed ER and PR positive tumors, respectively. Median overall survival (OS) was 45.5 months (range: 0.1-182.8). Our analysis showed that platinum free interval (PFI) was significant longer in patients with lower Ki67 ($p = 0.006$). Higher proliferation rates were significant associated with poorer progression free ($p = 0.011$, HR = 1.039, 95%CI: 1.009-1.070) and OS rates ($p = 0.001$, HR = 1.059, 95%CI: 1.025-1.095). No differences in clinical outcome were seen in patients with different ER and PR status. **Conclusions:** This is the first study showing that higher Ki67 values correlate with shorter PFI and poorer survival rates in LGSOC, underlying the heterogeneous character of this disease.

5563 Poster Session (Board #385), Sat, 1:15 PM-4:45 PM

Should MMMT of the endometrium/ovary be treated with anthracycline instead of taxane based chemotherapy? *First Author: Viola A. Heinzelmann-Schwarz, University Hospital Basel, Basel, Switzerland*

Background: Carcinosarcomas of endometrial (MMMT-E) and ovarian (MMMT-O) origin are rare biphasic tumors, associated with poor prognosis and thought to be epithelial in origin. In view of this, there has been a shift towards carboplatin and paclitaxel rather than anthracycline based chemotherapy regimens which were used when they were treated as "sarcomas". The purpose of this large retrospective study is to determine whether this change in chemotherapy is associated with better outcomes. **Methods:** Firstly, clinicopathological features of patients with all stages of MMMT-E (n=103) and -O (n=17) were compared to patients with adenocarcinoma of the endometrium (n=172) and ovary (n=189) in a case-controlled study. Clinicopathological characteristics, FIGO stage, first-line regimens and patient outcomes were analyzed. Secondly, primary tumor specimens of high grade serous ovarian cancers (HGSOC, n=1290) and MMMT-O (n=450) from an independent cohort were analyzed using immunohistochemistry and next generation sequencing to predict response to chemotherapeutic agents. **Results:** MMMT have a poor prognosis, however, there was a plateau in survival of MMMT-E after 2.5 years in patients with FIGO stage I/II disease, with no recurrence/cancer deaths observed beyond this. There was a statistically significant worse relapse-free survival in patients with MMMT-E treated with carboplatin and paclitaxel compared to carboplatin and anthracyclines ($p=0.0011$). In the second independent prospective cohort comparing HGSOC versus MMMT-O, both were driven predominantly by p53 mutations. MMMT-O expressed statistically more commonly PI3KCA and KRAS ($p=0.015$ and 0.018), respectively. Of particular interest, both HGSOC and MMMT-O showed a higher percentage of probability of responding to a combination of carboplatin/anthracyclins (71.2 vs. 73.9%) than carboplatin/taxanes (58.4 vs 39.4%). **Conclusions:** Patients with MMMT-E and stage I/II have an excellent prognosis if there is no recurrence by 2.5 years. Platinum/anthracyclines regimens appear to be associated with a better outcome than platinum/taxane in MMMT-E and MMMT-O. This could be tested in an international prospective randomized controlled trial.

5564 Poster Session (Board #386), Sat, 1:15 PM-4:45 PM

A re-analysis of the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial accounting for ovarian cancer (OVCA) heterogeneity. *First Author: Sarah Madhu Temkin, Virginia Commonwealth University, Richmond, VA*

Background: A mortality benefit from screening for OVCA has not been demonstrated, but screening efficacy could differ for histologic subtypes. We re-analyzed PLCO evaluating whether OVCA detection and outcomes were affected by the heterogeneous biologic behavior of this disease. **Methods:** Type 2 tumors (moderately/poorly differentiated serous and adenocarcinoma) were compared to all other tumor (OT) types (low grade serous and endometrioid, clear cell, other, low malignancy potential) (LMP). We examined differences in the distribution of tumor types and stage by study arm and method of diagnosis [screen detected (SD) and interval detected (ID) (i.e. assigned to screening but diagnosed between screening tests)]. Stage distribution and survival were analyzed. **Results:** Among the entire PLCO population, 531 women were diagnosed with OVCA during the study; 282 (53%) in the screening arm and 249 (47%) in the usual care arm. Of the tumors able to be characterized (n=408; 77%), 74% (n=300) were Type 2 and 26% OT (n=108). In the screening arm, 70% of tumors diagnosed were Type 2 compared to 78% in usual care ($p=0.07$). Overall, survival was significantly better for OT tumors compared to Type 2 tumors ($p<0.01$) but there was no difference in survival by study arm for either tumor type separately (Type 2: $p=0.50$; OT: $p=0.23$). Within the screening arm, 30% of Type 2 tumors were SD compared to 54% of OT tumors ($p=0.02$) (see Table). Only 15% of Type 2 SD tumors were Stage I/II, compared to 82% of SD OT tumors ($p<0.01$). Stage at diagnosis was similar among Type 2 patients whether they were SD or ID ($p=0.56$) and there was no difference in survival ($p=0.56$). **Conclusions:** A significant difference in tumor types by study arm was not observed. However, within the screening arm, Type 2 tumors were less likely to be SD or Stage I/II compared to OT tumors. Survival for Type 2 tumors was similar regardless of method of diagnosis.

Ovarian tumor types by diagnosis method.

	Type 2 N (%)	OT N (%)	p-value
Usual Care	144 (48)	41 (38)	0.07
Screening	156 (52)	67 (62)	
• Never screened	15 (9.6)	8 (11.9)	<0.01
• Post-screening	70 (44.9)	17 (25.4)	
• Interval	25 (16.0)	6 (9.0)	
• Screen Detected	46 (29.5)	36 (53.7)	

5565 Poster Session (Board #387), Sat, 1:15 PM-4:45 PM

Are symptoms of ovarian cancer evident: A retrospective analysis of claims data to determine prior symptoms to diagnosis. *First Author: Denise Manon Langabeer, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There are no standard of care screening methods for ovarian cancer. Over sixty percent (60%) of ovarian cancer cases are found at Stage III and IV, which ultimately impacts a woman's survival rate. The purpose of this study is to determine if specific symptoms are evident prior to diagnosis of ovarian cancer. **Methods:** A retrospective analysis of health insurance claims between 2008 through 2013 from a commercial payer was performed based on the following eligibility criteria: 1) women diagnosed with ovarian cancer, 2) at the time of diagnosis, 24 years of age or older, 3) enrolled in healthcare plan for a period of 24 months or more prior to diagnosis, and 4) resident in the state of Texas. Symptoms were identified based on ICD-9 diagnosis codes and categorized specific to pain, abdominal and pelvis, digestive, and bladder and were evaluated at minimum of six months prior to diagnosis. ICD9 codes are used for this analysis as the data is limited to years before the change to ICD10. **Results:** Baseline data of 3,641 women diagnosed with ovarian cancer were identified and were associated with 927,528 claims specific to the symptoms. The age of women diagnosed with cancer ranged between 24 and 88 (mean=52; SD: 0.1833). Nearly 70% of women were treated for one or more symptoms prior to diagnosis. The symptoms women experienced the most were associated with abdomen and pelvis at 60%. Pain, digestive, and bladder ranged between 20% and 30%. **Conclusions:** This research is intended to further explore whether symptoms are evident in women diagnosed with this disease, and if so, how long and how frequent did the symptoms occur prior to diagnosis. Additionally, a review of combination of symptoms is explored. This research is intended to provide a better understanding of the disease as well as support that women may need to be referred to an oncologist earlier for further evaluation should reoccurring symptoms present.

5566 Poster Session (Board #388), Sat, 1:15 PM-4:45 PM

Circulating free DNA and circulating tumor cells as new serum biomarkers in advanced ovarian cancer. *First Author: Jeronimo Martinez Garcia, Hospital Clinico Universitario Virgen de la Arrixaca, Murcia, Spain*

Background: Circulating free DNA (cfDNA) and circulating tumor cells (CTC) are new biomarkers for malignant tumors. Its role on ovarian epithelial cancer (OEC) is not yet well stablished. We analyze its role on advanced OEC compared with CA125 and HE4. **Methods:** Multicentric prospective observational study from November 2013 until February 2017, with OEC patients group (OECG), benign ovarian tumors group (BENIGNG) and health subjects control group (HEALTHG). CTCs were analysed by the CellSearch method and cfDNA by ALU-sequences-based quantitative PCR using two primers (115 and 247 bp); cfDNA integrity was calculated by ALU247/ ALU115 ratio. Samples were obtained before treatment (M0), after primary peritoneal surgery (M1), after one cycle of chemotherapy (M2), before (M3) and after interval surgery (M4). This study was approved on May 2013 by the corresponding Central Research Independent Ethics Committee. **Results:** We analyzed 102 subjects from all 3 groups (81 OECG, 14 BENIGNG y 7 HEALTHG); 68% were high grade serous subtype; most frequent staging was IIIC (58%). Within the follow-up (FU) period (average 14 months: min 0, max. 35) 36% relapses and 23% deaths were reported. CTCs were positive on 23% of OECG. In HEALTHG no positive were seen and only 1/14 in the BENIGNG group. Monitoring of cfDNA at the treatment points shows significant differences between M0 and M4 (p = 0.02). No differences were seen in the other determinations. cfDNA-ALU115 was 1.40178 ng / mcL (95% CI 1.18066-1.62290) in the OECG, 0.66383 (95% CI 0.44832-0.87935) in BENIGNG and 0.59923 in HEALTHG (95% CI, 0.14449-1.05397). The difference was significant between OECG and BENIGNG (P = 0.017) and near the significance between OECG and HEALTHG (p = 0.69). cfDNA integrity in OECG and HEALTHG was significantly different (P = .012). The area under the curve of Ca125, HE4, CTC, cfDNA and CFDNA integrity was 0.490, 0.526, 0.621, 0.587 and 0.450 respectively. New generation sequencing of circulating TP53 is ongoing. **Conclusions:** CTC and cfDNA are new biomarkers that might have an important role in the diagnosis and monitoring of OEC.

5567 Poster Session (Board #389), Sat, 1:15 PM-4:45 PM

Prognostic implications of lymph node metastasis in advanced ovarian cancer: Analysis of National Cancer Database. *First Author: Sukamal Saha, Easton Hospital, Easton, PA*

Background: During debulking surgery (Surg) for advanced ovarian cancer (OvCa), lymph node (LN) sampling are not routinely performed. Hence, prognostic implications of LN involvement following debulking surg and chemotherapy (ChemoRx) were analyzed from National Cancer Database (NCDB). **Methods:** Only Stage III and Stage IV patients (pts) from 2004 –2014 NCDB pts undergoing Debulking surg. and ChemoRx were included. Group A included pts with debulking surg without bowel resection; Group B with major bowel resection and Group C with bowel and bladder resection. Pts were further subdivided according to the use of 1) NeoAdjuvant (NeoAdj) 2) Adjuvant (Adj) and 3) Neo Adj and Adj ChemoRx. Survival analysis was done based on -ve or +ve LN status. using Pearson Chi Square testing. **Results:** Out of 10,737 Stage III and 3,102 Stage IV pts, there were 6828 Group A, 6413 Group B and 598 Group C pts. Five year overall survival (OS) for all pts in Stage III with LN-ve vs LN +ve was 59.9% vs 53.9% and Stage IV was 48.7% vs 41.2%. In Group A, B, and C, the 5 yr OS was better in LN – ve than LN +ve pts (Table1). The OS for both LN –ve and LN +ve groups were better in Adjuvant chemoRx in all 3 groups. OS was slightly better in Stage III vs Stage IV pts. **Conclusions:** Even though LN dissection are not routinely done during debulking surg, overall pts with LN metastasis do worse than LN –ve pts irrespective of the timing of ChemoRx. Hence, LN sampling during debulking surg should be strongly considered as it may provide important prognostic information.

Five year overall survival by LN +ve vs -ve.

		Stage 3 (n=10737)			
Surg (n)	**LN Status**	**NeoAdj (%)**	**Adj (%)**	**NeoAdj and Adj (%)**	**p value**
Grp A	LN-ve	46.0%	63.0%	57.8%	<0.001
5492	LN +ve	46.8%	58.8%	42.0%	<0.001
Grp B	LN-ve	50.4%	60.0%	45.0%	<0.001
4824	LN +ve	41.2%	51.8%	48.9%	0.051
Grp C	LN-ve	75.0%	63.9%	37.5%	0.249
421	LN +ve	27.3%	55.0%	33.3%	0.075
			Stage 4 (n=3102)		
Grp A	LN-ve	44.8%	45.5%	54.1%	0.232
1336	LN +ve	33.1%	42.4%	42.4%	0.150
Grp B	LN-ve	42.1%	50.0%	54.0%	0.334
1589	LN +ve	33.3%	42.4%	35.8%	0.083
Grp C	LN-ve	40.0%	57.1%	42.9%	0.618
177	LN +ve	30.0%	51.1%	33.3%	0.298

Group A = debulking without bowel resection; Group B = debulking with major bowel resection and Group C =debulking with bowel and bladder resection

5568 Poster Session (Board #390), Sat, 1:15 PM-4:45 PM

Phase I study of the safety and activity of formulated IL-12 plasmid administered intraperitoneally in combination with neoadjuvant chemotherapy in patients with newly diagnosed advanced stage ovarian cancer. *First Author: Premal H. Thaker, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: This study evaluated weekly intraperitoneal (IP) GEN-1, an IL-12 plasmid formulated with polyethyleneglycol-polyethyleneimine cholesterol lipopolymer, with intravenous (IV) weekly taxane (T) and carboplatinum (C) every 3 weeks in epithelial ovarian, fallopian tube or primary peritoneal cancer (EOC) patients undergoing neoadjuvant therapy (NAC). The primary objective was to evaluate the tolerability and safety of GEN-1 with NAC. Secondary objectives included objective clinical response and pathological response at interval debulking surgery (IDB). **Methods:** Newly diagnosed advanced stage EOC patients being treated with NAC were eligible. The trial utilized a 3+3 design with GEN-1 IP dose levels of 36 mg/m^2, 47 mg/m^2, 61 mg/m^2, and 79 mg/m^2 weekly for 8 treatments with concurrent IV T/C. Dose-limiting toxicity (DLT) was based on the first 4 doses of GEN-1 administered. **Results:** To date, 13 patients have been treated on-study with 12 patients receiving all 8 treatments of IP GEN-1 with no DLTs. The most common related toxicities were Gr 1 nausea, vomiting, abdominal pain and fatigue. One patient experienced Gr 2 fevers associated with GEN-1 but responded to acetaminophen and fluids. One patient did not undergo IDB while on-study due to a cancer related pulmonary embolism and severe deconditioning. This patient has since improved and will have IDB. **Conclusions:** Adding GEN-1 to neoadjuvant T/C is safe and appears to be active in EOC patients. We are reporting the interim findings; final results with translational data to be presented. Clinical trial information: NCT02480374.

Response		**Total n**	**36 mg/m^2**	**47 mg/m^2**	**61 mg/m^2**	**79 mg/m^2**
RECIST Response prior to IDB (n = 12)	CR	1	1	0	0	0
	PR	8	0	2	3	3
	SD	3	2	1	0	0
Debulking Status (n = 11)	R0	6	2	0	2	2
	R1	4	1	2	0	1
	R2	1	0	0	1	0
Pathologic (n = 11)	cPR	1	1	0	0	0
	Micro	5	1	1	1	2
	Macro	5	1	1	2	1

5569 Poster Session (Board #391), Sat, 1:15 PM-4:45 PM

Impact of genomic heterogeneity on PI3K/AKT/mTOR inhibitors (PAMi) efficacy in gynecologic cancer (GYN) patients (pts). *First Author: Victor Rodriguez Freixinos, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Aberrant PI3K/AKT/mTOR activation is common in GYN. Predictive biomarkers to PAMi in GYN have yet to be identified. **Methods:** Advanced GYN pts with available genomic data, treated with PAMi in phase I/II clinical trials were selected. Mutation (mut) allele fractions (MAFs) were corrected for tumor purity and defined as clonal (cl) ($\geq$ 0.4) or subclonal (scl) ($<$ 0.4). PAMi efficacy: (i) time to progression (TTP); (ii) clinical benefit rate (CBR: complete/partial response or stable disease $>$ 4 months [m]); and (iii) ratio TTP on PAMi/ TTP on non-standard chemotherapy pre- or post-PAMi (PAMi/nsChemo TTP). **Results:** From 2010 to 2016, 264 GYN pts (152 ovarian(OC); 75 endometrial(EC); 37 cervical(CC)) had genomic analysis; 50 pts (24 OC [11 PIK3CA mut, 5 KRAS mut], 15 EC [6 PIK3CA mut, 5 PTEN mut, 4 KRAS mut], and 11 CC [9 PIK3CA mut, 3 KRAS mut]) received PAMi (17 pan-PI3K/mTOR or AKT inh, 17 α-PI3K inh, 16 PAMi targeted combos). PAMi therapy was matched (MA) to PIK3CA/ PTEN mut in 30 pts (60%). Median age was 57 years (30-70); median number of prior lines was 2 (1-6) and 34 pts (68%) received nsChemo. Efficacy of PAMi: (i) median TTP (3.27 m [95% CI 2.1-4.4] with trend for longer TTP in OC compared to others [3.93 vs. 2.1 m, HR 0.57; p = 0.08], without differences according to MA status [p = 0.26] or regimen [p = 0.5]); (ii) CBR (42% [95% CI 27-58%], without differences according to tumor type [p = 0.47], MA status [p = 1] or regimen [p = 0.86]); and (iii) TTP PAMi/ nsChemo $\geq$ 1.3 (42% [95% CI 24-63%], without differences according to tumor type [p = 0.53], MA status [p = 0.23] or regimen [p = 0.41]). Partial responses were seen in 5 pts (4 PIK3CA mut on single agent PAMi; 1 KRAS mut on PI3K + MEK inh). Of 4 KRAS mut pts, none had CBR with single agent PAMi. PIK3CA mut were cl in 63% of OC, 17% of EC and 40% of CC. Clonal exon 20 PIK3CA mut were more frequent in OC (p = 0.03). We found longer TTP for cl PIK3CA events (4.0 vs. 1.5 m in scl, HR 5.1, p = 0.006) and a trend for exon 20 events (4.4 vs. 1.4 m in exon 9, HR 1.7, p = 0.25). **Conclusions:** Regardless of PIK3CA/PTEN mut status, PAMi confer CBR in almost 40% of GYN pts. Functionality and clonality of PIK3CA mut impact on TTP and interact with tumor type. Coexisting KRAS mut may drive resistance to single agent PAMi.

5570 Poster Session (Board #392), Sat, 1:15 PM-4:45 PM

Neoadjuvant BEP regimen in the treatment of extensively advanced yolk sac tumor: A single institutional experience. *First Author: Gong-Yi Zhang, Department of Gynecological Oncology, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Due to the highly aggressive biological behavior and early intra-abdominal spread potential of ovarian yolk sac tumor (YST), a considerable proportion of patients were inoperalbe at initial diagnosis. The aim of this study was to investigate the role of neoadjuvant chemotherapy (NACT) in this cohort of patients. **Methods:** Between July 1982 and December 2015, 58 patients diagnosed as YSTs were initially treated at Cancer Hospital of China Academy of Medical Science (CAMS), among which 18 were evaluated to be inoperable and received NACT. They were either too debilitated by the disease (ECOG ps≥2) to undergo a major surgery, or were with too extensively disseminated lesions to be optimally debulked. Massive ascites, pleural effusion, dyspnea, neoplastic fever, hypoproteinemia, or electrolyte disturbance were also common in these 18 patients. This cohort of patients was retrospectively reviewed. **Results:** One or 2 cycles of BEP regimens were prescribed to the majority of patients preoperatively. At the completion of NACT, all the 18 patients had ECOG ps≤1 . Seventeen of them (94.4%) exhibited clinical partial tumor regression and 1(5.6%) had clinical stable disease. Pathological complete tumor regression was observed in 2 (11.1%) patients, whereas the remaining 16(88.9%) had nearly complete pathological response. All these 18 patients were rendered operable at the completion of NACT, yielding a resection rate of 100%. Seventeen patients (94.4%) were cytoreduced to no macroscopic residual disease, 1 (5.6%) patient was cyto-reduced to macroscopic residual disease ≤2 cm. No major surgical complications occurred in our series. After a median follow-up of 83.5 months, 17 patients were free of recurrence. Five-year DFS and OS were both 94.4%. Fertility-sparing surgery was carried out in all the 17 patients with fertility desire, and 5 infants were delivered in 6 patients who attempted conception. **Conclusions:** One or 2 cycles of NACT followed by early cyto-reductive surgery offers a chance for cure in patients with extensively advanced YSTs. It allows for a more through and safe cyto-reductive surgery, improves survival outcomes, and helps pave the way for fertility-sparing surgery.

5571 Poster Session (Board #393), Sat, 1:15 PM-4:45 PM

Evaluating the repertoire of immune checkpoint markers expressed on peripheral and ascites CD8$^+$ T cells in ovarian cancer. *First Author: Stephanie Gaillard, Duke Cancer Institute, Duke University Medical Center, Durham, NC*

Background: Understanding the immune checkpoint marker repertoire can facilitate development of therapeutic strategies to improve efficacy of immune-based therapies. We used a novel high-dimensional flow cytometry panel to determine co-expression patterns of immune checkpoint markers and effector function of CD8+ T cells from peripheral blood and ascites of patients newly diagnosed with ovarian cancer. **Methods:** Peripheral blood and ascites samples were collected from patients with epithelial ovarian cancer (n=8). Cells isolated from peripheral blood and ascites were used for immune profiling by multiparameter flow cytometry of 5 inhibitory receptors (PD-1, LAG-3, TIM-3, TIGIT, and BTLA) on CD8+ T cells, along with 4 functional parameters (production of each of the following: TNF-α, IFN-γ, IL-2, and upregulation of CD107a). A complementary multiplex analysis on plasma and ascites fluid was performed to quantify 14 soluble checkpoint markers. **Results:** The concentrations of soluble PD-1, TIM-3, LAG-3, CTLA-4, BTLA, IDO, and CD137 were increased in ascites fluid compared to plasma from patients with ovarian cancer. Ascites CD8+ T cells co-express higher levels of inhibitory receptors than peripheral CD8+ T cells. In total, CD8+ T cells in ascites retained the ability to produce effector functions at levels similar to peripheral blood. However, IFN-γ production was retained in PD-1 only expressing CD8+ T cells and decreased in CD8+ T cells co-expressing multiple receptors. **Conclusions:** High-dimensional flow cytometry allowed for the phenotypic and functional characterization of CD8+ T cells from ovarian cancer patients. The profile of receptor co-expression was distinct in peripheral blood compared to ascites. Collectively, our study suggests that co-expression of factors beyond PD-1 influences CD8+ T cell activity. Thus blocking PD-1 and PD-L1 alone may not be sufficient for CD8+ T cells expressing multiple inhibitory receptors.

5572 Poster Session (Board #394), Sat, 1:15 PM-4:45 PM

A phase I dose-escalation study of intraperitoneal (IP) cisplatin, IV/IP paclitaxel, IV bevacizumab, and oral olaparib for newly diagnosed adenxal carcinoma. *First Author: Jason A. Konner, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: IP cisplatin (Cis) plus IV/IP paclitaxel (Tax) is a standard therapy for optimally debulked adnexal cancer. We previously demonstrated the feasibility of combining bevacizumab (Bev) with this IV/IP regimen. In this study IP Cis, IV/IP Tax, and IV Bev are combined with olaparib (Ola) as front-line therapy. **Methods:** Patients with newly diagnosed adnexal (ovarian, fallopian tube, or primary peritoneal) carcinoma, acceptable organ function, and KPS ≥ 70% are eligible. Patients receive 6 cycles of chemotherapy plus Bev: Tax 135 mg/m^2 IV over 3 hours on Day 1, Bev 15 mg/kg IV on Day 1 (starting cycle 2), Cis 75 mg/m^2 IP on Day 2, Tax 60 mg/m^2 IP on Day 8. Bev is continued every 3 weeks for 21 treatments after chemotherapy is complete. In addition, Ola is given at escalating doses (50/100/200mg tabs BID) on Days 2-8 during cycles 1-6, and then 300mg BID Daily during cycles 7-22. The primary objective is to evaluate the MTD and safety/tolerability of Ola when combined with IP Cis, IV Bev and IV/IP Tax using a 3+3 dose escalation scheme. **Results:** Seventeen women have been treated [median age 57 (47-73)]: 8 in cohort 1 (50mg), 3 in cohort 2 (100mg) and 6 in cohort 3 (200mg). Thirteen (76%) completed all 6 cycles of IV/IP cis/tax; 2 (12%) experienced IP port malfunction (both were removed and replaced); 2 (12%) switched from IP Cis to IV carboplatin due to nephrotoxicity (via ATN and/or OCT-2 inhibition). Grade 3/4 toxicities have included: neutropenia (50%), hyperglycemia (12.5%), leukopenia (12.5%), anemia (18.8%), fatigue (12.5%), and lymphopenia (31.3%). There were 2 occurrences of related grade 3 small bowel obstructions (12.5%), during cycles 2 and 7, respectively. There were no perforations or fistulae. Maintenance therapy with Bev + Ola was generally well tolerated. **Conclusions:** The addition of Ola to this IV/IP regimen appears to be feasible. Ola may increase the risk of creatinine elevation and myelotoxicity. The MTD of intermittent dosing of Ola tabs concurrent with chemotherapy appears to be 200mg BID, while maintenance bev + full-dose ola at 300mg BID continuous appears feasible following IV/IP. Updated results will be presented. Clinical trial information: NCT02121990.

5573 Poster Session (Board #395), Sat, 1:15 PM-4:45 PM

Phase I study to evaluate the tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) of PM01183 (Lurbinectedin) in combination with olaparib in patients with advanced solid tumors. *First Author: Andres Poveda, Clinical Area of Gynecologic Oncology, Instituto Valenciano de Oncología (IVO), Valencia, Spain*

Background: PM01183 (Lurbinectedin) is a new anticancer drug that exerts antitumor activity through inhibition of trans-activated transcription and modulation of tumor microenvironment and is highly active in platinum resistant ovarian cancer. (Poveda A et al. ASCO 2014.abstr #5505). Olaparib (AZD2281, KU-0059436) is a polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerase (PARP) inhibitor of PARP-1,-2 and-3 with proven antitumoral activity in homologous recombination deficient tumors. The combination of PM01183 and Olaparib has shown synergistic activity in cell-lines, independent of *BRCA* mutation status. **Methods:** This phase I study evaluates the safety, PK and PD of PM1183 in combination with short course of Olaparib tablet formulation [days (d) 1-5] a cycle of 21 d, through a 3+3 dose escalation design (NCT02684318**)** Patients with advanced or metastatic solid tumors without established standard therapeutic alternatives were selected. Primary endpoints: safety (MTD, DLT and RP2D). Secondary endpoints: PK and PD (western blot analysis of RAD51 and p-gH2AX) profiles at 0h,4.5h, 6.5h and 24h at first cycle of treatment. **Results:** 20 patients were enrolled from Nov 2015 to Sep 2016 (15 ovarian, 5 endometrial) to 5 dose levels. 19/20 were evaluable for toxicity. Two dose limiting toxicities (DLTs) (both grade 4 neutropenia ≥ 4 days) occurred at the highest dose level (PM01183 2 mg/m2 iv d1 + Olaparib 250 mg [BID] oral on d 1-5. Grade 3 toxicities occurred in 30% of patients, including grade 3 neutropenia (6%) and grade 3 asthenia (10%). PK data are available from 19 patients. Median of PM01183 total clearance (11.0 L/h) is the same as when PM01183 is given as single agent. Clearance of Olaparib (7 L/h) is consistent with results reported elsewhere (5.1 – 8.6 L/h). PD: An overall increase of RAD51 and p-gH2AX was observed, being particularly evident in 56% of patients. **Conclusions:** The Recommended Dose for Phase II (RP2D) was PM01183 1,5 mg/m2 iv d1 + Olaparib 250 mg BID on d 1-5. This combination is feasible and without evidence of drug-drug interactions. A phase-II study at RP2D is ongoing. Clinical trial information: NCT02684318.

5574 Poster Session (Board #396), Sat, 1:15 PM-4:45 PM

Incidence of secondary myelodysplastic syndrome and acute myeloid leukemia in patients with ovarian and breast cancer in real-world setting in the U.S. *First Author: Nicole Fulcher, Truven Health Analytics, an IBM Company, Cambridge, MA*

Background: Limited real-world data are available on cancer patients withsecondary malignancies such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) caused by use of certain chemotherapeutic agents that interfere with DNA. This study assessedthe incidence of secondary MDS and AML in patients (pts) with ovarian cancer (OC) or breast cancer (BC), including subcohorts tested for *BRCA* mutations and those exposed to DNA damaging therapy. **Methods:** Adult females with OC or BC between 1/1/2000 and 6/30/2014 (first observed diagnosis of OC or BC = index date) were identified from the MarketScan Commercial and Medicare claims databases. Patients had ≥12 months of pre- and ≥1 month of post-index continuous health plan enrollment. The incidence of MDS and AML (per 1000 person-years [PY]) was assessed using ICD-9 codes over a variable-length post-index period for each cancer cohort and separately for pts with *BRCA* testing and those exposed to DNA damaging therapy. **Results:** The study identified 23,862 OC pts (mean [SD] follow-up: 35.8 [31.4] months), and 281,473 BC pts (mean [SD] follow-up: 46.0 [37.2] months). Among OC pts, 10.9% had *BRCA* testing (OC-*BRCA*) and 56.6% had exposure to DNA damaging therapy (OC-DNA); 12.9% of BC pts were *BRCA* tested (BC-*BRCA*) and 28.1% had exposure to DNA damaging therapy (BC-DNA). The incidence of MDS and AML expressed as cases per 1,000 PY in the OC cohort was 0.51 (0.2%) and 0.39 (0.1%); in OC-*BRCA* pts, 0.62 and 0.25; and in OC-DNA pts, 0.68 and 0.41. In the BC cohort, the incidence of MDS and AML was 0.33 (0.1%) and 0.19 (0.1%); in BC-*BRCA* pts, 0.07 and 0.15; and in BC-DNA pts, 0.60 and 0.50. **Conclusions:** In addition to providing background rates in OC and BC pts, these data suggest that the incidence of MDS and AML in OC and BC pts was higher in patient subcohorts exposed to DNA damaging agents than in the overall cohort.

5575 Poster Session (Board #397), Sat, 1:15 PM-4:45 PM

Predictors of stopping chemotherapy early and short survival in patients with potentially platinum sensitive (PPS) recurrent ovarian cancer (ROC) who have had ≥3 lines of prior chemotherapy: The GCIG symptom benefit study (SBS). *First Author: Felicia Roncolato, Macarthur Cancer Therapy Centre, Sydney, Australia*

Background: PPS ROC is defined by a platinum free interval > 6 months. Women starting ≥3 lines of chemotherapy for PPS ROC are however a heterogeneous group with variable response to chemotherapy and OS. We sought to identify baseline characteristics (health related quality of life [HRQL] and clinical features) that were associated with stopping chemotherapy early and shorter OS to improve patient selection for palliative chemotherapy. **Methods:** 378 women with PPS ROC starting ≥3 lines chemotherapy enrolled in GCIG SBS. HRQL was assessed with EORTC QLQ-C30/QLQ-OV28. Associations with stopping chemotherapy early (by 8 weeks) were assessed with logistic regression. Associations with OS were assessed with Cox proportional hazards regression. Variables significant in univariable analysis ($p < 0.05$) were included as candidates for multivariable analyses using backward elimination to select those independently significant at $p < 0.05$. **Results:** Median age was 64 years. The line of chemotherapy was third in 40%, fourth in 29%, and ≥ fifth in 31%. Chemotherapy was stopped early in 45/378 (12%) and their median OS was 3.4 months. Poor physical function (PF) and global health status (GHS) at baseline were significant univariable predictors of stopping chemotherapy early ($p < 0.008$); PF remained significant in a multivariable model adjusting for clinical factors (haemoglobin [Hb], ascites, abdominal cramps, neutrophil: lymphocyte≥5, platelets, log CA125); p = 0.03. Median OS in the whole group was 16.6 months. PF, role function, GHS and abdominal/GI symptoms were significant univariable predictors of OS ($p < 0.001$); PF and GHS remained significant predictors of OS in multivariable models including Hb, ascites, neutrophil: lymphocyte≥5, platelets, log CA125, ECOG and BMI ($p < 0.007$). **Conclusions:** In women with PPS ROC ≥3 lines chemotherapy, baseline PF and GHS are independent significant predictors of stopping chemotherapy early and short OS. HRQOL is easily measured, prognostic and may improve clinical trial stratification, patient-doctor communication and support clinical decision making. Clinical trial information: 12607000603415.

5576 Poster Session (Board #398), Sat, 1:15 PM-4:45 PM

Homologous recombination deficiency and platinum rechallenge in platinum-resistant ovarian cancer patients. *First Author: Alexandre Andre B. A. Da Costa, A.C. Camargo Cancer Center, São Paulo, Brazil*

Background: Ovarian carcinomas show homologous recombination deficiency (HRD) in up to 50% of cases and in 15 to 20% of cases occur due to germline *BRCA1* or *BRCA2* mutations. *BRCA* mutated tumors are more sensitive to PARP inhibitors and platinum based chemotherapy. The objective of this study was to characterize a cohort of ovarian cancer patients regarding HRD and to evaluate the impact of these scores in prolonged platinum sensitivity. **Methods:** Thirty one ovarian cancer patients with platinum resistant recurrence reexposed to platinum based chemotherapy were selected. Paraffin embedded tumor samples from 14 patients were analyzed using ONCOSCAN assay (Affymetrix) to evaluate HRD scores. The association of the scores with response rate to platinum rechallenge, overall survival and clinical pathologic factors was evaluated. **Results:** From the cohort of 31 patients, 15 samples from 14 patients were analyzed for genomic alterations. Median scores were 19.5 for TAI, 12.5 for cnLOH+L, 26.0 for LST and 6.3 for HRD. High scores were found in 10 out of 14 (for cnLOH+L score) and 9 out of 14 (for LST score) patients. Seven of the 14 patients analyzed analyzed for genomic alterations had response, which suggested homologous recombination deficiency. No significant differences were observed between response rates for high versus low scores. Numerically, cnLOH+L, LST and HDR scores were higher in patients with response to treatment compared to those without response. Median overall survival was 13.4 months from the beginning of platinum rechallenge and no difference in survival according to scores was observed. Among the clinical pathologic factors, family history of breast or ovarian cancer or personal history of breast cancer was associated to higher response rate to platinum rechallenge. **Conclusions:** In conclusion,HRD scores showed to be potential markers of response to platinum rechallenge in the platinum resistant setting. Further studies are necessary to clarify the best cutoffs for each score, the impact of tumor heterogeneity and the analysis of tumor samples in the moment of treatment. Positive family history of cancer is a clinical factor predictvie of platinum rechallenge response.

5577 Poster Session (Board #399), Sat, 1:15 PM-4:45 PM

Open label phase II clinical trial of orteronel (TAK-700) in metastatic or advanced non-resectable granulosa cell ovarian tumors: The Greko II study. *First Author: Jesús García-Donas, Centro Integral Oncológico Clara Campal, Madrid, Spain*

Background: Granulosa-cell tumors (GCT) of the ovary are a rare entity characterized by presenting a punctual mutation at the FOXL2 gene 402C→G (C134W). Such mutation leads to a disregulation and overstimulation of the steroidogenic pathway and, ultimately, hormone overproduction. A prior trial by our group (GREKO I trial-GETHI 2011-03; NCT01584297) showed promising activity of ketoconazole, a CYP17 inhibitor used to control steroidogenesis in several conditions. Thus, we aimed to assess the activity of Orteronel (TAK700), a selective inhibitor of 17, 20-lyase, in GCT. **Methods:** An open-label phase II single arm clinical trial was designed for women with metastatic or locally advanced non-resectable GCT who harbored the somatic mutation FOXL2 402C→G (C134W) and who had not received prior treatment with any CYP17 inhibitor. Treatment consisted on Orteronel 300mg BID, given orally, continuously in a 28-day treatment cycle. The primary objective was clinical benefit rate; secondary objectives were response rate, progression free and overall survival, assessment of the impact of Orteronel in reducing hormonal overproduction and toxicity. Sample size calculation was based on a two stage Simon´s design. A power of 80% was set to differentiate between a 5% and a 25% clinical benefit rate. 20% of losses had been assumed thus 20 patients were scheduled to be enrolled. **Results:** Since 30/06/2014 to 11/01/2017 10 patients have been included in 9 participating institutions members of Spanish Group for Research in Orphan and Unfrequent Tumors (GETHI). Due to a low recrutiment rate the study was terminated early. Median PFS was 3 months 95%CI (0-12) with 3 patients achieving disease stabilization longer than 12 months. 2 patients remain on treatment after 16 and 14 months. Clinical benefit rate (CR + PR + SD) was 50%, 95%CI (19%-81%). Seven patients have progressed and 2 have died. Only 6 suspected unresected adverse reactions (SUSARs) have been communicated so far (chest pain, fever, febrile neutropenia, eosinophila, neutropenia and anemia). **Conclusions:** Orteronel achieved a significant clinical benefit in advanced GCT with an favorable toxicity profile. Clinical trial information: NCT02101684.

5578 Poster Session (Board #400), Sat, 1:15 PM-4:45 PM

Impact of beta blocker medication on survival outcome of ovarian cancer: A nationwide population-based cohort study. *First Author: Jeong-Yeol Park, Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea*

Background: In experimental studies, adrenergic hormones are involved in tumorigenesis of ovarian cancer and its progression. We investigated the impact of beta adrenergic blocker on survival outcome of ovarian cancer since few studies have investigated its relevance. **Methods:** Data of Korean National Health Insurance Service was analyzed (n = 866). We analyzed the impact of beta blocker on survival outcome of ovarian cancer according to the duration on medication and age groups of patients. Cox proportional hazards regression was used to analyze hazard ratios (HR) for all-cause mortality with 95% confidence intervals (CI) adjusting for confounding factors. **Results:** Median years of follow-up was 5.98 and 6.71 for non-users and users, respectively. Among the 866 patients, 206 (23.8%) were users and 660 (76.2%) were non-users. In total, there was no survival difference between the 2 groups. But, when patietns were grouped according to the duration of medication, patients with longer duration of medication ($\geq$1 year) showed better survival outcome (adjusted HR 0.305 [95% CI: 0.187-0.500], $P < 0.001$). Also, beta blocker use in patients with > 60 years showed better survival compared to younger patients (adjusted HR 0.579 [95% CI: 0.408-0.822], $P = 0.002$). In patients with > 60 years, medication longer than 720 days was associated with better survival outcome (adjusted HR 0.267 [95% CI: 0.140-0.511], $P < 0.001$). Both selective and non-selective beta blocker showed identical survival benefit in these settings without difference between each other. **Conclusions:** Beta blocker medication was associated with favorable survival outcome in ovarian cancer, especially when used in older patients and in long term duration.

5579 Poster Session (Board #401), Sat, 1:15 PM-4:45 PM

Racial disparities in ovarian cancer survival in New York state. *First Author: Sarah Madhu Temkin, Virginia Commonwealth University, Richmond, VA*

Background: Disparities between black and white patients are well documented in gynecologic cancers but information on the contributions of social factors and medical comorbidities is sparse. We examined differences in outcomes amongst black and white women with ovarian cancer in New York State. **Methods:** Patients with incident ovarian cancer in the New York State Cancer Registry and the Statewide Planning and Research Cooperative System from 2006-2013 were included. Differences in social and demographic factors, comorbidities and tumor characteristics between black and white women were examined with bivariate analysis. Multivariable analyses were used to examine factors associated with specific treatments and survival. **Results:** Of 5969 patients, 87% were white and 13% black. Age, Hispanic ethnicity and median income were similar between groups. Black women were less likely to be married (27 vs 48%, $p < 0.01$); and less likely to be privately insured (20 vs 50%, $p < 0.01$). More black women had comorbidities by Charlson Comorbidity Index (CCI) (63 vs 51%, $p < 0.01$). Black women were more likely to have Stage IV disease and non-serous histology ($p < 0.01$). More black women were treated at academic medical centers (67 vs 50%, $p < 0.01$). Marital status, insurance, CCI, stage, histology and treatment site correlated to the type of treatment received ($p < 0.01$). Black women received different treatment and had higher odds of receiving no treatment 1.63 (1.24, 2.14); chemotherapy without surgery 1.26 (1.00, 1.59); lower odds of undergoing primary surgical management 0.71 (0.58, 0.86) or chemotherapy following surgery 0.79 (0.66, 0.96; and similar rates of neoadjuvant chemotherapy. The risk of 5 year mortality was 1.14 (1.02, 1.27) times higher for black women compared with whites. Marital status, CCI, stage and histology correlated with overall and disease specific survival among both black and white women ($p < 0.01$). **Conclusions:** Multiple factors, including race, are associated with receipt of treatment and survival in ovarian cancer. Treatment for ovarian cancer was significantly different amongst black women than white in New York State. Understanding modifiable influences on racial disparities is imperative to reducing race based differences in outcomes.

5580 Poster Session (Board #402), Sat, 1:15 PM-4:45 PM

INNOVATE: A phase II study of TTFields (200 kHz) concomitant with weekly paclitaxel for recurrent ovarian cancer—Updated safety and efficacy results. *First Author: Ignace Vergote, Universitaire Ziekenhuizen Leuven, Leuven, Belgium*

Background: TTFields are a non-invasive, regional antimitotic treatment modality, which have been approved for the treatment of recurrent and newly diagnosed glioblastoma by the FDA. TTFields act by delivering intermediate frequency alternating electric fields to the tumor, predominantly by disrupting the formation of the mitotic spindle during metaphase. INNOVATE was the first trial testing TTFields (200kHz) in ovarian cancer patients. **Methods:** Thirty-one recurrent, platinum-resistant, unresectable ovarian cancer patients were enrolled in the INNOVATE trial and treated with TTFields in combination with weekly paclitaxel. The primary endpoint was treatment emergent adverse events. Secondary endpoints included progression free-survival, overall survival and radiological response rate. **Results:** The median age was 60 (range – 45-77), most patients (77%) had serous histology. 52% had an ECOG score of 0. The median number of prior chemotherapy regimens was 4.1 (range 1-11). All patients were platinum-resistant, and 97% of patients received prior taxane-containing regimens. Ten (32%) patients suffered from serious adverse events (SAEs) during the study, none were related to TTFields. Of all reported SAEs, 31% were related to gastrointestinal disorders (ileus, jaundice and ascites) and 31% were respiratory events (dyspnea, pleural effusion and pulmonary embolism). Only one SAE which, related to the tumor, led to permanent discontinuation of the device. Most patients were reported to have mild-moderate, TTFields-related skin irritation, out of whom only two patients (6.4%) had severe-grade events. The median PFS was 8.9 months (95% CI 4.7, NA). Of the evaluable tumors, 25% had partial response and another 46.4% stable disease – a clinical benefit of 71.4%. Six patients (19.4%) had a CA 125 response, translating into a decrease of 50% or more in serum levels. The median OS was not reached. **Conclusions:** TTFields concomitant to weekly paclitaxel are tolerable and safe in heavily pre-treated platinum-resistant ovarian cancer ovarian cancer patients. These data support further clinical testing of TTFields with chemotherapy in ovarian cancer. Clinical trial information: NCT02244502.

5581 Poster Session (Board #403), Sat, 1:15 PM-4:45 PM

Immunologic and genomic characterization of high grade serous ovarian cancer (HGSOC) in patients (pts) treated with pembrolizumab (Pembro) in the phase II INSPIRE trial. *First Author: Ilaria Colombo, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Checkpoint inhibitors have shown to be effective in different tumors and are under investigation in HGSOC. **Methods:** INSPIRE (NCT02644369) is a prospective multi-cohort study investigating tumor genomic and immune landscapes in pts treated with Pembro at 200 mg IV Q3W. Patients underwent tumor biopsy pre, on-treatment and at progression for DNA/RNA sequence, immune-profile, and PD-L1 expression by immunohistochemistry (IHC). Serial blood samples for immunophenotyping were collected. Correlative data are available for 6 pts: 3 with shrinkage in target lesion and 3 with progressive disease (PD). **Results:** At interim analysis as of January 2017, 18 pts with HGSOC have been enrolled and 16 have platinum-resistant disease, with median 3 prior lines of treatment (range 1-7). Of 14 evaluable pts, best response by RECIST 1.1 was stable disease (SD) in 5 (36%) and PD in 9 (64%). Mean Tumor Proportion Score of PD-L1 by IHC (Qualtek) was 6.4% (range 0-30%). Grade 3/4 adverse events possibly related to Pembro were observed in 4/18 (22%) pts; none was fatal and the most common were fatigue and hyponatremia. Preliminary correlative data showed no significant change in CD4, CD8 and myeloid-derived suppressor cells in peripheral blood after Pembro treatment. Mean PD-1 expression on CD4 and CD8 T cells on baseline tumor tissue (measured as product of PD-1+ cells and the per cell expression of PD-1 [% of mean fluorescence intensity]) was significantly higher in pts with tumor shrinkage compared to pts with PD (CD4: 2658 vs 678, p = .02; CD8: 1999 vs 451, p = .048). Genomic analysis of baseline tumor tissue was available for 3 pts with tumor shrinkage and 2 with PD. Mean mutation burden was higher for pts with tumor shrinkage (2.38 vs 1.0 mutations/Mb covered). The pt with the longest SD in our cohort (6 months) had the highest mutation burden (2.72), including somatic POLE (c.6331-6C > G) and germline *BRCA2*mutations. **Conclusions:** In HGSOC, pts with higher PD-1 level on tumor CD4 and CD8 T cells and higher mutation burden at baseline may have a better outcome following treatment with Pembro. POLE mutation is rare in HGSOC but may correlate with checkpoint inhibitor activity. Clinical trial information: NCT02644369.

5582 Poster Session (Board #404), Sat, 1:15 PM-4:45 PM

Circulating tumor DNA analysis using targeted sequencing of 508 clinically actionable genes in patients with high grade serous ovarian cancer. *First Author: Anniina Färkkilä, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

Background: The prediction of tumor chemoresponse and treatment toxicity is crucial for optimal patient care in high grade serous ovarian cancer (HGSC). We employed a targeted sequencing panel of 508 clinically annotated cancer genes to screen for actionable genetic variants in tumor tissue and ctDNA of patients with advanced HGSC. **Methods:** Tumor tissue, and serial plasma samples at diagnosis and during primary therapy were obtained from five patients with FIGO Stage IIIc HGSC. All patients were surgically debulked and received standard carboplatin and paclitaxel chemotherapy. DNA isolated from tumor tissue and plasma was analyzed for genetic alterations by targeted deep-sequencing of 508 previously annotated cancer genes. Somatic variants were systematically reported for alterations related to drug sensitivity and treatment toxicity, and analyzed with respect to clinical parameters and primary therapy outcomes. **Results:** In tumor tissues, and the corresponding pre-treatment ctDNA, oncogenic mutations were detected at a median of 13.0 and 1.6 allelic frequencies, respectively. The mutation frequency was higher, and also more unique mutations were detected in ctDNA of patients presenting with high tumor spread. Interestingly, a de-novo ctDNA MAPK1 mutation was detected in a sample taken during chemotherapy with partial response, while, no new mutations emerged in a patient with complete response. Analysis of the pretreatment plasma ctDNA revealed profiles of low and high drug sensitivities consistent with the clinical course of the patients. In two patients, increased risk profiles for treatment toxicities were identified via e.g. GSTP1. Consistently, these two patients were forced to discontinue standard therapy. **Conclusions:** Panel-based targeted sequencing of ctDNA identified potentially actionable mutations, and reflected tumor heterogeneity of HGSC. Further, the ctDNA gene panel annotations showed concordance with the chemoresponse- and treatment toxicity profiles, suggesting that ctDNA gene panel maybe a feasible approach to individualize treatment of HGSC patients.

5583 Poster Session (Board #405), Sat, 1:15 PM-4:45 PM

Hedgehog inhibition impaired platinum response in high-grade serous ovarian cancer harboring high hedgehog ligand expression and mTOR pathway activation. *First Author: Gwo Yaw Ho, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia*

Background: Elevated Glioma-associated Oncogene Homolog-1 (Gli1) protein expression is associated with Hedgehog (Hh) pathway activation in high-grade serous ovarian cancer (HGSOC). Inhibition of Hh signaling in Gli1-overexpressing HGSOC patient-derived xenograft (PDX) inhibited tumour growth, particularly in combination with chemotherapy. Early phase HGSOC clinical trials of vismodegib, a potent Hh inhibitor (SMO inhibitor), were disappointing. We identified a HGSOC PDX harboring both Indian Hh ligand-overexpression and bi-allelic deletion of *TSC1,* which latter event is reported to derepress the mTOR pathway, driving non-cannonical Gli1 expression. We explored the effect of vismodegib in combination with cisplatin or the mTOR inhibitor, everolimus, in this model. **Methods:** A cell-line was generated from the well-characterised PDX (identity confirmed by PDX-specific p53 mutation). *In vitro* response to vismodegib was assessed. qRT-PCR was performed to establish Hh-ligand and Gli1 expression with/without SMO inhibition. A PDX was generated from this cell-line and randomized to *in vivo* treatment with cisplatin, vismodegib, everolimus or vehicle alone, or vismodegib in combination with cisplatin or everolimus. **Results:** The HGSOC cell-line was sensitive to vismodegib *in vitro* (EC50 of 3.5μM) and qRT-PCR analysis revealed down-regulation of Hh-ligand and *Gli1* expression following *in vitro* SMO inhibition, confirming on-target vismodegib activity. *In vivo* treatment with vismodegib or everolimus alone did not result in reproducible *in vivo* efficacy. The combination of vismodegib + everolimus caused short-lived responses in 3 of 6 mice. Strikingly, *in vivo* treatment with vismodegib in combination with cisplatin impaired median survival (19 days) when compared with cisplatin treatment alone (43 days; p = 0.039) due to rapid tumour progression. **Conclusions:** Combining chemotherapy with Hh inhibition in Hh ligand-overexpressing HGSOC PDX with mTOR pathway activation may be detrimental. These findings highlight the importance of an in-depth understanding of tumour biology in order to effectively combine therapeutic approaches.

5584 Poster Session (Board #406), Sat, 1:15 PM-4:45 PM

Does treatment at a high volume center mitigate racial and ethnic disparities in ovarian cancer survival? *First Author: Renee A. Cowan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Population-based studies of women with advanced ovarian cancer report racial/ethnic disparities in access to high volume centers (HVCs), surgical outcomes after primary debulking surgery (PDS), and overall survival (OS). However, there is evidence that with equal utilization of expert ovarian cancer care, differences in survival dissipate. The objective of this study is to evaluate patients (pts) with advanced ovarian cancer who had PDS at a HVC to determine whether racial/ethnic disparities persist in surgical outcome and survival. **Methods:** With IRB approval, all pts with stages IIIB to IV high-grade ovarian cancer who underwent PDS from 1/2001-12/2013 were identified. Pts self-identified race/ethnicity as Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Asian (A), or Hispanic (H) in the medical record. The main outcome measures were PDS $<$1cm residual and OS. A Cox proportional hazards model was used to compare OS by race/ethnicity. Pt and clinical factors, including age, income, BRCA status, BMI, ASA, grade, carcinomatosis, bulky abdominal disease, were adjusted for in the multivariate analysis. **Results:** 963 pts were identified: 851 NHW (88%); 43 A (4%), 34 H (4%), 28 NHB (3%), 7 Other (0.7%). Asian pts were younger at diagnosis ($p<0.0001$); there were no differences in other demographic or clinical characteristics among racial/ethnic groups. After adjusting for pt and clinical factors, the likelihood of PDS to residual $<$1cm was similar among NHB and H compared to NHW pts; Asian pts were more likely than NHW to have $>$1cm residual (OR 2.32, 95%CI 1.1-4.9, p=.03). Median OS was 55.1 mos (95%CI: 51.8-58.5) for the entire cohort. On both univariate and multivariate analysis, there was no disparity in OS among racial or ethnic groups (p=0.615). **Conclusions:** Racial and ethnic disparities in overall survival and surgical outcomes in women with advanced ovarian cancer can be reduced by treatment at a HVC. Additional research is needed to determine what factors are associated with receiving treatment at HVCs, and what interventions could increase the diversity of patients treated at HVCs.

5585 Poster Session (Board #407), Sat, 1:15 PM-4:45 PM

Clinical activity, safety and biomarker results from a phase Ia study of atezolizumab (atezo) in advanced/recurrent endometrial cancer (rEC). *First Author: Gini F. Fleming, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: The prognosis for patients (pts) with rEC remains poor, with a 5-y OS of 20%-26%. We report safety, clinical activity and biomarker data from a Phase Ia study of atezo (anti–PD-L1) monotherapy in rEC. **Methods:** Atezo 1200 mg or 15 mg/kg IV q3w was administered until toxicity or loss of clinical benefit. Pts were initially eligible based on PD-L1 status ($>$ 5% of tumor-infiltrating immune cells [IC; IC2/3], VENTANA SP142 IHC assay) and then enrolled regardless of PD-L1 status. Tumor-infiltrating lymphocytes (TILs) were assessed by H&E. The FoundationOne NGS panel was used for microsatellite instability (MSI) and tumor mutation load analyses. Confirmed ORR and PFS were assessed by RECIST v1.1. **Results:** As of March 31, 2016, 15 pts were evaluable for safety and efficacy (minimum follow-up, 11.2 mo). The median age was 61 y (range, 20-74 y), 53% were ECOG PS 1 and 93% had $\geq$ 2 prior systemic therapies; 10 (67%) pts had prior RT. Pts were MSI-H (1/15), MSS (7/15) or MSI unknown (7/15). EC subtypes were endometrioid (5/15), serous (5/15), ER+ leiomyosarcoma (1/15) or unknown (4/15). Five (33%) pts were IC2/3, and 10 (67%) pts were IC0/1. Seven (47%) pts had any related AE, mainly G1-2 (5 pts). No G4-5 related AEs occurred. Two pts had related SAEs (colitis; rash). ORR was 13% (2/15) by RECIST. Both pts achieved PR and were IC2/3. ORR for IC2/3 pts was 40% (2/5). One responder was MSS and heavily infiltrated with TILs (IC3, 70% TILs, 1.8 Mut/Mb, unknown subtype); the other responder was hypermutated, MSI-H and moderately infiltrated with TILs (IC2, 10% TILs, 237 Mut/Mb, endometrioid). DOR in the 2 responders was 7.3 and 8.1+ mo. mPFS was 1.7 mo (range, 0.6-11+ mo); mOS was 9.6 mo (range, 0.6-11.8+ mo). Of the remaining pts, 2 had SD, 9 had PD and 2 were non-evaluable. DCR (PR + SD) was 27%. A trend for higher PFS and OS was seen in IC2/3 vs IC0/1 pts. **Conclusions:** Atezo had a favorable safety profile in rEC, with durable clinical benefit in some pts. Clinical benefit appeared to increase with higher PD-L1 expression, suggesting a link between PD-L1 status and response. Hypermutation and/or high immune infiltration may be linked to response to PD-L1 blockade, and further evaluation is merited. Clinical trial information: NCT01375842.

5586 Poster Session (Board #408), Sat, 1:15 PM-4:45 PM

Activity of lurbinectedin (PM01183) as single agent and in combination in patients with endometrial cancer. *First Author: Martin David Forster, University College London Hospitals, London, United Kingdom*

Background: Lurbinectedin (L) is a new anticancer drug that blocks transactivated transcription, induces DNA double-strand breaks and modulates the tumor microenvironment. Advanced endometrial cancer (EC) is an unmet medical need. **Methods:** Activity in EC patients was reviewed in 3 trials: a phase IB study of lurbinectedin combined with doxorubicin (L+DOX), a phase I study of PM combined with paclitaxel (L+TAX) and a phase II single-agent basket trial (L). Baseline characteristics, safety and efficacy were analyzed. **Results:** 97 patients were evaluated: 34 (2 cohorts) with L+DOX, 11 with L+TAX and 52 with L. Median age was similar in the 3 studies. Endometrioid was the most frequent histology. Median (range) of prior chemotherapy lines for advanced disease was: L+DOX, 1(0-2); L+TAX, 2(1-3); L, 1(0-2). Responses were observed in the 3 studies (see table). Main adverse event was myelosuppression (grade 3-4 neutropenia/thrombocytopenia/febrile neutropenia: L+DOX Cohort A, 94%/26%/40%; L+DOX Cohort B, 79%/10%/16%; L+TAX, 54%/0%/0%; L, 33%/6%/6%). Non-hematological toxicity was mostly grade 1-2: fatigue, nausea and vomiting, and transaminase increase. **Conclusions:** Lurbinectedin is active as single agent and in combination in patients with advanced EC, with remarkable activity in terms of response rate, duration of response and PFS when combined with doxorubicin. Safety was acceptable in L+DOX Cohort B, L+TAX and L, and myelosuppression was well managed. Clinical trial information: NCT01970540.

	L+DOX (q3wk)		L+TAX (q3wk)	L alone (q3wk)
Response (evaluable patients)	Cohort A L 3-5 mg FD D1 + DOX 50 mg/m^2 D1 (n=14)	Cohort B L 2 mg/m^2 D1 + DOX 40 mg/m^2 D1 (n=18)	L 2.2 mg/m^2 D1 + TAX 80 mg/m^2 D1 & D8 (n=11)	L 3.2 mg/m^2 D1 (n=40)
CR	2 (14%)	-	-	1 (3%)
PR	2 (14%)	8 (44%)	3 (27%)	4 (10%)
ORR	4 (28%)	8 (44%)	3 (27%)	5 (12.5%)
SD	8 (57%)	7 (39%)	2 (18%)	15 (38%)
PD	2 (14%)	3 (16%)	6 (55%)	20 (50%)
DCR	9 (85%)	15 (83%)	5 (45%)	20 (50%)
DOR (mo)	19.5	6.8	6.1	4.3+
PFS (mo)	7.8	7.7	1.9	2.5+

CR, complete response; D, day; DCR, disease control rate; DOR, duration of response; DOX, doxorubicin; FD, flat dose; mo, months; ORR, overall response rate; PD, progressive disease; PFS, progression free survival; PM, PM1183, PR, partial response; q3wk, every 3 weeks; SD, stable disease; TAX, paclitaxel.

5587 Poster Session (Board #409), Sat, 1:15 PM-4:45 PM

Exploratory phase II evaluation of cabozantinib in recurrent/metastatic uterine carcinosarcoma (CS): A study of the Princess Margaret, Chicago, and California phase II consortia. *First Author: Victoria Mandilaras, McGill University Health Centre, Montréal, ON, Canada*

Background: Carcinosarcoma (CS) is a rare ($<$ 5%) aggressive subtype of endometrial cancer (EC). Patients (pts) with progression on platinum-based chemotherapy (CTX) have limited options, there is no standard 2ndline treatment and median progression-free survival (PFS) is $<$ 2months (mt), 6-mt PFS less than 20%. Limited molecular data on CS aligns with epithelial EC, providing rationale for evaluating similar strategies such as targeting MET and angiogenesis. Cabozantinib (cabo) is multi-targeted tyrosine kinase inhibitor against MET, VEGFR, TIE2, RET, AXL and KIT. **Methods:** PHL-86 (NCI#9322/NCT01935934) is a multi-centre, non-randomized, phase II trial of cabo (60 mg oral daily dose on a 28-day cycle) in EC pts recurring within a year of adjuvant CTX or with progression after 1stline of CTX for metastatic disease. Pts with rare histology including CS, were enrolled in an exploratory cohort. Activity of interest for further evaluation was defined as 4 responses (either partial response [PR] or 12-wk PFS) out of 10 pts of a given histotype. CT scans were performed after cycle 3 and every 2 cycles thereafter. **Results:** From 2013 to 2016, 32 pts were treated in the exploratory cohort, 19 pts with CS. Median age was 66 years (range 25-75); prior treatment included CTX (17: 1 line, 6: 2 lines) and/or radiation (11). Fifteen pts were evaluable for response, with 1 PR (7%) and 8 pts with 12-wk PFS (53%). Median PFS was 3 mt (95% CI: 2.7 – 4.6) with estimated 6-mt PFS of 13% (2 to 33%). Toxicity evaluation is available for 19 pts. Common events were fatigue and GI upset. Most frequent $>$ Grade3 toxicities were hypertension (5), anemia (4), diarrhea (2). Four pts had GI fistula (2) or perforation (2). Mutation profiling in archival tissue showed *TP53* (73%), *PIK3CA* (40%), *KRAS* (27%), *PTEN*(13%) with $>$ 1 mutation present in 14/15 pts analyzed. The 1 pt with no somatic mutations had a PR (31% decrease) on cabo (PFS 6.7mt). **Conclusions:** Cabo in CS cohort met the predefined endpoint for further evaluation and compares favourably with other agents in this poor prognosis disease. Larger studies are required to define depth and durability of response and identify relevant biomarkers. Clinical trial information: NCT01935934.

5588 Poster Session (Board #410), Sat, 1:15 PM-4:45 PM

Utility of multi-gene panel testing with next generation sequencing in women with endometrial cancer. *First Author: Jing-Yi Chern, NYU Langone Medical Center, New York, NY*

Background: Lynch syndrome (LS) accounts for 2-6% of all endometrial cancers (EC), and women with a germline mutation in the mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, and PMS2*) have an average lifetime risk of EC of 40%. As with breast and ovarian cancer syndromes, there are likely other genes implicated in the development of EC outside of the MMR genes. Multi-gene panel testing (MGPT) with next generation sequencing (NGS) allows for simultaneous analysis of numerous genes.We sought to evaluate the characteristics and incidence of gene mutations in women with newly diagnosed EC. **Methods:** We conducted a review of EC patients diagnosed from 6/2013 to 12/2016 who had MGPT at our institution. Demographics, family history, genetic testing results, and tumor characteristics were collected and analyzed using χ^2 tests. **Results:** Of the 129 patients who had MGPT, 13 (10%) had a mutation and only 5 (38%) were in patients $<$ 50 years old. The median age of EC diagnosis is 55 (31-100) years and median BMI = 27.5 (21-59). Majority were stage 1, 76 (59%) and grade 1, 50 (39%). Patients with additional primary cancers, breast or colon were not more likely to have a mutation. However, patients with a family history of gynecologic cancer were more likely to have a mutation identified, 10 (77%) mutation vs no mutation 34 (29%), p = 0.003. Among all patients tested, 8 (6%) had a mutation in LS genes, and 6 (5%) had mutations in other genes (*BRCA1, BRCA2, RAD51C, MUTYH, CHEK2*); 1 (0.8%) had both *MSH2* and *CHEK2* mutation. Three patients had prior testing for breast cancer; 2 were found to have a *BRCA1/ 2* mutation and the other was on Tamoxifen and *BRCA* negative. IHC was performed on 7 of 13 patients, and 5 (71%) had a loss of MMR protein expression. Variants of uncertain significance were noted in 35/129 (27%) of patients tested. **Conclusions:** Majority of EC patients with a mutation detected with NGS were $>$ age 50. We identified additional new mutations in non-LS genes including, *CHEK2, RAD51C*, and *MUYTH* with MGPT. These accounted for 29% of the mutations and would have not been not detected using classic LS gene testing. These genes are implicated in breast, ovary or colon cancer. MGPT testing is feasible and useful in identifying additional actionable gene mutations.

5589 Poster Session (Board #411), Sat, 1:15 PM-4:45 PM

Role of adjuvant chemoradiation in treatment of elderly women with advanced high-grade endometrial cancer: A SEER-Medicare analysis. *First Author: Hyo K. Park, Karmanos Cancer Institute, Detroit, MI*

Background: Use of combined adjuvant chemoradiation (CRT) in treatment of advanced stage endometrial cancer is increasing, but the survival benefit over chemotherapy (CT) or radiation therapy (RT) alone remains unclear. We examined adjuvant treatment patterns and survival associated with CRT for Stage III-IV high-grade endometrial cancer using a large population-based database. **Methods:** Women 66 years of age or older who underwent primary surgical treatment for Stage III-IV high-grade endometrial cancer between 2000-2011 were identified from the SEER-Medicare database. Demographic and clinical predictors for receipt of adjuvant CRT vs. CT or RT alone were examined using multinomial logistic regression. In addition, overall survival (OS) by adjuvant treatment type, histology (endometrioid vs. non-endometrioid), stage, and age group were examined using Kaplan-Meier estimates and Cox proportional hazards regression. **Results:** Of the 2,735 eligible women, 13.1% received CRT vs. 42.5% CT alone vs. 13.2% RT alone, and 31.1% received no adjuvant treatment. Hispanic ethnicity, carcinosarcoma, serous histology, and Stage IV disease were significant predictors of receiving CRT over CT alone. Increasing age group, non-Hispanic black race/ethnicity, endometrioid histology, having 3+ comorbidities at the time of surgery, and not being partnered were associated with receiving RT alone over CRT. For Stage III disease, those who received CT (HR 1.30; 95% CI 1.09-1.55) or RT alone (HR 1.34; 95% CI 1.09-1.64) had poorer 5-year OS compared to CRT. In a subgroup analysis, the relative survival benefit of CRT vs. CT was only significant for women $<$ 75 years of age and was more pronounced for endometrioid (HR 1.72; 95% CI 1.22-2.41) vs. non-endometrioid histology (HR 1.22; 95% CI 0.99-1.49). For Stage IV disease, there was no survival difference among those who received CT or RT only compared to CRT regardless of histologic subtypes. **Conclusions:** Adjuvant CRT was associated with improved OS in elderly women with Stage III high-grade endometrial cancer. This survival benefit was more pronounced for endometrioid histology and women $<$ 75 years of age.

5590 Poster Session (Board #412), Sat, 1:15 PM-4:45 PM

Association of delayed adjuvant therapy and overall survival in early stage endometrial cancer. *First Author: Leo Luo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The primary treatment for early stage endometrial cancer includes definitive surgical staging procedure followed by adjuvant therapy in women with high risk of recurrence. The optimal interval time between surgery and adjuvant therapy is unclear. **Methods:** 349,404 patients with primary uterine carcinoma diagnosed from 2004 and 2012 were extracted from National Cancer Database (NCDB). Study population was limited to patients with FIGO 2009 stage I and II endometrial cancer with endometroid, mucinous, clear cell, or serous histology. Adjuvant therapy included radiation therapy, chemotherapy, or a combination. A binary variable of interval time between surgery and adjuvant therapy ("early" vs. "delayed") was created by using the median time as a cutoff. Analysis of relationship between the interval time and overall survival was performed. **Results:** Final analysis included 118,373 early stage endometrial cancer patients who had definitive surgical treatment. Median age was 61 (interquartile range 55-69). 87,189 patients (74%) had stage IA disease, 21,573 (18%) patients had stage IB disease, and 9,611 (8%) patients had stage II disease. 28,824 (24%) patients received adjuvant therapy after surgery. The median time from surgery to adjuvant therapy was 1.6 months (interquartile range 1.3-2.2 months). Of the patients that received adjuvant therapy, 48% received intra-vaginal brachytherapy alone, 31% received pelvic external beam radiation, and 7% received a combination of chemotherapy and brachytherapy. There was a significant difference in overall survival in patients who received adjuvant therapy within 1.6 months from surgery and 1.6 months after surgery (Log-rank test, $p = 0.04$). Patients with advanced age, African-American or Hispanic race, and uninsured status or government-sponsored insurance were associated with delayed treatments. **Conclusions:** In this large retrospective review of early stage endometrial cancer patients, delayed time between surgery and adjuvant therapy is associated with worse overall survival. Further analysis will be performed to determine an optimal timing between surgery and adjuvant therapy.

5591 Poster Session (Board #413), Sat, 1:15 PM-4:45 PM

High-intermediate risk endometrial cancer: Can gene expression predict recurrence? *First Author: Cindy Tawfik, TL1 Predoctoral Trainee University of Alabama, Birmingham, AL*

Background: Studies have shown that adjuvant therapy increases progression free survival, but does not affect overall survival in patients with high-intermediate risk (H-IR) endometrial cancer (EMCA). Our objective was to develop a gene expression signature that may help identify H-IR EMCA patients with the highest risk of recurrence to help guide treatment strategies. **Methods:** Data was collected on all patients that met H-IR EMCA criteria diagnosed between 2000-2010 at UAB (n = 292). Of the patients that did not receive adjuvant treatment, 13 patients that recurred were matched to 13 patients that did not recur and original tumor was compared. Of those that recurred, 5 patients had original and recurrent tumor available for analysis. Gene expression data was collected using the Nanostring nCounter PanCancer Pathway 770 gene panel. Data was analyzed using nSolver Advanced Analysis Software. A fold change (FC) of $\geq \pm 2$ ($p < 0.05$) was used to identify genes with a significant expression difference. **Results:** Comparing the 13 patients that recurred to the 13 that did not, there were 5 genes with FC $\geq$ +2: BAIAP3, PLCB1, IL1R1, NOS3 and RAD50. There were 29 genes with FC $\geq$ -2; the top 3 genes with decreased expression (FC $\geq$ -10) were: BMP7, FGF18, WNT7A. Genes in the Cell Cycle (CC) pathway were significantly different in the patients that recurred ($p = 0.02$). There were 61 genes with FC $\geq$ +2 when comparing the original tumor to recurrent tumor; the top 3 genes with increased expression (FC $\geq$ 10) were: FGF18, CCND1, HIST1H3H ($p < 0.05$). There were 50 genes with FC $\geq$ -2; the top 3 genes with decreased expression (FC $\geq$ -1000) were: HOXA11, LEFTY2 and SFRP4. Wnt, Hedgehog, Chromatin Modification, DNA repair, TGF-β, MAPK, and CC pathways were significantly different in the recurrent samples compared to the original tumor ($p < 0.05$). **Conclusions:** Our data suggests that gene expression panels could better identify patients that warrant adjuvant treatment. The CC pathway, which is significantly different in the original tumor from those that recurred and those that did not, was further altered in the recurrent tumor samples. Additional studies are on-going to validate these findings and to further investigate DNA mutation differences in larger cohort of patients.

5592 Poster Session (Board #414), Sat, 1:15 PM-4:45 PM

Clinical activity of the selective DRD2 antagonist ONC201, an imipridone, in metastatic endometrial cancer (mEC). *First Author: Lorna Rodriguez-Rodriguez, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: mEC is a generally incurable, with limited therapeutic options. ONC201 is the founding member of the new class of compounds called imipridones that are orally active small molecules. ONC201 a specific antagonist of the G protein-coupled receptor DRD2 exerts antitumor activity via a series of established signaling pathways (dual inhibition ERK/AKT, integrated stress response). DRD2 expression is elevated in malignant versus normal endometrial tissue. Furthermore ONC201 has shown anti-cancer activity in preclinical models of EC. **Methods:** In a Phase I trial that included an expansion cohort, a total of 28 evaluable patients (pts) were treated with ONC201 at doses from 125mg every 3 weeks to 625 weekly. Five of these patients had advanced mEC. **Results:** The median age for the mEC patients was 60 years (56-72), the median number of prior treatments was 5 (3-6), 3 patients had prior radiation and all patients had prior surgery. One patient received 375mg ONC201 while the other 4 patients received 625mg ONC201, orally every 3 weeks. The median number of doses was 3 (2-14). Two of 5 patients exhibited regressions in individual metastatic lesions, however they did not qualify as overall objective responses by RECIST criteria. One of these two patients experienced stable disease for 42 weeks. There were no reported SAEs and no Grade > 1 AEs attributed to study drug. **Conclusions:** ONC201 is clinically active and well tolerated with oral administration in refractory mEC patients. Clinical trial information: NCT02250781.

ONC201 (mg)	375mg	625mg	625mg	625mg	625mg
Histology	Clear cell endometrial (Type II)	Endometrioid (Type I)	Poorly differentiated papillary (Type II)	Serous (Type II)	Endometrioid (Type I)
Time on study (weeks)	7.4	17.7	42.9	6.3	8.9
Tumor response	Mixed Response	Stable Disease	Stable Disease (Lung regression)	Progressive Disease	Progressive Disease
Tumor DRD2 expression	+	+	+	N/A	N/A

5593 Poster Session (Board #415), Sat, 1:15 PM-4:45 PM

Assessment of a custom designed next generation DNA sequencing gene panel to profile endometrial cancers. *First Author: Eirwen M Miller, Montefiore Medical Center, Bronx, NY*

Background: Using whole genome sequencing (WGS), the Cancer Genome Atlas (TCGA) identified four genomic subtypes of endometrial cancer (EC) with survival differences. Limited clinical data is available in the TCGA dataset restricting correlation of WGS with clinical endpoints. We sought to determine if high depth target sequencing allows for genomic classification of EC and prediction of the tumor biology when clinical variables are known. **Methods:** Using a custom designed sequencing panel targeting the coding regions of 156 EC genes we analyzed 47 EC samples and matching normal controls. Variants were annotated for pathogenicity. Charts were reviewed for clinicopathologic data. Routine statistical analyses were applied. **Results:** Endometrioid (EEC) tumors had a significantly higher frequency of total and pathogenic SNVs than serous (USC). Pathogenic PTEN and PIK3CA SNVs were more common in EEC while pathogenic TP53 SNVs were more frequent in USC. The presence of pathogenic TP53 SNVs was significantly associated with disease recurrence/progression. A pathogenic SNV at PTEN locus chr10:89692904 was associated with grade 1 EEC. Six hypermutated specimens were identified with 99-272 SNVs (mean 185.8 v 8.7 in non-hypermutated samples). All 6 were grade 3 EEC, of which 4 patients are alive without clinical evidence of disease (mean follow up 35 months). NTRK3, LRP1B, SLIT2, APC, RAD50, PIK3R1, and JAK2 SNVs were more common in grade 3 EEC than the other histologies. **Conclusions:** Pathogenic variants in EC associated with PTEN, PIK3CA, and TP53 and the number of somatic variants, as identified by a targeted sequencing, can predict histologic features and clinical behavior. Targeted sequencing panels may be a useful tool to predict the clinical phenotype and guide individualized therapeutic intervention.

	EEC (n = 34)	USC (n = 13)	P value
Number of somatic SNVs	8 (6-14)	3 (3-8)	< 0.01
Number of pathogenic somatic SNVs	3 (2-5)	1 (1-2)	< 0.01
PTEN SNV	76%	15%	< 0.01
PIK3CA SNV	68%	23%	< 0.01
TP53 SNV	15%	77%	< 0.01

	Grade (n = 12)	Grade 2 (n = 10)	Grade 3 (n = 12)	USC	
Number of somatic SNVs	8 (7-9)	7 (5-16)	13 (6-272)	3 (3-8)	0.02
Number of pathogenic somatic SNVs	2 (2-4)	3 (2-3)	5 (3-23)	1 (1-2)	< 0.01
chr10: 89692904	42%	10%	8%	0%	0.02

5594 Poster Session (Board #416), Sat, 1:15 PM-4:45 PM

Evaluation of systemic and local immune responses in patients with endometrial cancer. *First Author: Martin Ore, Clinical Area of Gynecologic Oncology, Instituto Valenciano de Oncología (IVO), Valencia, Spain*

Background: Several studies suggest that systemic immune response (SIR) and local immune response (LIR) have independent roles in multiple types of cancer. In endometrial cancer (EC), the correlation between SIR and LIR and its prognostic value remains unclear. **Methods:** A total of 146 EC patients (stage I-IV) who had undergone surgery from 2009 to 2015, were identified from a prospective institutional database. Lymphocyte/monocyte ratio (LMR) to represent SIR was calculated from preoperative blood samples. The presence of intratumoral and peritumoral infiltrating lymphocytes (TILs) on hematoxylin and eosin-stained slides was considered as a surrogate of LIR. LMR and TILs were correlated to pathological findings and survival outcomes (overall survival: OS, disease free survival: DFS). **Results:** A LMR cutoff value of 4.4 for survival was determined based on receiver operating characteristic (ROC) curve analysis. LMR high was significantly associated with endometrioid histology (p=0.03), lower grade (G1-2; p=0.003), < 50% myometrial invasion (p=0.01) and I-II stage (p=0.02). TILs were correlated with MSI-high (p<0.005), but not with LMR (p=0.3). Low LMR was associated with worse 5-year OS rates (64.5% vs 93.9%; p<0.01) and presence of TILs with better 5-years OS rates (72% vs 27%; p=0.04). On multivariate analysis (table 1) LMR, histology, stage and grade remained independent prognostic factors for OS (p=0.01). Using the combination of LMR and TILs, four groups with decreasing 5-years OS rates were identified: LMR-high/TILs+ (100%) > LMR-high/no-TILs (87%) > LMR-low/TILs+ (71%) > LMR-low/no-TILs (61%). **Conclusions:** In our series of resected EC patients, SIR (defined by LMR) constituted an independent prognostic factor for OS and LIR for DFS. We did not find any correlation between SIR and LIR, but the combination of both higher SIR and LIR showed better OS.

Multivariate analysis.

OS	VARIABLE	*HR (95% CI)*	*P VALUE*
	LMR low vs. high	6.4 (1.3-30.6)	0.01
	Stage III-IV vs. I-II	4.8 (1.3-16.8)	0.01
	Endometrioid G3, serous vs. Endometrioid G1-2	9.9 (2.3-42.1)	<0.01
DFS	Stage III-IV vs. I-II	8.3 (2.3-29-6)	<0.01
	Endometrioid G3, serous vs. Endometrioid G1-2	10.4 (2.5-40)	<0.01
	TILs present vs. absent	0.1 (0.03-0.5)	<0.01

5596 Poster Session (Board #418), Sat, 1:15 PM-4:45 PM

Spectroscopy of blood samples for the diagnosis of endometrial cancer and classification of its different subtypes. *First Author: Maria Paraskevaidi, University of Central Lancashire, Preston, United Kingdom*

Background: Symptoms of endometrial cancer often appear in early stages, thus a diagnosis, based on microscopic histological examination of endometrial tissue, can be given relatively on time. However, this procedure interferes subjective interpretation allowing human error, while screening of the asymptomatic population is not widely performed because of the high cost of the available tests (e.g. transvaginal ultrasound) and the relative invasiveness [biopsy or dilation and curettage (D+C)]. Consequently, there is a widespread need to develop inexpensive, non-invasive techniques that would accurately diagnose endometrial cancer, as well as classify the different subtypes. Spectrochemical methods generate a signature fingerprint of biological material in the form of spectra. Unlike immunological methods, which detect only one molecule at a time, the spectra obtained from a clinical sample represent all the molecular constituents within that sample, including proteins, lipids and carbohydrates; this provides a holistic picture of the sample. Previous studies have confirmed spectroscopy's ability to diagnose gynecologic cancers in blood. **Methods:** Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy was used to analyse blood plasma and serum from 71 women with endometrial cancer and 18 age-matched healthy controls; classification algorithms were then applied to extract the underlying biological information. **Results:** Principal component analysis followed by support vector machine (PCA-SVM) diagnosed endometrial cancer with 100% accuracy in plasma and 95% in serum. Discrimination between the different subtypes [endometrioid adenocarcinoma (n = 43) vs carcinosarcoma (n = 14)] was achieved with 98.33% accuracy in both plasma and serum. The spectral regions responsible for discrimination were attributed to protein and lipid alterations. **Conclusions:** Our preliminary results suggest an accurate and objective diagnostic tool for endometrial cancer with blood testing, allowing therefore thoughts for a potential screening test in high risk populations. Future work will include higher number of normal cases and different subtypes and grades.

5597 Poster Session (Board #419), Sat, 1:15 PM-4:45 PM

Outcome of patients with advanced endometrial and cervical cancer treated in a phase 1 unit. *First Author: Rowan Miller, Department of Medical Oncology, University College London Hospital, London, United Kingdom*

Background: Patients (pts) with advanced endometrial (EC), cervical and vulval (CVC) cancer have limited therapeutic options and poor prognosis. Early phase trials may be a suitable option for pts with good performance status aided by molecular selection. We sought to determine the outcome of EC and CVC pts treated in a phase 1 unit. **Methods:** Medical records of pts with EC and CVC treated within an early phase trial between 2010 and 2016 were reviewed. Data comprised pt and tumor characteristics, prior therapy, trial therapy and outcome. **Results:** 38 pts, median age 59 years (21-74) with EC (19) or CVC (19) were identified. Median prior therapies for advanced disease: 1 (1-3). Histological subtypes: endometrioid (4), high grade serous (HGS 7), carcinosarcoma (CS 4), clear cell (1), and adenosquamous (3) for pts with EC; adenocarcinoma (5), squamous (11), clear cell (2) and neuroendocrine (1) for CVC pts. 20 pts (53%) had Next Generation Sequencing (NGS) using a targeted panel with actionable mutations identified in 10 (KRAS (4), PIK3CA (6) and EGFR (1)). Pts were allocated in order of priority to a trial (1) on the basis of NGS ('genomic' 8%), (2) within a 'tumor specific' expansion cohort (45%) or (3) a 'generic' study (47%). The overall response rate (ORR) was 21% with 34% stable disease (SD) and median progression free survival (PFS) and overall survival (OS) of 11 and 42 weeks respectively, with 10 pts still on study. Within the EC cohort ORR was 21% with 32% SD and PFS and OS of 9 and 38 weeks respectively. For the CVC cohort ORR was 21% with 37% SD and PFS and OS of 12 and 42 weeks respectively. Outcomes were better for the pts in the genomic and tumour specific groups. Both PFS and OS were longer with median PFS of 42, 32 and 8 weeks and OS of 91, not reached and 37 weeks for genomic, tumor specific and generic trials respectively. **Conclusions:** Early phase trials represent a good option for pts with advanced EC and CVC with meaningful clinical benefit observed even in this small cohort. Encouraging RR and PFS were observed in these pts with limited standard treatment options. This includes pts with difficult to treat histological subtypes such as HGS and CS EC and clear cell and adenocarcinoma CVC. NGS is feasible in real time and increasing use may benefit pts further.

5598 Poster Session (Board #420), Sat, 1:15 PM-4:45 PM

A phase Ib/II trial of lenvatinib (LEN) plus pembrolizumab (Pembro) in patients (Pts) with endometrial carcinoma. *First Author: Vicky Makker, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: LEN is a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptor 1−3, fibroblast growth factor receptor 1−4, platelet-derived growth factor receptor α, RET, and KIT. Pembro, an antibody targeting programmed cell death protein 1 (PD-1), prevents T cell deactivation. In addition to its antiangiogenic effects, LEN may act in part by preventing VEGF-mediated immune suppression, suggesting combination with pembro could improve its activity. We report results in pts with endometrial carcinoma from a phase Ib/II trial of LEN + pembro. **Methods:** In this multicenter, open-label study, pts had confirmed metastatic endometrial cancer that progressed after approved therapy, measurable disease, and ECOG performance status ≤ 1. Pts received oral LEN 20 mg/day plus pembro 200 mg intravenously every 3 weeks. Tumor assessments were by the investigator. The primary phase II endpoint was objective response rate (ORR) based on immune-related RECIST (irRECIST). Secondary endpoints included progression-free survival (PFS), disease-control rate (DCR; complete response [CR] + partial response [PR] + stable disease [SD]), clinical-benefit rate (CBR; CR + PR + durable SD), and duration of response (DOR), all by irRECIST, and safety. **Results:** 23 Pts enrolled (phase II: 21; phase Ib: 2); median age was 64 years (range: 51−80); 87% were white; and all had ≥ 1 prior anticancer therapy. Confirmed ORR was 48% (all PR). Median PFS and DOR were not estimable (NE; see table). All pts had a treatment-emergent adverse event (TEAE). The most common TEAEs were hypertension, fatigue, arthralgia, diarrhea, and nausea. Toxicities were manageable with dose interruption and/or modification and no new safety signals were found. Updated data will be presented. **Conclusions:** Promising efficacy was observed in pts receiving LEN + pembro. In addition, toxicities were generally expected and manageable with dose modification. These results warrant further study of LEN + pembro in pts with endometrial carcinoma. Clinical trial information: NCT02501096.

Parameter	Pts (n = 23)	95% CI
ORR, n (%)	11 (48%)	27−69
DCR, n (%)	22 (96%)	78−100
CBR, n (%)	17 (74%)	52−90
Median PFS, months	NE	4.1−NE
Median DOR, months*	NE	2.6−NE

*For pts with CR or PR. CI, confidence interval.

5599 Poster Session (Board #421), Sat, 1:15 PM-4:45 PM

Prognostic importance of p16 status for women with vulvar squamous cell carcinoma (SCC) treated with radiotherapy. *First Author: Larissa Janeen Lee, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA*

Background: To evaluate the association between p16 status and in-field recurrence (IFR), progression-free (PFS) and overall (OS) survival in patients with vulvar SCC treated with radiation (RT) with or without surgical resection. **Methods:** In a multi-institutional retrospective cohort study, we identified 105 women with vulvar SCC who received RT between 1985-2011. Immunostaining for p16 was performed on archival tumor tissue using the Leica Bond III staining platform. Histopathology and p16 stains were reviewed by pathologists with expertise in gynecologic cancer; the intensity and extent of p16 staining in tumor cells were classified as negative (focal, weak, patchy) or positive (moderate or strong diffuse linear positive). Actuarial estimates of PFS, OS and IFR were calculated using the Kaplan-Meier method and compared by the logrank test. Multivariable analysis (MVA) was performed using the Cox proportional hazards model. **Results:** Patients with p16-positive disease were significantly younger at diagnosis (median 67 vs. 77 years) and were more likely to be current smokers (51% vs. 0%) and to have received concurrent chemotherapy (68% vs. 47%, all $p<0.05$). FIGO stage distribution, RT intent and median RT doses were similar by p16 status. With a median follow-up of 61 months, 5-year PFS and OS rates were 35% and 40%, respectively. Women with p16-positive tumors had significantly better 5-year PFS and OS rates than those with p16-negative tumors (61% and 23%, $p<0.01$ and 64% and 29%, $p=0.01$, respectively). The 5-year IFR rate was also lower for those with p16-positive disease (17% vs. 65%, $p<0.01$). On univariate analysis, use of concurrent chemotherapy was not associated with PFS ($p=0.5$), OS ($p=0.3$) or IFR ($p=0.8$). On MVA adjusted for age and stage, p16 positivity was significantly associated with better PFS (HR 0.57, 95% CI 0.33-0.97) and lower IFR (HR 0.24, 95% CI 0.09-0.6). **Conclusions:** In a multi-institutional setting, women with p16-positive vulvar SCC treated with RT had a lower IFR rate and longer survival than those with p16-negative disease. The magnitude of prognostic importance of p16 status is similar to that seen in oropharyngeal, anal and cervical cancers treated with RT.

TPS5600 Poster Session (Board #422a), Sat, 1:15 PM-4:45 PM

Phase III randomized trial of image-guided bone marrow-sparing intensity modulated radiation therapy (IG-BMS-IMRT) for locoregionally advanced cervical cancer: The INTERTECC-3 trial. *First Author: Loren K. Mell, University of California San Diego Moores Cancer Center, La Jolla, CA*

Background: Cervical cancer is a leading cause of cancer death in women worldwide. Image-guided bone marrow-sparing intensity modulated radiation therapy (IG-BMS-IMRT) has shown potential to reduce acute toxicity of chemoradiotherapy and improve chemotherapy delivery in phase I and II trials (Mell LK, Sirák I, Wei L, et al. Bone Marrow-sparing IMRT With Concurrent Cisplatin For Stage IB-IVA Cervical Cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2). *Int J Radiat Oncol Biol Phys* 2017;97:536-545. Mell LK, Saenz CC, Yashar CM, et al. Phase I Trial of Bone Marrow Sparing IMRT With Concurrent Cisplatin and Gemcitabine in Stage IB-IVA Cervical Cancer (abstr.) *Int J Radiat Oncol Biol Phys* 2016; 96: S14.). **Methods:** INTERTECC-3 is a randomized phase III trial designed to test the effect of IG-BMS-IMRT on progression-free survival (PFS) for women with unresected FIGO stage IB-IVA cervical carcinoma (clinicaltrials.gov #NCT01554397). It presently involves centers in the U.S., Czech Republic, U.K., India, Japan, and China. Women are randomized 3:2 to either (A) IG-BMS-IMRT or (B) standard chemoradiation, with 6 cycles of concurrent cisplatin (40 mg/m^2) weekly in both arms. Secondary objectives are to compare overall survival, treatment-related toxicity, disease recurrence, quality of life, chemotherapy delivery, and radiation quality assurance. Planning objectives require maintaining pelvic marrow and active marrow mean doses < 27 Gy and < 28.5 Gy respectively. Correlative studies involve longitudinal collection of magnetic resonance restriction spectrum imaging and ^{18}F-fluorothydimine positron emission tomography scans to assess imaging biomarkers of treatment response in select patients. 415 women will be enrolled to determine if IG-BMS-IMRT improves the median PFS from 3.2 to 5.0 years with 80% power and alpha = 0.05. INTERTECC-3 opened in the U.S. and Czech Republic in 2016. To date, 17 patients have been randomized. The trial will be activated at additional international sites in late 2017 and 2018. We are seeking to recruit sites who wish to collaborate. Clinical trial information: NCT01554397.

TPS5601 Poster Session (Board #422b), Sat, 1:15 PM-4:45 PM

A randomized phase II study of chemoradiation and pembrolizumab for locally advanced cervical cancer. *First Author: Linda R. Duska, University of Virginia Health System, Charlottesville, VA*

Background: The standard of care for patients with LACC is concurrent chemoradiation therapy (CRT) with weekly cisplatin. Five-year disease overall survival after contemporary CRT for LACC is only 66%. Human Papillomavirus (HPV) DNA is detected in virtually all cervical cancers, and HPV specific CD4+ helper and CD8+ cytotoxic T cells are found in cervical tumors, indicating the inherent immunogenicity of these tumors. The failure of the immune system to eradicate HPV DNA integration is thought to be associated with the cancer cells' acquisition of mechanisms to avoid cytotoxic T cells, including, but not limited to, the expression of checkpoint inhibitory molecules such as PD-L1 and the recruitment of FoxP3+ immunosuppressive regulatory T cells. Low ratios of CD8+ T cells: regulatory T cells are associated with poor survival for cervical cancer patients, suggesting that strategies to enhance immune response would be effective. Additionally, in cervical cancer, PD-1 is expressed by the majority of infiltrating CD8+ T cells, suggesting that blocking of PD-1 could have therapeutic potential, inducing tumor-specific immunity in cervical cancer patients. We hypothesized that CRT may increase tumor responsiveness to anti-PD-1 therapy by enhancing antigen availability and disrupting immune-regulatory networks. However, it is unclear how treatment with cisplatin and/or ionizing radiation could influence the quality and quantity of the immune response. **Methods:** A randomized Phase II open-label multi-center study was designed in which 88 eligible subjects with LACC will be treated with standard CRT plus the PD-1 monoclonal antibody pembrolizumab. The primary objectives in the study are to estimate the safety and immune response to pembrolizumab given either sequentially or concurrently with CRT. Secondary objectives will evaluate the metabolic response and rates of distant metastases following treatment with pembrolizumab given sequentially or concurrently with CRT. The study design also affords the opportunity to characterize the effect of treatment on immune response pathways by estimating the effects of treatment on specific immune markers. Clinical trial information: NCT02635360.

TPS5602 Poster Session (Board #423a), Sat, 1:15 PM-4:45 PM

TRUST: Trial of radical upfront surgical therapy in advanced ovarian cancer (ENGOT ov33 / AGO-OVAR OP7). *First Author: Sven Mahner, Department for Gynecology and Obstetrics, University of Munich, Munich, Germany*

Background: Primary cytoreductive surgery (PDS) followed by chemotherapy has been considered as standard management for advanced ovarian cancer patients (pts) over decades. An alternative approach of interval debulking surgery (IDS) following neoadjuvant chemotherapy (NACT) was subsequently reported by two randomized phase III trials (EORTC-GCG, CHORUS). Owing to important limitations of these studies, especially regarding surgical quality, optimal timing of surgical therapy in advanced ovarian cancer is still unclear. **Methods:** TRUST is an international open, randomized, controlled multicenter trial investigating overall survival (OS; primary endpoint) after PDS vs NACT and subsequent IDS in pts with FIGO stage IIIB-IVB ovarian, tubal, and peritoneal carcinoma. Secondary objectives are safety of complete tumor resection, progression-free survival and quality of life (QoL) as well as surgical morbidity. In order to guarantee adequate surgical quality, participating centers need to fulfill specific quality assurance criteria (e.g. $\geq$50% complete resection rate in upfront surgery for FIGO IIIB-IV pts, $\geq$36 debulking-surgeries/year) and agree to independent audits by TRUST Quality committee delegates. A 1:1 randomization to PDS or NACT followed by IDS stratified by center and age-ECOG combination (ECOG 0 and age $\leq$65 years vs ECOG $>$ 0 or age $>$ 65 years) is performed. Pts in the PDS arm will undergo surgery followed by 6 cycles of platinum-based chemotherapy, whereas pts in the IDS arm will be treated with 3 cycles of NACT after histologic confirmation of the disease, followed by IDS and subsequently 3 cycles of platinum-based chemotherapy. Intention of surgery for both groups will be complete tumor resection as per guideline recommendations. Health related QoL will be assessed using the EORTC QLQ-C30, QLQ-OV28, and EQ-5D-3L questionnaires. For sample size planning, we considered a prolongation of median OS from 45 months in the IDS arm to 60 months in the PDS arm (HR 0.75) as clinically relevant. 380 events are needed to obtain a power of 80% in two-sided log-rank test with significance level of 0.05. The primary analysis will be done in the ITT-population of 686 randomized pts. By Feb 3 2017, 46 pts were randomized. Clinical trial information: NCT02828618.

TPS5603 Poster Session (Board #423b), Sat, 1:15 PM-4:45 PM

ARIEL4: An international, multicenter randomized phase 3 study of the PARP inhibitor rucaparib vs chemotherapy in germline or somatic *BRCA1*- or *BRCA2*-mutated, relapsed, high-grade ovarian carcinoma. *First Author: Amit M. Oza, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: In high-grade epithelial ovarian carcinoma (OC), ≈18% of patients (pts) have tumors with a germline *BRCA1* or *BRCA2* mutation; ≈7% have tumors with a somatic *BRCA1* or *BRCA2* mutation (Pennington et al. *Clin Cancer Res.* 2014;20:764-75). The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib is approved in the United States for treatment of pts with OC associated with a deleterious *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have received ≥2 chemotherapies. Although PARP inhibitors have demonstrated clinical activity in OC in both treatment and maintenance settings, comparison to standard of care (SOC) has only been evaluated in the maintenance setting. Randomized studies are needed to assess the benefit-risk profile of PARP inhibitors vs current SOC as treatment for *BRCA1*- or *BRCA2*-mutated, relapsed, high-grade OC. **Methods:** ARIEL4 (NCT02855944) is evaluating rucaparib vs chemotherapy as treatment for pts with germline or somatic *BRCA1*- or *BRCA2*-mutated, relapsed, high-grade OC (regardless of histology) who have received ≥2 prior chemotherapy regimens. Approximately 345 pts will be randomized 2:1 to receive rucaparib (600 mg BID) (n = 230) or chemotherapy (n = 115) and stratified by progression-free interval after their most recent platinum regimen. Pts with platinum-resistant (progressive disease [PD] 1– < 6 mo after last platinum) or partially platinum-sensitive disease (PD 6– < 12 mo after last platinum) will be randomized to rucaparib or weekly paclitaxel; pts with platinum-sensitive disease (PD ≥12 mo after last platinum) will be randomized to rucaparib or platinum-based therapy (single-agent or doublet at the discretion of the investigator). Pts receiving chemotherapy have the option to cross over to rucaparib upon radiographic disease progression. The primary endpoint is progression-free survival. Secondary endpoints include investigator-assessed objective response rate (ORR) (RECIST version 1.1), ORR/CA-125 response, duration of response, overall survival, and pt-reported outcomes. Safety will be summarized descriptively using standard adverse event reporting. Clinical trial information: NCT02855944.

TPS5604 Poster Session (Board #424a), Sat, 1:15 PM-4:45 PM

Clinical trial in progress: A phase 3 study of maintenance bi-shRNA-furin/GM-CSF-expressing autologous tumor cell vaccine in women with stage IIIb-IV high-grade epithelial ovarian cancer. *First Author: Jonathan Oh, Texas Oncology, Dallas, TX*

Background: Vigil is an immuno-stimulatory autologous cellular therapy, which uses patient tumor cells transfected with a plasmid encoding genes for GM-CSF and furin (to down regulate TGFβ 1&2). In Phase I, systemic immune activation was demonstrated in the majority of patients using an IFNγ ELISPOT assay. A randomized Phase 2 assessment of Vigil maintenance therapy vs. observation in ovarian cancer demonstrated prolonged relapse free survival (RFS) (Oh J, Barve M, et al. Gynecologic Oncology, 2016; 143: 504–510.). Based on these observations, a Phase 3 study of maintenance Vigil therapy in patients with advanced ovarian cancer was initiated (NCT02346747). **Methods:** This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of maintenance Vigil in women with Stage IIIb,c or IV high-grade papillary serous/clear cell/ endometrioid ovarian, fallopian tube or primary peritoneal cancer. Patients will have a minimum of 4 and a maximum of 12 Vigil doses manufactured from tumor obtained at primary debulking surgery. Patients must achieve a complete clinical remission following primary surgery and chemotherapy before being randomized 1:1 to receive either monthly intradermal Vigil or placebo. Randomization is stratified by extent of surgical cytoreduction (complete/ microscopic vs. macroscopic residual disease) and neoadjuvant vs. adjuvant chemotherapy. The primary objective is to compare RFS of subjects randomized to Vigil vs. placebo, and the key secondary objective is overall survival (OS). The sample size calculation of 222 patients assumes 24 months for accrual and 36 months of follow-up with a median RFS of 19 months from randomization, in the control group. This provides 90% power to detect a hazard ratio (HR) of 0.6 favoring Vigil at the 0.05 level of significance. To date, 61 patients have been randomized and an additional 55 patients are receiving chemotherapy in anticipation of randomization. Tumor tissue is being obtained from approximately 20 patients per month at multiple sites across the U.S. At their last meeting in January, 2017 the independent DSMB recommended that the study continue without change. Clinical trial information: NCT02346747.

TPS5605 Poster Session (Board #424b), Sat, 1:15 PM-4:45 PM

PAOLA-1: An ENGOT/GCIG phase III trial of olaparib versus placebo combined with bevacizumab as maintenance treatment in patients with advanced ovarian cancer following first-line platinum-based chemotherapy plus bevacizumab. *First Author: Isabelle Laure Ray-Coquard, GINECO Group and Centre Léon Bérard, Lyon, France*

Background: Olaparib (Lynparza) is an oral PARP inhibitor indicated in the EU for the maintenance treatment of patients (pts) with platinum-sensitive relapsed *BRCA*-mutated high grade serous ovarian cancer (HGSOC). Bevacizumab is an anti-VEGF monoclonal antibody indicated in the EU in first line or relapse for the treatment of OC in combination with specific chemotherapeutic agents. Bevacizumab treatment is associated with increasing hypoxia-induced homologous recombination repair deficiencies in tumor cells, and is hypothesized to increase ovarian tumor sensitivity to olaparib. **Methods:** PAOLA-1 (ENGOT-ov25) is a randomized, placebo-controlled trial evaluating the efficacy and safety of olaparib (tablet formulation) in pts with advanced HGSOC receiving bevacizumab maintenance therapy. Eligible pts are those in complete or partial response following first-line platinum chemotherapy plus bevacizumab, and for whom bevacizumab maintenance therapy is planned. Approximately 762 European and 24 Japanese pts will be randomized 2:1 to olaparib 300 mg twice daily or placebo for up to 24 months. All pts will receive standard maintenance care of bevacizumab (15 mg/kg every three weeks) for up to 15 months. Primary objective: PFS1 according to RECIST 1.1 Secondary objectives: PFS2, OS, Safety, PRO/QoL, TFST, TSST All pts will undergo tumor *BRCA* testing prior to randomization. Central *BRCA* testing (tumor) will be performed in five screening platforms in France. Tumor *BRCA* test results have to be available within two months of sample provision. PFS will be evaluated using a log-rank test stratified by response to first-line treatment and *BRCA* mutation status. Treatment effect hazard ratio of 0.7 is expected and final PFS1 analysis will be performed after 372 events. The first pt from eight ENGOT groups plus Japan (10 participating countries) was randomized in July 2015. As of 31 January 2017, 549 pts have been randomized. The median period between the provision of a tumor sample and returned *BRCA* test result is 40 days. Accrual is expected to be complete before July 2017. Clinical trial information: NCT02477644.

TPS5606 Poster Session (Board #425a), Sat, 1:15 PM-4:45 PM

A phase 2 study to assess olaparib by homologous recombination deficiency status in patients with platinum-sensitive, relapsed, ovarian, fallopian tube, or primary peritoneal cancer. *First Author: Karen Anne Cadoo, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: The poly (ADP-ribose) polymerase (PARP) inhibitor olaparib is approved for treatment of patients (pts) with germline *BRCA* mutations (*BRCAm*) and advanced ovarian cancer (OC). *BRCA* mutations are genetic alterations leading to homologous recombination deficiency (HRD) and tumor susceptibility to DNA-damaging agents, including PARP inhibitors. Loss of genetic heterozygosity, telomeric-allelic imbalance, or large-scale state transitions may identify additional pts who could benefit from PARP inhibitor therapy. **Methods:** LIGHT is a non-randomized, open-label, phase 2 study to assess the efficacy and safety of olaparib in patient cohorts identified by different HRD genetic tests (NCT02983799). Patients will have platinum-sensitive (progression > 6 mo after the end of the last platinum-based chemotherapy), relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer; ECOG performance status 0–1; and ≥2 prior lines of platinum-based chemotherapy for OC. Key exclusion criteria include prior PARP inhibitor treatment; concomitant use of potent CYP3A4/5 inhibitors or inducers; and symptomatic uncontrolled brain metastases. Patients will be enrolled into 4 cohorts of 30 pts each based upon *BRCAm* or tumor HRD status determined by genetic test results: germline *BRCAm*; somatic *BRCAm*; MyChoice HRD-positive and wildtype *BRCAm*; MyChoice HRD-negative and wildtype *BRCAm*. All pts will receive 300 mg olaparib tablets twice daily until disease progression (RECIST v1.1) or unacceptable toxicity. The primary endpoint is investigator-assessed objective response rate (ORR) according to RECIST v1.1 criteria. The maximum precision of the ORR is approximately ±18.7% for 30 pts. Secondary endpoints include duration of response, cancer antigen-125 response rate, disease control rate, progression-free survival, time to any progression, overall survival, and homologous recombination repair gene panel mutation status related to clinical outcome. Planned enrollment of 120 pts at sites in the United States was initiated in December 2016. Clinical trial information: NCT02983799.

TPS5607 Poster Session (Board #425b), Sat, 1:15 PM-4:45 PM

FORWARD I (GOG 3011): A randomized phase 3 study to evaluate the safety and efficacy of mirvetuximab soravtansine (IMGN853) versus chemotherapy in adults with folate receptor alpha (FRα)-positive, platinum-resistant epithelial ovarian cancer (EOC), primary peritoneal cancer, or primary fallopian tube cancer. *First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: Elevated FRα expression is characteristic of a number of solid tumors, including EOC, thereby providing an attractive candidate for targeted therapeutic approaches. Mirvetuximab soravtansine is an antibody-drug conjugate (ADC), comprising a FRα-binding antibody linked to the tubulin-disrupting maytansinoid DM4, that has shown single agent clinical activity and a favorable safety profile in an ongoing, first-in-human phase 1 trial (NCT01609556). **Methods:** FORWARD I is a randomized phase 3 study designed to evaluate the efficacy of mirvetuximab soravtansine compared with that of standard-of-care chemotherapy in adult patients with platinum-resistant EOC, primary peritoneal cancer, or fallopian tube cancer. Confirmation of FRα positivity by immunohistochemistry (medium or high expression; ≥ 50% of cells with at least moderate staining intensity) and ≤ 3 prior lines of therapy are required for inclusion. A maximum of 333 patients are expected to be recruited. Patients will be randomized 2:1 to Arm 1 (intravenous mirvetuximab soravtansine at a dose of 6.0 mg/kg, calculated using adjusted ideal body weight, on Day 1 of a 21-day cycle) or Arm 2 (investigators' choice chemotherapy: paclitaxel, pegylated liposomal doxorubicin, or topotecan). The primary efficacy endpoint is progression-free survival (PFS; by blinded independent central review) and secondary endpoints include objective response rate, quality of life, overall survival, safety and tolerability, and duration of response. The first patient was enrolled in January 2017. Clinical trial information: NCT02631876.

TPS5608 Poster Session (Board #426a), Sat, 1:15 PM-4:45 PM

Phase II open-label randomized multi-centre study of neoadjuvant olaparib in patients (pts) with platinum sensitive (PS) relapsed high grade serous ovarian cancer (OC): The NEO trial. *First Author: Yada Kanjanapan, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Olaparib is a PARP inhibitor with clinical benefit in relapsed OC, especially in pts with germline *BRCA1/2* mutation (*gBRCA*). Study 19 (NCT00753545) found a progression free survival (PFS) gain from maintenance olaparib, post chemotherapy for PS relapse. Olaparib treatment in *gBRCA* OC pts relapsing post ≥ 3 prior chemotherapy regimens gave a response rate (RR) of 46% in the PS subgroup (Study 42; NCT01078662). Efficacy of olaparib may extend to OC with homologous recombination DNA repair pathway deficiency (HRD); susceptible to synthetic lethality from PARP inhibition. NEO [NCT02489006] is a window of opportunity study to assess tumor heterogeneity and the pharmacodynamic effects of olaparib given prior to surgery in PS OC, analyse the tumor genomic landscape pre and post olaparib, and assess for predictive biomarkers beyond *BRCA* mutation. **Methods:** This phase 2 study enrols pts with high grade serous OC, primary peritoneal or fallopian tube cancer with a progression free interval of ≥6 months and sensitive to their last line of platinum therapy. Pts must be suitable for secondary debulking surgery and agree to pre-operative tumour biopsy. All pts receive olaparib tablets 300mg po bid for 6 ± 2 weeks pre-surgery. Post-operatively, pts are randomised 1:1 to olaparib or 6 cycles of platinum-based chemotherapy followed by maintenance olaparib. The primary endpoint is the degree of PAR and PARP-1 inhibition in the blood and tumor following pre-operative olaparib in PS relapsed OC. Clinical efficacy is assessed by RR (RECIST 1.1), CA125, PFS and PFS2. Translational studies include next generation sequencing HRD panel to assess for somatic and germline mutations including RAD51B/C/D, PPM1D, FANCM, BRIP1, PALB2 and BARD1; evaluation of gene expression change in tumor tissue pre and post olaparib; assessment for resistance mechanisms and impact of heterogeneity. Circulating tumor DNA measured weekly pre-surgery is assessed for its prognostic value, alone and compared with CA125. The study will enrol 50-70 pts with estimated accrual of 3 pts/month across multiple sites, and opened at Princess Margaret Cancer Centre in 7/2016. Clinical trial information: NCT02489006.

TPS5609 Poster Session (Board #426b), Sat, 1:15 PM-4:45 PM

OCTOPUS: A randomised, multi-centre phase II umbrella trial of weekly paclitaxel+/- novel agents in platinum-resistant ovarian cancer—Vistusertib (AZD2014). *First Author: Susana N. Banerjee, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: There is an urgent need to improve outcomes for patients with platinum-resistant and refractory ovarian cancer (PROC). OCTOPUS is an umbrella phase II framework for testing whether the addition of novel targeted agents to weekly paclitaxel (wPxl) improves efficacy in PROC. The first agent to be evaluated is the dual mTORC1/mTORC2 inhibitor, vistusertib (AZD2014), as preclinical studies support targeting the PI3kinase/Akt/mTOR pathway in PROC and the combination of vistusertib and wPxl has shown promising preliminary activity in high grade serous ovarian cancer (HGS) patients in a phase I trial (Banerji et al poster discussion ESMO 2016). This is the first randomised trial of wPxl and a dual mTORC1/2 inhibitor in ovarian cancer. **Methods:** OCTOPUS is an investigator-initiated, randomised, double-blind, placebo-controlled, multicentre, phase II trial. 140 patients with PROC (histologically confirmed HGS) are randomised 1:1 to receive wPxl (80mg/m2 D1, D8, D15 of 28 day cycle) plus oral vistusertib (50mg BD) or placebo (D1-3, D8-10, D15-17). The primary endpoint is progression-free survival (PFS) based on combined RECIST v1.1/GCIG CA125 criteria. The study is designed to detect a 50% improvement in median PFS from 3.7 months on placebo to 5.55 months on the experimental arm with 90% power, at the 20% 1-sided level of statistical significance (or equivalently with 80% power at the 10% level of statistical significance) using a 3-outcome design. Secondary endpoints include response (based on RECIST 1.1 and GCIG CA125 criteria), overall survival, toxicity and quality of life. Patients whom received prior wPxl for PROC are not eligible. A mandatory pre-treatment biopsy (if technically feasible), archival tissue, and serial blood samples will be collected for translational research studies. 49 patients have been recruited. The study is part of the NIHR CRN Cancer/Astrazeneca Alliance, sponsored by NHS Greater Glasgow and Clyde/University of Glasgow and endorsed by Cancer Research UK (CRUKE/14/052). Clinical trial information: ISRCTN16426935.

TPS5610 Poster Session (Board #427a), Sat, 1:15 PM-4:45 PM

A phase II trial of enzalutamide in patients with androgen receptor positive (AR+) ovarian, primary peritoneal or fallopian tube cancer and one, two, or three prior therapies. *First Author: Rachel N. Grisham, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: Approximately 75% of women with epithelial ovarian cancer (OC) present with advanced disease. Most of these women will ultimately recur and require life-long treatment for their cancer. Well tolerated therapies for treatment in the recurrent setting are needed. The AR is expressed in greater than 60% of cases of OC and is more prevalent than the estrogen or progesterone receptor. All past clinical studies of AR inhibition in OC have focused on unselected populations of heavily pretreated women; however preclinical data suggests that AR expression decreases in OC cells with increasing lines of therapy. Enzalutamide is a small molecule androgen receptor-antagonist that is FDA approved for treatment of prostate cancer and is currently being investigated as treatment for breast and ovarian cancer. **Methods:** This is a phase II, single-institution trial of enzalutamide 160mg po QD in patients with AR+ ovarian, fallopian tube or primary peritoneal cancer. Eligible patients must be found to have greater than or equal to 5% AR staining by IHC on FFPE tumor tissue and been treated with only 1,2 or 3 prior cytotoxic therapies. Patients must have RECIST 1.1 defined measurable disease. Enrolled patients are treated with enzalutamide until progression of disease or unacceptable toxicity. The primary endpoint is to estimate the proportion of women who achieve a complete or partial response by RECIST 1.1 criteria or survive progression free for at least 6 months. Secondary objectives include the retrieval of optional tumor biopsies at time of progression to evaluate the effect of enzalutamide on AR expression and to observe the effect of enzalutamide on serum testosterone and estradiol levels. This study will enroll 58 patients at Memorial Sloan Kettering Cancer Center and its regional sites. The study utilizes a safety lead-in phase and a two-stage design. The first patient enrolled in April 2015. The safety lead-in phase has been completed. The prespecified activity goal for the first stage was met; second stage accrual began in October 2016. Thus far, 35 patients have initiated treatment. Clinical trial information: NCT01974765.

TPS5611 **Poster Session (Board #427b), Sat, 1:15 PM-4:45 PM**

Combination chemotherapy with nintedanib/placebo for patients with advanced or recurrent endometrial cancer: The NSGO ENGOT-EN1/FANDANGO trial. *First Author: Mansoor Raza Mirza, NSGO and Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark*

Background: Endometrial cancer (EC) patients with advanced and recurrent disease relapse despite treatment with combination chemotherapy and have a short progression-free survival (PFS). With the emerging clinical data on anti-angiogenic agents and with promising results of nintedanib in ovarian cancer, it is apparent to explore its role in EC. Nintedanib is a potent, orally available triple receptor tyrosine kinase inhibitor targeting VEGFR 1-3, PDGFR α/β, and FGFR 1-3. This placebo-controlled, multicenter, two-arm, phase 2 trial compares nintedanib versus placebo as concomitant and maintenance therapy in combination with chemotherapy in patients with advanced or recurrent EC. **Methods:** The primary objective of this trial is to evaluate efficacy of nintedanib against placebo in combination with chemotherapy, defined by PFS. Key eligibility criteria include: histologically confirmed EC, stage 3C 2 or 4 A & B or relapsed after adjuvant therapy for stage 1-3 disease; prior surgery; adjuvant chemotherapy; radiation therapy; hormonal therapy are permitted; measurable/non-measurable disease. 148 patients will be randomized 1:1 to receive nintedanib 200mg twice daily or placebo days 2-21 during chemotherapy (six cycles of Carboplatin (AUC5) and paclitaxel (175mg/m2) every 21 days) and continuously in maintenance phase. Nintedanib/placebo is continued until disease progression, unacceptable toxicity, or withdrawal. Secondary endpoints include PFS in sub-populations, PFS2, disease specific survival, time to first subsequent therapy, time to second subsequent therapy, overall survival, objective response, disease control rate, patient reported outcoms (assessed via EORTC QLQ-C30 and EORTC QLQ-EN24) and safety. Trial is enrolling patients. The following cooperative groups are participating: NSGO (DK, FIN, SWE, NOR), NOGGO (GER), BGOG (BEL), & GINECO (FRA). Clinical trial information: NCT02730416.

TPS5612 **Poster Session (Board #428a), Sat, 1:15 PM-4:45 PM**

Palbociclib versus placebo in combination with letrozole for patients with advanced or recurrent endometrial cancer: The NSGO ENGOT-EN3/PALEO trial. *First Author: Mansoor Raza Mirza, NSGO and Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark*

Background: Endometrial cancer (EC) patients with advanced or recurrent disease and endometrioid histology have a short progression-free survival (PFS). These malignancies are hormone dependent and endocrine therapy with aromatase inhibitors is well established. Palbociclib is an oral and selective inhibitor of cyclin-dependent kinases CDK4 and CDK6. Studies in breast cancer have demonstrated superiority of letrozole treatment in combination with palbociclib vs. letrozole monotherapy in oestrogen receptor positive (ER+) HER2- advanced disease. The combination is generally well tolerated with an acceptable toxicity profile. This multicenter, prospective, double-blind, placebo-controlled, randomized, phase II trial is evaluating the efficacy of letrozole when combined with palbociclib against letrozole-placebo combination therapy in women with ER+ advanced or recurrent EC. **Methods:** The primary objective of this trial is to demonstrate superiority of palbociclib against placebo in combination with letrozole, as defined by investigator-assessed progression-free survival (PFS). Key eligibility criteria include: histologically confirmed ER+ EC of endometrioid type; stage 4 or recurrent disease; prior surgery, adjuvant chemotherapy, radiation therapy, hormonal therapy (e.g. megestrol acetate) is permitted; measurable/evaluable disease according to RECIST 1.1. 78 patients will be randomized 1:1 to receive palbociclib 125mg daily or placebo on days 1-21 and letrozole 2.5mg daily on days 1-28 in a 28 days cycle until disease progression, unacceptable toxicity, or withdrawal. Secondary endpoints include PFS in sub-populations, overall response rate, disease control rate, PFS2, time to first subsequent therapy, time to second subsequent therapy, overall survival, safety & tolerability, patient reported outcomes (assessed via EORTC QLQ-C30 and EORTC QLQ-EN24) and PFS in patients with or without retinoblastoma protein-expressing tumors. The following cooperative groups are participating: NSGO (DK, FIN, NOR), MITO (ITA), GEICO (SPA) & NOGGO (GER). Clinical trial information: NCT02730429.

TPS5613 **Poster Session (Board #428b), Sat, 1:15 PM-4:45 PM**

Postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate or high risk endometrial cancer: The ENGOT-EN2/DGCG trial. *First Author: Mansoor Raza Mirza, The Finsen Centre, Ballerup, Denmark*

Background: Patients with medium and high-risk stage I and II endometrial cancers (EC) have, despite radical surgery, a high risk for progression. Adjuvant brachytherapy or EBRT is the traditional therapy for many decades although without impacting on survival. Several studies have failed to demonstrate superiority of adjuvant chemotherapy in unselected population with a high number of low-risk patients. It is of utmost importance to demonstrate efficacy of adjuvant combination chemotherapy in a randomized trial comparing to no further treatment in the medium and high-risk node negative stage I and stage II patients. **Methods:** The primary objective of this trial is to evaluate the effect on overall survival of carboplatin-paclitaxel combination chemotherapy against no further systemic treatment. Key eligibility criteria include: histologically confirmed EC, stage I grade 3 endometrioid adenocarcinoma or stage II endometrioid adenocarcinoma or stage I and II type 2 histology (clear cell, serous, squamous cell carcinoma, carcinosarcoma or undifferentiated carcinoma); prior surgery with pelvic lymphadenectomy or sentinel lymph node biopsy. Patients may receive vaginal brachytherapy in both arms. 240 patients are randomized to receive six courses of adjuvant carboplatin (AUC5) and paclitaxel (175mg/m2) combination on day one every 21 days or no further treatment (1:1 randomization). Primary endpoint is overall survival of endometrioid subgroup. Secondary endpoints include overall survival of whole study population, disease specific survival, progression-free survival, toxicity, compliance, Quality of Life (assessed via EORTC QLQ-C30 and EORTC QLQ-EN24), rate of isolated pelvic or distant relapses, as well as mixed relapses. Trial is enrolling patients. The following cooperative groups are participating: DGCG (DK), NSGO (DK, FIN, SWE), BGOG (BEL), MaNGO (ITA), MITO (ITA), GEICO (SPA), NOGGO (GER), CEEGOG (Czech), ISGO (ISR) & MDACC (USA). Clinical trial information: NCT01244789.

TPS5614 **Poster Session (Board #429a), Sat, 1:15 PM-4:45 PM**

A phase II trial of durvalumab (Medi 4736) in advanced endometrial cancer: PHAEDRA. *First Author: Yoland Catherine Antill, Cabrini Health, Brighton, Australia*

Background: Advanced endometrial cancer (EC) progressing after 1 or more lines of chemotherapy is an area of unmet need with objective tumour response rates to subsequent lines of chemotherapy of $\leq$20%. DNA mismatch repair (MMR) deficiency, seen in approximately 15% of EC, is associated with a high mutational load and in addition, up to 90% of ECs are reported to have PDL1/ PD1 expressions. These factors make immune check point inhibition an ideal target for treatment. **Methods:** DESIGN: Multicentre phase 2 trial in two cohorts. ELIGIBILITY: Advanced, unresectable endometrial cancer that is either MMR-proficient and progressing after 1-3 lines of chemotherapy, or MMR-deficient and progressing after 0-3 lines of chemotherapy. ENDPOINTS: Objective tumour response rate (OTRR) according to iRECIST (primary) and RECIST 1.1, disease control rates at 16 and 24 weeks, progression free survival, overall survival, duration of OTR and DC, adverse events, health related quality of life. Tertiary correlative objectives: Associations between immunologic (including PD-L1), DNA mismatch repair (MMR) and other genetic characteristics with clinical outcomes; and family history of cancer and referral to familial cancer services. INTERVENTION: Durvalumab 1500 mg intravenously every 28 days until disease progression or prohibitive toxicity. STATISTICS: Total of 70 participants in two cohorts (35 each) will have 90% power to distinguish a difference in observed OTRR of $\geq$20% versus $\leq$5% (uninteresting rate) using Simon's 2-stage minimax design with 10% type 1 error rate and allowing 10% ineligibility and missing data. Durvalumab will be considered worthy of pursuit if 4 or more OTR are observed in the first 32 participants in each cohort (OTRR $\geq$12.5%). BIOSPECIMENS: Tumour tissue and serial bloods (5 time points) will be collected for translational research. PHAEDRA is an investigator-initiated, cooperative-group trial led by ANZGOG, in collaboration with NHMRC Clinical Trials Centre, University of Sydney. Australian New Zealand Clinical Trials Registry: Clinical trial information: ACTRN12617000106336.

TPS5615 Poster Session (Board #429b), Sat, 1:15 PM-4:45 PM

Phase 2, two-group, two-stage, open-label study of avelumab in patients with microsatellite stable, microsatellite instable and *POLE*-mutated recurrent or persistent endometrial cancer. *First Author: Panagiotis A. Konstantinopoulos, Dana-Farber Cancer Institute, Boston, MA*

Background: The Cancer Genome Atlas project identified 2 groups of hypermutated endometrial cancers (ECs): an ultramutated group that harbored mutations in the exonuclease domain of polymerase e (*POLE*), and a hypermutated group with microsatellite instability (MSI), the majority of which harbored *MLH1* promoter methylation. We (Howitt, JAMA Onc 2015) and others have shown that *POLE* and MSI ECs are associated with higher number of predicted neoepitopes and tumor infiltrating lymphocytes, which is counterbalanced by overexpression of PD-1/PD-L1, suggesting that they may be excellent candidates for PD-1/PD-L1 blockade. Anti-PD-1 therapy has also demonstrated promising activity in mismatch repair deficient colorectal cancers and collectively in non-colorectal cancers (Le, NEJM 2015). **Methods:** This is an open-label, two-cohort, two-stage, phase 2 trial, of avelumab, a fully human IgG1 antibody directed against PD-L1, in two cohorts: i) a MSI/*POLE* cohort including ECs with immunohistochemical (IHC) complete loss of expression of at least one of the mismatch repair (MMR) proteins and/or documented mutation in the exonuclease domain of *POLE* and ii) a MSS cohort including ECs with normal IHC expression of all MMR proteins. Key eligibility criteria include measurable disease, no upper limit of prior therapies, and any EC histology. Co-primary objectives include objective response rate and rate of progression-free survival at 6 months. Avelumab is administered at 10 mg/kg as 1-hour IV infusion every 2 weeks until disease progression or unacceptable toxicity; therapy may continue at the investigator's discretion while awaiting radiologic confirmation of disease progression 4 weeks later. Maximum target enrollment is 70 patients (35 for each cohort). In the first stage, 16 patients will be enrolled in each cohort; if there are at least two objective responses or two patients progression-free at 6 months, accrual will continue to the second stage where 19 more patients will be enrolled for each cohort. Thus far, 16 patients have been enrolled, 13 on the MSS cohort and 3 on the MSI/*POLE* cohort. Clinical trial information: NCT02912572.

6000 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase III randomized trial of chemotherapy with or without bevacizumab (B) in patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): Survival analysis of E1305, an ECOG-ACRIN Cancer Research Group trial. *First Author: Athanassios Argiris, Thomas Jefferson University, Philadelphia, PA*

Background: The addition of B, an anti-VEGF monoclonal antibody, to chemotherapy has improved outcomes in several solid tumors. Pemetrexed plus B showed promising efficacy in R/M SCCHN (Argiris et al. *JCO* 2011). E1305 was designed to evaluate the addition of B to a platinum doublet in R/M SCCHN. **Methods:** B-eligible pts with performance status 0-1, not having received chemotherapy for R/M SCCHN (prior chemotherapy for locally advanced disease allowed ≥ 4 months) and without factors predisposing to bleeding (history of bleeding due to SCCHN, anticoagulation, central cavitary lung metastasis, carotid invasion) were randomized to: A) one of 4 regimens (investigator's choice) given every 3 weeks: A1, cisplatin (C) 100 mg/m^2, 5-FU 1000 mg/m^2/day x 4 days; A2, carboplatin (Cb) AUC 6, 5-FU 1000 mg/m^2/day x 4 days; A3, C 75 mg/m^2, docetaxel (D) 75 mg/m^2; A4, Cb AUC 6, D 75 mg/m^2, or B) the same regimen (B1, B2, B3, B4) plus B 15 mg/Kg IV, every 3 weeks, until progression. Chemotherapy could be stopped after 6 cycles after maximum response. All pts received prophylactic antibiotics. The primary endpoint was overall survival (OS). Control median OS of 8.5 months (mo) was projected; the addition of B was hypothesized to increase median OS to 11.5 mo with a hazard ratio (HR) of 0.74. **Results:** 403 pts were randomized (200 in arm A; 203 in arm B). Baseline characteristics were well balanced. 38% in arm A/42% in arm B had an oropharyngeal primary; 87% received C or Cb plus D. With a median follow-up of 23.1 mo, median OS was 11 mo in arm A and 12.6 mo in arm B; HR 0.84 (95% CI 0.67-1.05), p = 0.13. The 1-, 2-, 3-, and 4-year OS were 46% vs 51%, 18% vs 26%, 8% vs 16%, 6% vs 13%, in arm A vs B, respectively. Median PFS was 4.4 mo in arm A and 6.1 mo in arm B (HR 0.71, 95% CI 0.58-0.87; p = 0.0012). Objective response rate was 25% in arm A vs 36% in arm B (p = 0.013). Grade 3-5 bleeding occurred in 3.5% in arm A vs 7.7% in arm B (p = 0.08). **Conclusions:** B added to a standard platinum doublet improved response rate and PFS but not OS in first-line treatment of R/M SCCHN. The control arm in this study performed better than expected. Clinical trial information: NCT00588770.

6001 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

LUX-head and neck 2: Randomized, double-blind, placebo-controlled, phase III trial of afatinib as adjuvant therapy after chemoradiation (CRT) in primary unresected, high/intermediate-risk, squamous cell cancer of the head and neck (HNSCC) patients (pts). *First Author: Barbara Burtness, Yale School of Medicine, New Haven, CT*

Background: Locally advanced HNSCC is treated curatively, but recurrence is common. In HNSCC, EGFR is richly expressed and EGFR inhibition is validated treatment (tx); the ErbB family blocker afatinib (A) showed efficacy in recurrent/metastatic disease. This Phase III trial assessed if A after definitive CRT improves disease-free survival (DFS). **Methods:** Eligible pts had complete response after CRT ≥66 Gy (or equivalent) with concurrent cisplatin or carboplatin but not prior EGFR inhibition, for HNSCC of oral cavity, hypopharynx, larynx, or oropharynx with >10 pack years (pk yrs) tobacco use. Pts were stratified by ECOG PS (0/1) and nodal stage (N0–2a/N2b–3), and randomized 2:1 to A 40 mg/d or placebo (P); tx continued for 18 m if tolerated, or until disease recurrence. The primary endpoint was DFS. **Results:** Of 669 pts planned, 617 were randomized; A 411, P 206. Median age was 58 yrs; 86% were male; 65% ECOG PS 0; most had smoked (A/P ex-smoker: 66/72%; current: 28/22%). Subsites (A/P) were: oropharynx 53/54%; hypopharynx 21/23%; larynx 18/12%; oral cavity 9/10%. The majority had T3 or 4 (A/P 70/68%) and N2 disease (67/63%). Accrual was halted for futility on independent DMC recommendation: at a pre-planned interim analysis (40% of DFS events), median DFS was A 43.4 m vs P not reached (NR; HR 1.13 [95% CI 0.81–1.57], p=0.48); the Table shows key subgroups. Median treatment duration was A 300.0 d, P 455.5 d. Recurrence was A 23%, P 23%. Dose reduction of A was required in 53% (mostly due to diarrhea, stomatitis). Tx was discontinued due to AEs in A 15%, P 4%. **Conclusions:** A after CRT did not improve DFS vs P. Subgroup analyses were underpowered to provide definitive conclusions. Harrington and Cohen contributed equally. Clinical trial information: NCT01345669.

	n		Median DFS, m		
Subgroup	**A**	**P**	**A**	**P**	**HR, A vs P [95% CI]**
p16					
positive	53	41	NR	NR	1.16 [0.41–3.25]
negative	135	61	NR	40.1	0.75 [0.44–1.26]
PTEN IHC					
>150	52	32	NR	NR	0.78 [0.33–1.86]
≤150	30	22	NR	NR	2.52 [0.80–7.92]
Nodal stage					
N0–N2a	159	83	37.4	NR	2.23 [1.18–4.22]
N2b–N3	252	123	43.4	40.1	0.82 [0.55–1.21]
Tobacco, pk yrs					
<10	42	18	NR	25.6	0.54 [0.21–1.42]
≥10	368	188	43.4	NR	1.26 [0.88–1.79]

6002 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

A multicenter randomized controlled trial (RCT) of adjuvant chemotherapy (CT) in nasopharyngeal carcinoma (NPC) with residual plasma EBV DNA (EBV DNA) following primary radiotherapy (RT) or chemoradiation (CRT). *First Author: Anthony T. C. Chan, Department of Clinical Oncology, State Key Laboratory of Oncology in South China, The Chinese University of Hong Kong, Hong Kong, Hong Kong*

Background: The benefit of adjuvant CT in NPC is unclear. Post-RT EBV DNA predicts poor survival and may be a biomarker of subclinical residual disease. We conducted a biomarker driven RCT using post-RT EBV DNA to select high risk NPC patients (pts) for adjuvant CT while sparing low risk pts from unnecessary toxicity. **Methods:** Eligible pts had biopsy proven NPC of AJCC (6th Ed) stage IIB-IVB, detectable EBV DNA (> 0 copy/ml) at 6-8 weeks post-RT, no persistent locoregional disease or distant metastasis, ECOG 0 or 1, and adequate organ function. Pts were randomized with stratification for primary therapy (RT Vs CRT) and tumor stage (II/III Vs IV) to arm A (adjuvant cisplatin 40 mg/m2 and gemcitabine 1000 mg/m2, both given on D1+8 q3w x 6 cycles) or arm B (clinical follow-up). Primary endpoint was relapse free survival (RFS). With a hazard ratio (HR) of 2, 100 pts were required with a power of 0.8 and an alpha at 0.05. **Results:** From 9/2006 to 7/2015, 789 pts consented for EBV DNA screening, 218 (27.6%) pts had detectable EBV DNA, and 104 (13.2%) pts were randomized (arm A: 52; arm B: 52). The two arms were well balanced in baseline characteristics. 84.6% received prior neoadjuvant and/or concurrent CT and all received curative RT. Staging distribution: IIB 27.9%, III 37.5%, IVA 19.2%, IVB 15.4%. 8 pts refused adjuvant CT after randomization. Overall 69% and 50% completed 3 and 6 cycles of adjuvant CT respectively. After median follow up of 6.5 years (yr), the 3-yr and 5-yr survival outcomes were summarized in Table. **Conclusions:** In NPC pts who had residual EBV DNA after curative RT/CRT, adjuvant CT with cisplatin-gemcitabine did not improve survival. Clinical trial information: NCT00370890.

	Arm A: Adjuvant CT (n = 52)	Arm B: Clinical follow up (n = 52)	Log rank p-value	HR (95% C.I)
Relapse free survival (RFS)			0.79	0.92 (0.51-1.68)
No. of event	20	23		
3-yr	58.2%	57.3%		
5-yr	58.2%	57.3%		
Overall survival (OS)			0.92	1.04 (0.53-2.01)
No. of event	17	18		
3-yr	70.6%	80.1%		
5-yr	66.2%	67.6%		
Loco-regional failure free survival			0.46	1.42 (0.56-3.59)
No. of event	10	8		
3-yr	78.0%	83.6%		
5-yr	78.0%	83.6%		
Distant failure free survival			0.38	0.72 (0.34-1.51)
No. of event	12	17		
3-yr	74.2%	68.9%		
5-yr	74.2%	68.9%		

6003 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Impact of prophylactic human papillomavirus (HPV) vaccination on oral HPV infections among young adults in the U.S. *First Author: Maura L. Gillison, Ohio State University, Columbus, OH*

Background: The incidence of HPV-positive oropharyngeal cancers has risen in recent decades among US men. The potential impact of HPV vaccines on oral HPV infections has yet to be evaluated in efficacy-trials or surveillance studies. **Methods:** To evaluate the impact of prophylactic HPV vaccination on oral HPV infections in the US population, we conducted a cross-sectional study among men and women aged 18-33 years (n = 2,627) in the National Health and Nutrition Examination Survey, 2011-2014. We examined the effect of self-reported receipt of ≥1 vaccine dose on oral HPV infection (vaccine-types 16/18/6/11) prevalence among vaccinated vs. unvaccinated individuals. Additional outcomes included percent reduction in infection-prevalence among vaccinated individuals and population-level effectiveness of vaccination. Analyses accounted for the complex sampling design. Comparisons between vaccinated and unvaccinated individuals were conducted using binary logistic regression, with adjustment for age, gender, and race. Statistical significance was assessed using a quasi-score test. **Results:** During 2011-2014, 18.3% of the US population aged 18-33 years reported receipt of ≥1 HPV vaccine-dose prior to age 26 (29.2% in women and 6.9% in men; $P < 0.001$). The prevalence (population-weighted) of oral HPV16/18/6/11 infections was significantly reduced in vaccinated vs. unvaccinated individuals (0.11% vs. 1.61%; $P = 0.008$), corresponding to an estimated 88.2% (95%CI = 5.7%-98.5%) reduction in prevalence. Notably, oral HPV16/18/6/11 prevalence was significantly reduced in vaccinated vs. unvaccinated men (0.0% vs. 2.13%; $P = 0.007$). In contrast, prevalence for 33 non-vaccine HPV types was similar (3.98% vs. 4.74%; $P = 0.24$). Accounting for HPV vaccine-uptake, the population-level effectiveness of HPV vaccination on the burden of oral HPV16/18/6/11 infections was 17.0% overall, 25.0% in women and 6.9% in men. **Conclusions:** HPV vaccination substantially reduced vaccine-type oral HPV infection prevalence among young adults (ages 18-33 years) in the US population during 2011-2014. However, due to low vaccine uptake, population-level effectiveness was modest overall and particularly low in men.

6004 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Developing and validating a multivariable predictive biomarker for treatment selection for oropharyngeal squamous cell carcinoma: The PREDICTR-OPC study. *First Author: Hisham Mohamed Mehanna, University of Birmingham, Birmingham, United Kingdom*

Background: To date there are no validated predictive tests to inform treatment selection for patients with oropharyngeal cancer (OPC). Currently treatment is decided on disease resectability, clinician preference and patient choice. **Methods:** Objective To develop a predictive test to select treatment for advanced OPC. Participants Training cohort: 543 cases from 10 cancer centres. External validation cohort: 442 cases from 3 centres. Design Multivariable logistic regression of 8 clinical parameters and 10 biomarkers to develop biomarker-only and composite clinical/biomarker predictive models; subsequently validated on a separate cohort. Biomarkers scored by ≥2 'blinded' pathologists. Outcomes Primary: overall survival (OS). **Results:** 724 males, 261 females; Median follow-up =8.8 (6.86-10.47) years. More validation cases received surgery (53.5% vs 37.9%, p=0.001) and fewer received chemo/radiotherapy (42%vs67.5%; p=0.001) compared to training cohort. The biomarker-only model performed better than the clinical/biomarker one. The final OS model - comprising p16, high risk HPV DNA ISH, survivin and tumour infiltrating lymphocyte score (TILS)- was not only prognostic for OS, but importantly was predictive for surgery+/-adjuvant RT over CRT (3yr OS 63%, vs 42.5% respectively) in the High Risk group. Treatments were equally effective in the Low Risk group. The RFS model (p16, PLK1, survivin, TILS) was prognostic, but not predictive for treatment. Validation testing confirmed good calibration and concordance (C-index =0.73; 0.68-0.79). The OS model remained prognostic and predictive for surgical treatment in High Risk group (HR=0.51; 95%CI= 0.3-0.85, p=0.01). **Conclusions:** To our knowledge, this is the first-ever validated model for treatment selection in HNC. Clinicians can now recommend the treatment most likely to be effective on the basis of an easily-applied, relatively inexpensive panel of 4 biomarkers.

	OS Hazards Ratio (95% CI)	p - value	RFS Hazards Ratio (95% CI)	p - value	3 yr OS treated by SURG	3 yr OS treated by CRT
High risk (HR) group	0.51 (0.3-0.85)	0.01	0.83 (0.43-1.62)	0.58	63%	42.5%
Low risk group	0.85 (0.31-2.35)	0.76	0.87 (0.31-2.44)	0.79	89%	82%

6005 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: A phase III multicentre randomised controlled trial. *First Author: Ming-Yuan Chen, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: The role of neoadjuvant chemotherapy (NACT) for locoregionally advanced nasopharyngeal carcinoma (NPC) is unclear. We aimed to evaluate the feasibility and efficacy of NACT followed by concurrent chemoradiotherapy (CCRT) versus CCRT alone in locoregionally advanced NPC. **Methods:** Patients with stage III-IVB (excluding T3N0-1) NPC were randomly assigned to receive NACT followed by CCRT (investigational arm) or CCRT alone (control arm). Both arms were treated with 80 mg/m^2 cisplatin every three weeks concurrently with radiotherapy. The investigational arm received cisplatin (80 mg/m^2 d1) and fluorouracil (800 mg/m^2 civ d1-5) every three weeks for two cycles before CCRT. The primary endpoint was disease-free survival (DFS) and distant metastasis-free survival (DMFS). Secondary endpoint was overall survival (OS). **Results:** 476 patients were randomly assigned to the investigational (n = 238) and control arms (n = 238). The investigational arm achieved higher 3-year DFS rate (82.0%, 95% CI = 0.77-0.87) than the control arm (74.1%, 95% CI = 0.68-0.80, P = 0.028). The 3-year DMFS rate was 86.0% for the investigational arm versus 82.0% for the control arm, with marginal statistical significance (P = 0.056). However, there were no statistically significant differences in OS or locoregional relapse-free survival (LRRFS) rates between two arms (OS: 88.2% vs 88.5%, P = 0.815; LRRFS: 94.3% vs 90.8%, P = 0.430). The most common grade 3–4 toxicity during NACT was neutropenia (16.0%). During CCRT, the investigational arm experienced statistically significantly more grade 3–4 toxicities (P < 0.001). **Conclusions:** NACT improved tumor control compared with CCRT alone in locoregionally advanced NPC, particularly at distant sites. However, there was no early gain in overall survival. Longer follow-up is needed to determine the eventual therapeutic efficacy. Clinical trial information: NCT00705627.

6006 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Concurrent chemoradiotherapy with 3-weekly versus weekly cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: A phase 3 multicentre randomised controlled trial (ChiCTR-TRC-12001979). *First Author: Hu Liang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: In intensity-modulated radiotherapy (IMRT) era, concurrent chemoradiotherapy (CCRT) with either every three week (ETW) or once a week (OAW) cisplatin is accepted practice for locoregionally advanced nasopharyngeal carcinoma (LANPC). However, ETW and OAW were never prospectively compared in phase 3 clinical trials. This study is to assess the efficacy and toxicity profiles of CCRT with ETW versus OAW schedule of cisplatin. **Methods:** We conducted an open-label phase 3 multicentre randomised controlled trial in an endemic area. Patients with stage II-IVB NPC were randomly assigned to receive either cisplatin 100 mg/m^2 every 3 weeks for 2 cycles or cisplatin 40 mg/m^2 weekly up to 6 cycles concurrently with IMRT. IMRT in both groups was given as 2.19-2.34 Gy per fraction with five daily fractions per week for 6-7 weeks to a total dose of 68-70 Gy to the primary tumor and 62-68 Gy to the involved neck area. The primary endpoint was failure-free survival. Intention-to-treat population was adopted for efficacy analyses. **Results:** Of the 526 eligible patients, 267 were assigned to OAW arm, and 259 to ETW arm. Two arms were well-balanced in all prognostic factors. No difference was observed in overall tumor response between OAW and ETW (99.6% vs 98.9%, P = 0.624). After a median follow-up of 17.5 months (range 1.6-64.1), estimated 2 year failure-free survival rate was 92% (95% CI 87.7-96.3) in OAW and 88.3% (95% CI 83.2-93.4) in ETW (hazard ratio 1.056, 95% CI 0.58-1.92). The grade 3 or 4 toxicities were similar between two arms, but leucopenia and thrombocytopenia were significantly higher in OAW compared with ETW (24.8% vs 15.9%, P = 0.015 and 5.2% vs 1.1%, P = 0.01, respectively). Stomatitis (35.2% vs 32.6%, P = 0.576), leucopenia and nausea/vomiting (11.2% vs 12.5%, P = 0.684) were the most commonly observed grade 3 or 4 toxicities during both OAW and ETW arms. **Conclusions:** Weekly regimen of cisplatin as CCRT shows similar treatment efficacy but increased toxic effect of leucopenia and thrombocytopenia compared with 3-weekly schedule in LANPC. Longer follow-up is needed to fully assess prognosis and late toxicities. Clinical trial information: ChiCTR-TRC-12001979.

6007 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase III randomized trial comparing weekly versus three-weekly (W3W) cisplatin in patients receiving chemoradiation for locally advanced head and neck cancer. *First Author: Vanita Noronha, Tata Memorial Hospital, Mumbai, India*

Background: Chemoradiation (CRT) with cisplatin 100mg/m^2 given 3-weekly is the standard of care in locally advanced head and neck squamous cell cancer (HNSCC). Substituting low dose weekly cisplatin has pharmacological rationale due to lower toxicity and enhanced radiosensitization but has never been compared to 3-weekly cisplatin. **Methods:** Phase III non-inferiority trial (CTRI/2012/10/003062) in patients with Stage III or IV (non-metastatic) HNSCC planned for radical CRT. Pts were stratified for T-category, N-category and intent of therapy (adjuvant versus definitive) and centrally randomized 1:1 to cisplatin 30mg/m^2 weekly or 100mg/m^2 3-weekly concurrently with radiotherapy. Primary endpoint was locoregional control (LRC); secondary endpoints included toxicity, compliance, response, progression-free survival and overall survival. The upper boundary of non-inferiority margin was set at 15%, assuming LRC of 60% with power 80% and alpha 0.05. **Results:** 300 pts were randomized,150 to each arm; median age 44 years (range: 25-67), males 89%; 71% were smokeless tobacco users. 61% were T4, 71% > N2. 93% pts received CRT as adjuvant therapy for high-risk disease; indication was perinodal extension in 84%, close/ positive margins 8%. Median total treatment time was 86 days (IQR: 79-95). Median RT dose was 60 Gy (IQR 60-60 Gy) using shrinking field technique. In the weekly arm, 133 pts (88.7%) received > 6 cycles; 14 (9%) required dose reduction, median cumulative cisplatin dose 210 mg/m^2 (IQR 180-210). In the 3-weekly arm, 143 pts (95%) received > 2 cycles, median cumulative cisplatin dose 300 mg/m^2 (IQR 200-300); 12 (8%) required dose reduction. At a median follow up of 20 months (range: 1-49), locoregional relapses (LRR) occurred in 42.2% pts in the weekly arm and 29.6% pts in the 3-weekly arm, leading to an absolute difference in LRR of 12.7% (95%CI:1.89-23.41), p=0.035 by Gray's test, HR-1.58 (95% CI:1.02-2.46). Acute > grade 3 toxicity occurred in 85.3% pts in 3-weekly arm and 70.7% pts in weekly arm, p=0.002; 30.7% pts in the 3-weekly arm and 14% patients in the weekly arm required hospitalization for management of toxicity, p=0.001. **Conclusions:** 3-weekly cisplatin leads to 42% relative reduction in locoregional recurrence; it is superior to weekly cisplatin and should be the preferred regimen in CRT for HNSCC. Clinical trial information: CTRI/2012/10/003062.

6008 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Post-operative concurrent chemo-radiotherapy versus post-operative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: A randomized phase III trial (Trans Tasman Radiation Oncology Group 05.01 Trial; POST study). *First Author: Sandro Virgilio Porceddu, University of Queensland, Brisbane, Australia*

Background: We report on the first multi-centre randomized phase III trial of post-operative radiotherapy (PORT) vs post-operative chemo-RT (CRT) in high-risk cutaneous squamous cell carcinoma of the head and neck (cSCCHN) (NCT00193895). **Methods:** The primary objective was to determine whether there was a freedom from loco-regional relapse (FLRR) difference between patients randomly assigned to 60-66Gy (6-6.5 weeks) with or without weekly carboplatin (AUC 2) following resection of gross disease. Patients were stratified to high-risk nodal (either extracapsular nodal extension, intra-parotid nodal disease of any size or number, cervical nodal disease with ≥2 nodes or largest node > 3cm) or high-risk primary (T3-T4 or in-transit metastases). Patients with both features were stratified to the high-risk nodal group. Secondary objectives included disease-free survival (DFS), overall survival (OS) and acute & late toxicity (CTCAE V3). **Results:** 321 patients were randomly assigned between 2005-2014, with 11 not commencing treatment protocol due to disease progression or withdrawal of consent. Of the 310 patients commencing treatment protocol (157 RT and 153 CRT), 230 (74%) had high-risk nodal, 70 (22%) high-risk primary and 10 (3%) both. Median follow up was 60 months, median RT dose was 60Gy and 85% randomised to CRT completed 6 cycles of carboplatin. The 2- & 5-year FLRR (95% CI) for the RT arm was 88% (83-93%)/83% (77-90%) and for CRT 89% (84-94%)/87% (81-93%) (HR 0.85; 95%CI [0.46-1.55]; p = 0.59). The 2- & 5 year DFS (95% CI) for the RT arm was 78% (72-85%)/67% (60-76%) and for CRT 83% (77-89%)/73% (66-81%) (HR 0.85; 95%CI [0.55-1.29]; p = 0.43). The 2- & 5 year OS (95% CI) for the RT arm was 88% (83-93%)/76% (69-84%) and for CRT 88% (83-94%)/79% (72-86%) (HR 0.95; 95%CI [0.58-1.57]; p = 0.84). 134 (43%) experienced Grade 3/4 skin toxicity; 49% RT, 37% CRT (p = 0.039). 12 (3.9%) experienced Grade 3/4 subcutaneous fibrosis; 2.5% RT, 5.2% CRT. **Conclusions:** While surgery and PORT provided excellent FLRR with acceptable toxicity, the addition of weekly carboplatin did not improve outcomes in high-risk cSCCHN. Clinical trial information: NCT00193895.

6009 Clinical Science Symposium, Tue, 8:00 AM-9:30 AM

Genomic determinants of response to pembrolizumab in head and neck squamous cell carcinoma (HNSCC). *First Author: Robert I. Haddad, Dana-Farber Cancer Institute, Boston, MA*

Background: Somatic mutational load (ML) is associated with response to anti CTLA-4 and PD-1/-L1 immunotherapies in select tumors, due to formation of neoepitopes not subject to central immune tolerance. Neoepitopes specific to HPV, EBV virus infection are also present in some HNSCC. An IFNγ gene expression profile (GEP) characteristic of tumor inflammation is also related to response to anti PD-1/-L1 therapy. This study evaluated relationships between ML and clinical outcome and independent predictive values of ML and GEP in patients with HNSCC treated with pembrolizumab. **Methods:** Whole exome sequencing (WES) and GEP were assessed in FFPE tumor specimens of patients with HNSCC (KEYNOTE 012; subsets of B1 [PD-L1$^+$, n = 34] and B2 [PD-L1$^+$/$^-$, n = 73] cohorts). ML, neoantigen load (NL), HPV/EBV status and clonality were assessed by standard WES analytical methods. GEP score is a weighted sum of normalized expression values of 18 genes. Statistical testing of ML and response, and ML and GEP relationship by HPV/EBV status was prespecified. **Results:** There were 73 patients identified as HPV$^-$ and EBV$^-$ (n = 25 in B1; n = 48 in B2). In HPV$^-$ and EBV$^-$ patients in B1 and B2 cohorts, respectively, associations between ML and objective response (OR) (P = 0.029 and 0.055; AUROC 0.89 and 0.63), and GEP and OR (P = 0.064 and 0.01; AUROC 0.82 and 0.74) were statistically significant. In combined cohorts of HPV$^-$ and EBV$^-$ patients, ML and GEP were significantly associated with OR (P = 0.009 and 0.002; AUROC 0.70 and 0.76, respectively). ML and GEP were only weakly correlated (r = 0.173). In a joint model, ML was significantly associated with response (p = 0.020) after adjusting for GEP (also significant, p = 0.006). NL and clonality weighted ML were also significantly associated with response (P = 0.026 and 0.006, respectively). In HPV$^+$ or EBV$^+$subjects, OR association was not significant for ML, possibly due to a dominance of viral vs somatic neoepitopes; GEP was significant, likely due to tumor inflammation. **Conclusions:** ML and GEP are independently predictive of response to pembrolizumab in HPV$^-$/EBV$^-$ patients with HNSCC; GEP was predictive regardless of viral status. ML and GEP may have utility in characterizing responses to anti PD-1 therapies and novel cancer regimens in HNSCC. Clinical trial information: NCT01848834.

6010 Clinical Science Symposium, Tue, 8:00 AM-9:30 AM

Epacadostat plus pembrolizumab in patients with SCCHN: Preliminary phase I/II results from ECHO-202/KEYNOTE-037. *First Author: Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA*

Background: Indoleamine 2,3-dioxygenase 1 (IDO1) is a tryptophan-catabolizing enzyme that induces immune tolerance by T-cell suppression. IDO1 overexpression has been associated with poor survival in SCCHN. Epacadostat (E) is a potent, selective oral IDO1 inhibitor. ECHO-202/KEYNOTE-037 is an open-label, phase I/II (P1/2) study evaluating E plus PD-1 inhibitor pembrolizumab (P) in multiple tumor types. We report preliminary P1/2 efficacy, safety, and tolerability findings in the SCCHN cohort as of a 29OCT2016 data cutoff. **Methods:** Eligible adult patients (pts) had metastatic SCCHN and received ≥1 prior chemotherapy regimen that included a platinum agent. Prior checkpoint inhibitor therapy (tx) was not permitted, and pts with carcinoma of the nasopharynx or salivary gland were excluded. In P1 dose escalation (3+3+3), pts received E (25, 50, 100, or 300 mg PO BID) + P (2 mg/kg or 200 mg IV Q3W); MTD was not exceeded. E (100 mg BID) + P (200 mg Q3W) dosing was selected for P2 cohort expansion. Response was assessed in RECIST 1.1 evaluable pts. **Results:** A total of38 pts (P1, n = 2; P2, n = 36) were evaluated. Median age was 63 years, 87% of pts were men, 95% were white, and 66% received prior cetuximab. Of 36 efficacy-evaluable pts, 81% (n = 29) received 1–2 prior lines of tx and 19% (n = 7) received ≥3 prior lines of tx. ORR (CR+PR) and DCR (CR+PR+SD) for pts with 1–2 prior tx were 34% (2 CR, 8 PR) and 62% (8 SD), respectively; for pts with ≥3 prior tx, ORR and DCR were 14% (1 PR) and 43% (2 SD). Response was observed regardless of HPV status. At data cutoff, 9/11 responses were ongoing (range, 1+ to 563+ days). PFS and biomarker analyses are ongoing. The most common TRAEs in all 38 pts were fatigue (24%), nausea (11%), and decreased weight (11%). Grade ≥3 TRAEs occurred in 11% of pts; only increased amylase and lipase (both asymptomatic) were grade ≥3 TRAEs that occurred in > 1 pt. TRAEs led to discontinuation in 1 pt (increased amylase and lipase). **Conclusions:** In pts with advanced SCCHN, E + P was generally well tolerated and associated with encouraging response rates, particularly in pts with 1–2 prior lines of tx. A phase III SCCHN study is planned. Clinical trial information: NCT02178722.

6011 Clinical Science Symposium, Tue, 8:00 AM-9:30 AM

Safety of pembrolizumab with chemoradiation (CRT) in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). *First Author: Steven Francis Powell, Sanford Health, Sioux Falls, SD*

Background: Pembrolizumab (pembro) is a humanized monoclonal antibody that blocks the programmed death receptor-1 (PD-1) interaction with its ligands (PD-L1, PD-L2). While pembro is approved for platinum-refractory, recurrent/metastatic SCCHN, its role in definitive therapy for LA-SCCHN is not yet defined. Here we present the safety results of pembro with cisplatin-based CRT for patients (pts) with LA-SCCHN (NCT02586207). **Methods:** 27 pts with oropharyngeal (OP), hypopharyngeal (HP), and laryngeal (L) stage III-IVB SCCHN (any HPV status) eligible for cisplatin-based, definitive CRT were enrolled from November 2015 to August 2016 as part of a safety cohort. Pembro was given at a fixed dose of 200 mg IV 4-7 days prior to initiation of CRT and then every 3 weeks during CRT (2 concomitant doses) and then following CRT for 5 additional doses. CRT consisted of weekly cisplatin 40 mg/m2 IV x 6 doses (240 mg/m2 maximum) given concurrently with radiation at a dose of 2 Gy once daily for 35 fractions (total 70 Gy). Safety was determined by the occurrence of CRT or pembro dose-limiting adverse events (AEs) and immune-related AEs (irAEs). Efficacy was defined as complete response (CR) rate on imaging or with salvage surgery at 100 days post-CRT completion. **Results:** 20 (74%) pts with OP HPV+ and 7 (26%) pts with HPV- (4 L, 2 OP, 1 HP) tumors were enrolled. 21 (78%) completed all planned doses of pembro. 3 discontinued due to irAEs (G2 peripheral motor neuropathy, G3 AST elevation, G1 Lhermitte-like syndrome). 3 discontinued due to protocol reasons (early neck dissection -2 pts, prolonged hospitalization-1 pt). All pts completed the full radiation dose (70 Gy) without significant delay (defined as > 5 days). 23 (85%) received the goal target dose of cisplatin (≥200 mg/m2). There was one pt death due to concurrent illness, unrelated to treatment. The study has been reopened with expansion cohorts of 34 HPV+ pts and 23 HPV- pts to evaluate efficacy. **Conclusions:** Pembro in combination with weekly cisplatin-based CRT is safe and does not significantly impair radiation or chemotherapy dosing. Efficacy of this combination is being explored further in this study and through larger phase III clinical trials. Clinical trial information: NCT02586207.

6012 Clinical Science Symposium, Tue, 8:00 AM-9:30 AM

Neoadjuvant pembrolizumab in surgically resectable, locally advanced HPV negative head and neck squamous cell carcinoma (HNSCC). *First Author: Ravindra Uppaluri, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA*

Background: Pembrolizumab has efficacy in metastatic HNSCC. We hypothesized that treatment intensification in surgically resectable HPV-negative, Stage III/IV HNSCC with neoadjuvant plus post-operative adjuvant (POA) pembrolizumab would be safe and reduce 1-year locoregional recurrence/distant metastases (LRR/DM) from 35% (historical: Cooper and Bernier NEJM 2004) to 15%. **Methods:** Phase II trial where all eligible patients received 1 dose of pembrolizumab (200 mg) prior to surgery and only those with high-risk pathologic features (HRPF: extracapsular extension/positive margin) were given POA cisplatin and radiation followed by pembrolizumab. PD-L1 staining was assessed by immunohistochemistry (9A11 antibody). **Results:** The study continues to enroll. Characteristics of 21 enrolled patients (pts) were median age 59 (32-87) yrs, tobacco use 81% (17 pts), clinical T2 (n = 2), T3 (n = 1), T4 (n = 18), and cN0/1 (n = 8), cN2 (n = 13). Preliminary analyses revealed five important findings: 1) No serious study drug-related AEs or unexpected surgical delays/complications, 2) No LRR/DM events in the first 10 patients with $>$ 1-year follow-up after surgery 3) HRPF rate of 38% (95% CI: 18%-62%) (expected: 80%), 4) 43% of pts (95% CI: 22%-66%) with pathologic treatment response to neoadjuvant pembrolizumab (definition: tumor necrosis and/or giant cell/histiocytic reaction to keratinous debris in $>$ 10% of tumor area), and 5) 48% of pts (95% CI:26%-70%) with clinical-to-pathologic downstaging. Pathologic treatment effect (TE) in $\geq$ 70% of the resected tumor or lymph node tissue area occurred in 6/21 pts (29%). Baseline tumor biopsies were PD-L1 positive ($>$ 1% of tumor cells) in 11/19 (58%) evaluable samples and in 7/8 (88%) evaluable pathologic responders. A significant correlation existed between baseline PD-L1 expression on tumor cells and pathologic treatment effect in the tumor (correlation coefficient: 0.72 and p = 0.0005). **Conclusions:** Neoadjuvant and adjuvant pembrolizumab was safe and well tolerated. We observed several lines of evidence supporting an anti-tumor effect in these pts with a single dose of pre-operative pembrolizumab. Further evaluation of this strategy is warranted. Clinical trial information: NCT02296684.

6013 Poster Discussion Session; Displayed in Poster Session (Board #1), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

The role of PET for predicting nodal response in locally advanced (LA) head and neck squamous cell carcinoma (HNSCC) treated with chemoradiotherapy (CRT): Results of a prospective multicenter trial. *First Author: Sandra Schmitz, Department of Head and Neck Surgery, St-Luc Hospital, Catholic University of Louvain, Brussels, Belgium*

Background: Controversy about neck management after CRT in patients with LA HNSCC persists due to low accuracy of CT/MR to asses the neck. As already demonstrated (Mehanna, NEJM 374, 2016), PET is an alternative to planned neck dissection (ND) thanks to its high negative predictive value (NPV). However, no conclusion could be drawn for patients (pts) with equivocal response (e.g. suspicion of residual disease on CT/MR but negative PET) because pathologic confirmation was lacking. **Methods:** Multicenter, prospective, nonrandomized trial including pts with LA HNSCC of oral cavity, oro- hypopharynx, larynx, staged N1, N2, N3, treated with CRT and evaluated 12 weeks after CRT by overall assessment (OA): clinical examination (CE), PET and CT/MR. ND was performed in incomplete regional response based on at least 1 positive evaluation method. Pathologic analyses (HE and KI67) were performed on ND samples. Primary objective was to determine the NPV and accuracy of PET as a single examination in the post CRT nodal assessment. Primary outcome was 2-year regional recurrence free survival rate (RRFSR). **Results:** 264/318 pts included completed full treatment and had post CRT OA. Median follow up was 40 months. No ND was proposed in 119 patients because of a negative OA; 145 patients had ND. The presence of viable cells was reported in 27 ND (18.6%). Sensitivity, specificity, PPV, NPV, accuracy of OA were 90.0%, 49.6%, 18.6%, 97.5%, 54.2% vs 69.7%, 75.3.%, 28.8%, 94.6%, 74.6% for PET alone. Kappa coefficient was of 0.838, indicating an almost perfect agreement. In pts with negative OA, RRFSR was 61.3% vs. 56.6% in pts with positive OA and ND (p=0.45). Using post CRT assessment with PET alone, RRFSR in pts with negative PET was 63.0% vs. 48.8% in pts with positive PET (p=0.04). Using PET assessment alone, 65/145 ND (44.8%) could have been avoided without compromising RRFSR. **Conclusions:** NPV using PET alone is 94.6%. Post CRT evaluation using only PET would have resulted in considerably fewer ND without jeopardizing neck control. PET alone is more accurate and more discriminant for predicting pts outcome. Clinical trial information: NCT00634777.

6014 Poster Discussion Session; Displayed in Poster Session (Board #2), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Validation of the pathological classification of lymph node metastasis for head and neck tumors (HNSCC) according to the 8th edition of the TNM Classification of Malignant Tumors (8th TNM). *First Author: Antonio Lopez-Pousa, Hospital Sant Pau, Barcelona, Spain*

Background: Changes in 8th TNM edition are a specific staging for p16 +oropharyngeal carcinoma and the inclusion of extracapsular spread (ECS) in N extension. We evaluate the improvement in prognostic capacity from the inclusion of the ECS in HNSCC patients treated with a neck dissection (ND). **Methods:** Retrospective study based on prospectively collected information of 1188 HNSCC patients (oral cavity, HPV-oropharynx, hypopharynx, or larynx) diagnosed from 1990 to 2013, treated with unilateral or bilateral ND and a minimum fw-up of 2 years. We performed 1820 ND: 410 radical, 1410 selective ND; 683 patients (60.1%) had bilateral ND. Mean lymph nodes/patient: 32.6 (SD 19.9, 7-118). In 157 cases (13.8%) ND was performed after radiotherapy (RT, n =71) or chemoradiotherapy (CHRT, n = 86) with a median interval of 8.5 weeks (6-10). 596 patients (52.4%) had post-operative RT (n=525) or CHRT (n=71). Mean fw-up: 5.6 years (SD 4.9): 213 patients (18.7%) had local failure, 158 (13.9%) regional failure, 172 (15.14%) metastases. **Results:** 570 patients (50.1%) had lymph node metastases, 288 (50.5%) with ECS. The 8th TNM produced upstaging of 20.9% of pN1 patients to pN2a (n=33), and of 58.4% of the patients classified as pN2 to pN3b (n=220). The 7th TNM Classification (7thTNM), 5-year cause-specific survival for pN2 (35.5%) was similar to pN3 (21.6%). In the 8th TNM, 5-year cause-specific survival for pN2 (53.3%) sits in an more intermediate position between pN1 (70.5%) and pN3 (24.0%). Five-year cause-specific survival for pN2 patients with ECS (n=217) was 22.4%, and for patients without ECS (n=157) was 51.4%. There were statistically significant differences in survival between the two reclassified groups (P=0.0001). pN1 patients in the 7thTNM did not show survival differences when stratified by the presence of ECS: 5-y SV: 63.5% for ECS (n=33), 70.5% for non-ECS (n=125) (p=0.838). **Conclusions:** Inclusion of ECS in the pathological classification of the 8th TNM Classification edition improved the prognostic capacity, as compared with the previous version, basically produced by the migration of 58.4% of pN2 in the 7th TNM to the new pN3b category

6015 Poster Discussion Session; Displayed in Poster Session (Board #3), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Dose escalation of radiotherapy (RT) for locally advanced head and neck carcinomas treated with concomitant chemotherapy (CT) and RT: Results of the GORTEC 2004-01 randomized trial. *First Author: Jean Bourhis, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*

Background: Concomitant CT-RT is a well established standard of care (SoC) in locally advanced (LA) squamous cell carcinomas of the head and neck (SCCHN). While there is a well established dose effect relationship for RT alone in these cancers, it is not known whether this also applies to concomitant CT-RT. **Methods:** Patients were randomized between 75 Gy/7 weeks (Arm A) versus 70 Gy/35F in 7 weeks (Arm B). A sequential boost of 10 times 2.5 Gy after 50Gy/25F was given to the initial gross tumor volume (GTV) in Arm A. IMRT was used for arm A and 3D conformal RT for arm B. In both arms, patients (pts) received during RT 3 cycles of cisplatin at 100 mg/m2. Inclusion criteria were pts fit for receiving high dose cisplatin, non metastatic, non operated stage III-IV SCC of oral cavity, oro/hypopharynx. A 1:1 randomization was done by minimization on centers, N & T stages & GTV uni/bilateral. To detect a hazard ratio (HR) of 0.56 in locoregional (LR) control, inclusion of 310 pts was required to observe 109 LR progressions and achieve 85% power at 2-sided significance level of 0.05. **Results:** Between 2005 and 2015, 188 pts were randomized: 82% males, median age 58 years, 85% oropharynx. The accrual rate was slower than expected, due to the fact that IMRT became a SoC and was only allowed in arm A. As a consequence the trial was discontinued after inclusion of 188 patients. The majority of pts had stage IVa (73% vs 72%). All initial characteristics were well balanced between arms. The median follow-up was 4.7 years, not different between arms. Acute and late xerostomia were markedly improved in arm A (IMRT arm). The 1-year grade 0-1 salivary toxicity (RTOG) was 81% and 34% ($p< 0.0001$) in arm A and B respectively. At 3 years these rates were 92% vs 53% (p=0.0003). The increase of the dose to the GTV with IMRT did not transfer in a higher LR control probability with an adjusted HR of 0.88 [95%CI 0.51-1.52] (p=0.63). PFS, overall survival were not significantly different between the 2 arms. **Conclusions:** The dose escalation of RT to the GTV did not improve LR control in patients treated with concomitant CT-RT. This trial adds some new evidence level 1 in favor of IMRT in LA SCCHN. Clinical trial information: NCT00158678.

6016 Poster Discussion Session; Displayed in Poster Session (Board #4), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Randomised phase-III-trial of concurrent chemoradiation (CRT) for locally advanced head and neck cancer (stage III-IVB): Comparing dose reduced radiotherapy (63,6 Gy) with paclitaxel/cisplatinum to standard radiotherapy (70,6 Gy) with fluorouracil/cisplatinum. *First Author: Rainer Fietkau, Universitatsklinikum Erlangen, Department of Radiation Oncology, Erlangen, Germany*

Background: Concurrent CRT with 70.6 Gy is the standard treatment for locally advanced head and neck cancer (LA-SCCHN). There exist no prospective data on safety and efficacy of a reduced radiation (RT) dose. **Methods:** Pts with stage III-IVB LA-SCCHN were randomized 1:1 to receive 70.6 Gy with concurrent cisplatinum (20mg/m²/d IV on days 1-5 and 29-33) and fluorouracil (600 mg/m²/d CIV on days 1-5 and 29-33) (standard arm A) versus 63,6 Gy with intensified chemotherapy using concurrent cisplatinum (20mg/m²/d IV on days 1-4 and 29-32) and paclitaxel (20mg/m²/d IV on days 2, 5, 8, 11 and 25, 30, 33, 36) (experimental arm B). After a planned interim analysis recruitment was stopped due to statistical reasons. **Results:** Between 06/2010 and 02/2015 a total of 221 pts were randomized with 105 pts receiving treatment in arm A and 112 in arm B (4 pts dropped out). Median follow-up was 38 months. Pts' characteristics: Oral cavity (15%), oropharynx (54%), hypopharynx (28%), larynx (14%); 17 pts had more than one primary site; tumor stage: III (14%), IV (86%); HPV-status (p16) was positive in 20%, negative in 38%, currently pending in 42%. A total of 96 PFS-related events occurred. 3-year PFS (ITT) was 58% in the standard arm A and 48% in experimental arm B (p = 0.454). 3-year OS (ITT) was 64% in arm A and 59% in arm B (p = 0.688). 3-year rates of distant metastases, loco-regional recurrences and death were 10% vs 12%, 17% vs 21% and 15% vs 19% for pts in arm A and B, respectively. As for the p16-positive subgroup, 3-year PFS/OS were 77%/76% in arm A (n = 21) and 69%/80% in arm B (n = 22), respectively. Grade 3+ hematologic adverse events during therapy (arm A/arm B): Anemia 11%/4% (p = 0.038); neutropenia 40%/16% ($p < 0.001$); thrombocytopenia 8%/3% (p = 0.130). **Conclusions:** These preliminary results indicate that pts receiving concurrent CRT for LA-SCCHN did not benefit from a lower total RT dose of 63.6Gy despite intensified chemotherapy. However, in the subgroup of p16-positive pts a reduced RT dose may be sufficiently effective. Clinical trial information: NCT01126216.

6017 Poster Discussion Session; Displayed in Poster Session (Board #5), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Randomized, double-blind, placebo-controlled, phase II trial of first-line platinum/docetaxel with or without erlotinib (E) in patients (pts) with recurrent and/or metastatic (R/M) head and neck squamous cell carcinomas (HNSCCs). *First Author: William Nassib William, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In a single-arm, phase 2 study, we previously demonstrated that in pts with R/M HNSCC, cisplatin, docetaxel and E improved progression-free survival (PFS) compared to historical data (Kim et al., ASCO 2006). Herein, we evaluated this regimen in a single center, randomized, phase 2 trial. **Methods:** Pts with R/M HNSCC, with a performance status (PS) 0-2, were randomized (1:1) to receive up to 6 cycles of first-line chemotherapy with cisplatin 75 mg/m2 (or carboplatin AUC 6) and docetaxel 75 mg/m2 i.v. on day 1 every 21 days, plus placebo (P) vs. E 150 mg p.o. daily, followed by maintenance P or E until disease progression. The primary endpoint was PFS. With 120 pts, the study had 80% power to detect an improvement in median PFS from 3.0 to 4.9 months with a two-sided type I error rate of 0.1. **Results:** From 05/2010 to 07/2015, 120 pts were randomized to the P (N = 60) or E (N = 60) groups. All pts but one initiated treatment and were eligible for evaluation of the primary endpoint – 92 males; median age 62 years; 52 oropharynx, 40 oral cavity, 19 larynx, 8 hypopharynx cancer pts; 86 current/former smokers; 43 with recurrence within 6 months of completion of local treatment; 27 with prior exposure to EGFR inhibitors. Median PFS was 4.4 vs. 6.1 months for the P and E groups, respectively (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.42-0.95 months, p = 0.026). Response rates were 44% vs. 56% for P vs. E (p = 0.21). Median overall survival (OS) for P- and E-treated pts was 13.7 vs. 17.0 months (HR = 0.67, 95% CI 0.43-1.04, p = 0.07). Benefits from E on PFS and OS were more pronounced in pts with oropharyngeal tumors ($p \leq 0.05$ for interaction). In the E group, first-cycle rash grade 2-4 (34% pts) was associated with longer OS (HR = 0.40, p = 0.02). E-treated pts experienced a higher incidence of grade 3-4 adverse events (33.9 vs. 53.3%), including diarrhea (3 vs.17%), dehydration (5 vs. 15%), nausea (5 vs. 14%), rash (0 vs. 12%). **Conclusions:** This study met its primary endpoint. Addition of E to first-line platinum/docetaxel improved PFS and OS. This regimen may warrant further evaluation in randomized, phase 3 trials. Clinical trial information: NCT01064479.

6018 Poster Discussion Session; Displayed in Poster Session (Board #6), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Results of a phase II randomized controlled clinical trial comparing efficacy of cabazitaxel versus docetaxel as second-line or above therapy in recurrent head and neck cancer. *First Author: Amit Joshi, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Center, Mumbai, India*

Background: Cabazitaxel has shown activity in squamous cancer cell lines and in taxane resistant cell lines. Hence we planned a randomized phase 2 study to evaluate the efficacy and safety of cabazitaxel against docetaxel in recurrent head and neck cancer, post first line treatment. **Methods:** This was a phase 2 open label, investigator initiated, randomized controlled trial of Docetaxel (75 mg/m2) versus Cabazitaxel (20 mg/m2), in adult patients with head and neck cancer, ECOG performance status 0-2, with measurable disease, who have been exposed to at least one line of chemotherapy (CTRI/2015/06/005848). 1:1 central randomization was performed and chemotherapy was administered till progressive disease or until patient had intolerable side effects. The sample size of 92 (46 per group) was determined based on an assumption for a difference in disease control rate of 25%, an alpha of 0.05 and 80% power. The data was censored for analysis on 3rd March 2017. Primary analysis of disease control at 6 weeks (CR/PR/SD) was assessed and compared using the chi-square test. Progression free survival (PFS) and overall survival (OS) curves were estimated using the Kaplan-Meier method. Cox proportional hazard model was used for comparison of PFS and OS between the 2 arms. **Results:** 92 patients were accrued in the study with 46 in each arm. The disease control rate at 6 weeks was better in the docetaxel arm which was statistically significant over the cabazitaxel arm (13.6% versus 52.3%, p = 0.017). The median PFS was 21 days (95% CI 5.28-36.72 days) in the cabazitaxel arm versus 61 days (95% CI 16.21 to 105.79 days) in the docetaxel arm (HR = 1.466, 95% CI 0.923-2.328, p = 0.105). The median OS was 172 days (95% CI 111.78 to 232.22 days) in the cabazitaxel arm versus 188 days (95% CI 134.4 to 241.6 days) in the docetaxel arm (HR-1.408, 95% CI 0.738-2.688, p = 0.299). **Conclusion:** In this phase 2 study, docetaxel had a superior disease control rate at 6 weeks and PFS compared to cabazitaxel. Clinical trial information: CTRI/2015/06/005848.

6019 Poster Discussion Session; Displayed in Poster Session (Board #7), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Nivolumab (Nivo) vs investigator's choice (IC) for platinum-refractory (PR) recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN; Checkmate 141): Outcomes in first-line (1L) R/m patients and updated safety and efficacy. *First Author: Maura L. Gillison, The Ohio State University, Columbus, OH*

Background: In CheckMate 141, a randomized, phase 3 trial, nivo demonstrated superior overall survival (OS) and better tolerability in patients (pts) with PR R/M SCCHN compared with IC. Pts with SCCHN progressing within 6 mos of platinum in the primary treatment setting have dismal prognosis. We report outcomes in pts who were PR in the primary or adjuvant setting, and updated results in the overall population. **Methods:** Pts (N = 361) with PR R/M SCCHN were randomized 2:1 to nivo 3 mg/kg every 2 weeks or weekly IC (methotrexate, docetaxel, or cetuximab). Primary endpoint was OS estimated by Kaplan-Meier method. Cox proportional hazards models were used to estimate hazard ratios (HRs) and confidence intervals (CIs). Additional endpoints include objective response rate (ORR) and safety. Outcomes were analyzed overall and post hoc in pts who were PR in the primary/adjuvant setting and received nivo/IC as 1L R/M therapy. **Results:** Characteristics of the 78 (21.6%) pts who received nivo (n = 52) or IC (n = 26) in the 1L R/M setting were similar to the overall population.Nivo significantly improved OS vs IC among 1L R/M pts (median [95% CI]: 7.7 mo [3.1, 13.8] vs 3.3 mo [2.1, 6.4]; HR [95% CI] = 0.56 [0.33, 0.95]); 12-mo OS rate: 39.2% vs 15.4%. ORR was 19.2% for nivo vs 11.5% for IC in this subgroup. At 11.4-mo minimum follow-up, updated efficacy and safety in the overall population were similar to the primary analysis. Median OS (95% CI) was 7.7 mo (5.7, 8.8) for nivo vs 5.1 mo (4.0, 6.2) for IC; HR (95% CI) = 0.71 (0.55, 0.90); $P = 0.0048$. For nivo vs IC, the 18-mo OS rate was 21.5% vs 8.3% and ORR was 13.3% vs 5.8%. Nivo doubled the median duration of response vs IC (9.7 vs 4.0 mo). Grade 3–4 treatment-related adverse event rates for nivo vs IC were 15.3% vs 36.0% overall and 27.5% vs 32.0% for 1L R/M pts; there were no new deaths due to study drug toxicity. **Conclusions:** Nivo significantly improved OS and increased ORR vs IC in a 1L R/M subgroup, supporting its use as 1L therapy for pts with PR R/M SCCHN. Nivo continued to show a significant survival benefit and better tolerability vs IC in pts with PR R/M SCCHN. Clinical trial information: NCT02105636.

6020 Poster Discussion Session; Displayed in Poster Session (Board #8), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Nivolumab (Nivo) vs investigator's choice (IC) in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Efficacy and safety in CheckMate 141 by prior cetuximab use. *First Author: Robert L. Ferris, University of Pittsburgh Medical Center Cancer Center Pavilion, Pittsburgh, PA*

Background: In CheckMate 141, nivo resulted in significantly prolonged overall survival (OS), favorable safety, and stable quality of life vs IC in patients (pts) with platinum-refractory (PR) R/M SCCHN. Cetuximab, a formal trial stratification factor, permits exploratory subgroup assessment. Outcomes by prior cetuximab use are described. **Methods:** CheckMate 141 was a randomized, open-label, phase 3 trial (NCT02105636) in which pts (N = 361) with PR R/M SCCHN were randomized 2:1 and stratified by prior cetuximab use to nivo 3 mg/kg every 2 weeks or IC of methotrexate, docetaxel, or cetuximab. The primary endpoint was OS; additional endpoints were progression-free survival (PFS), objective response rate (ORR), and safety. A multivariate analysis will explore influence of additional factors. **Results:** Nivo improved OS vs IC regardless of prior cetuximab, and improvement was greater in pts without prior cetuximab (Table). Median OS was longer for nivo vs IC in pts with PD-L1 expression $\geq$ 1% regardless of prior cetuximab, and in pts with PD-L1 expression $<$ 1% without prior cetuximab. Among pts with PD-L1 expression $\geq$ 1%, ORR was higher with nivo vs IC with/without prior cetuximab. PFS was similar regardless of prior cetuximab. Grade 3–4 treatment-related adverse event rates for nivo vs IC were 11.7% vs 40.9% with prior cetuximab and 15.4% vs 26.7% without prior cetuximab. **Conclusions:** OS and ORR improved with nivo vs IC regardless of prior cetuximab use, and the magnitude of benefit was greater in pts without prior cetuximab exposure. These results support the use of nivo for R/M SCCHN regardless of prior cetuximab use. Clinical trial information: NCT02105636.

	Without Prior Cetuximab		With Prior Cetuximab	
	Nivo (n = 93)	IC (n = 47)	Nivo (n = 147)	IC (n = 74)
Median OS (95% CI), mo	8.1 (5.3, 12.7)	4.7 (3.0, 7.2)	6.9 (4.9, 8.8)	5.2 (4.1, 6.8)
HR (95% CI)	0.55 (0.35, 0.86)		0.81 (0.57, 1.15)	
ORR, % (n/N)	17.2 (16/93)	4.3 (2/47)	10.9 (16/147)	6.8 (5/74)
ORR among HPV+ pts, % (n/N)	29.6 (8/27)	0 (0/11)	5.6 (2/36)	5.6 (1/18)
ORR among pts with PD-L1 $\geq$ 1%, % (n/N)	19.4 (7/36)	0 (0/21)	15.4 (8/52)	2.5 (1/40)

HPV = human papillomavirus; HR = hazard ratio; PD-L1 = programmed death ligand 1

6021 Poster Discussion Session; Displayed in Poster Session (Board #9), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

PREDICTOR (UNICANCER GEP11): Randomized phase II study of preoperative afatinib in untreated head and neck squamous cell carcinoma (HNSCC) patients. *First Author: Christophe Le Tourneau, Institut Curie - Centre de Lutte Contre le Cancer (CLCC) de Paris, Paris, France*

Background: Afatinib, a pan-HER irreversible tyrosine kinase inhibitor, demonstrated limited antitumor activity compared to methotrexate in unselected recurrent and/or metastatic HNSCC patients (LUX-HN1, Machiels et al, Lancet Oncol 2015). The UNICANCER (GEP 11) PREDICTOR study's objective was to identify predictive and pharmacodynamic biomarkers of biological activity and efficacy of afatinib (EUDRACT N° 2010-024046-29). **Methods:** This open-label, randomized, multicentric, controlled, phase II study included untreated patients with operable T2-4N0-2M0 HNSCC of the oral cavity, pharynx and larynx, with a PS $<$ 2, adequate organ function and LVEF $>$ 50%. Patients were randomized (2:1) to: oral afatinib (A) 40mg/day (d) for 14-28d or no treatment (NT). Patients had pre-treatment tumor biopsies, tumor imaging, and PET CT scan, with a 2nd tumor imaging before surgery and a PET scan at D15. Adverse events were classified by NCI CTCAE criteria. Based on the biological primary endpoint of tumor reduction the sample size was designed to identify biomarkers associated with a 20% difference between the study arms. **Results:** 61 patients were included (A: 41/NT: 20). 2 patients in the NT arm were not analyzed (consent withdrawal, no surgery). 7 patients in arm A received $<$ 14d of treatment, including 6 patients with unacceptable toxicity. Afatinib-related toxicities were: grade (G)1 37%, G2 41%, G3 7%, G4 5%, and G5 0%. G$\geq$3 toxicities were mainly gastrointestinal. Partial responses (RECIST1.1) were observed in 3 patients (7.3%) in arm A versus none in the NT arm (p = 0.018). Progressive disease was not observed in arm A versus 3 (16.6%) in the NT arm. Partial responses on PET CT scan by PERCIST were observed in 15/31 evaluable patients (48%) in arm A versus 1/15 (6.7%) in the NT arm (p = 0.005). **Conclusions:** Afatinib given to HNSCC patients in the preoperative setting is safe and is associated with improved response according to RECIST1.1 and PERCIST compared to no treatment. Clinical trial information: NCT01415674.

6022 Poster Discussion Session; Displayed in Poster Session (Board #10), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Results of randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in BRAF-mutated papillary thyroid carcinoma. *First Author: Manisha H. Shah, Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: BRAF mutations are present in ~44% of papillary thyroid carcinoma (PTC) and its role in development of PTC is well established. We hypothesized that dabrafenib (BRAF inhibitor) would have efficacy in BRAF mutated PTC and that combining it with trametinib (MEK inhibitor) would result in greater clinical efficacy than dabrafenib alone, through vertical inhibition of the RAF/MAP/ERK pathway and mitigation of potential mechanisms of resistance. **Methods:** Patients (pts) with BRAF mutated radioiodine refractory PTC who had evidence of disease progression within 13 months prior were randomized to Arm A (dabrafenib 150 mg PO BID) or Arm B (dabrafenib 150 mg PO BID + trametinib 2 mg PO qd). Cross-over to Arm B was allowed at time of progression. Responses were assessed by modified RECISTv1.1 every 2 months. Primary endpoint was objective response rate (ORR) (complete-, partial- and minor-response). With assumed true ORR of 15% vs 35%; and 90% power to identify the correct regimen as most promising, 26 pts were to be accrued in each Arm. **Results:** In this randomized phase 2 trial, 53 pts (median age 63 years, 38 females) were enrolled; 25% of pts had 1-3 prior therapy with multi-kinase inhibitors. Median follow up was 13 months. Preliminary efficacy results are outlined in Table. The treatment-related adverse events were similar to previously reported phase III clinical trial of these drugs in melanoma. **Conclusions:** Single agent dabrafenib, as well as combination of dabrafenib/trametinib are well tolerated therapies that result in similar high objective response rates with durable responses in pts with progressive BRAF-mutated PTC. BRAF-pathway targeted therapies provide novel treatment options. Clinical trial information: NCT01723202.

	Arm A (n=26) Dabrafenib	Arm B (n=27) Dabrafenib + Trametinib	p-value
Assessable pts (n)	22	24	
Partial response	10	9	
Minor response (MR)*	1	4	
Objective Response	11/22 (50%)	13/24 (54%)	0.78
Stable ds	9	10	
Progressive ds	2	1	
Median Progression Free Survival (months) (95% CI)	11.4 (3.8 – NR)	15.1 (11.7 –NR)	0.27
Median Duration of response (months)(95% CI)	15.6 (4.2 – NR)	13.3 (9.7 – NR)	0.87

*MR was defined as 20-29% decrease in the sum of diameters of target lesions; NR=not reached

6023 Poster Discussion Session; Displayed in Poster Session (Board #11), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Efficacy of dabrafenib (D) and trametinib (T) in patients (pts) with *BRAF* V600E–mutated anaplastic thyroid cancer (ATC). *First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ATC is a rare, aggressive malignancy with a dismal prognosis. Median overall survival (OS) is $<$ 6 mo. Combined BRAF and MEK inhibition is efficacious in *BRAF* V600–mutated melanoma and lung cancer. One-fourth of ATCs harbor activating *BRAF* V600E mutations; thus, D (BRAF inhibitor) + T (MEK inhibitor) was evaluated as a treatment for pts with *BRAF* V600E–mutated ATC. **Methods:** In this phase 2, open-label trial (NCT02034110), pts with *BRAF* V600E mutations in 9 rare tumor types, including ATC, received continuous D (150 mg BID) + T (2 mg QD) until unacceptable toxicity, disease progression, or death. Eligible pts had advanced or metastatic cancer with no standard-of-care treatment options. The primary endpoint was investigator-assessed overall response rate (ORR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), OS, and safety. We report data from the ATC cohort. **Results:** 16 pts with *BRAF* V600E–mutated ATC had evaluable data with a median follow-up time of 47 wk (range 4-120 wk). *BRAF* V600E mutations were centrally confirmed in 15/16 pts. Median age was 72 y; all 16 pts had undergone prior tumor radiation and/or surgery and 6/16 pts (38%) had received $\geq$1 prior line of systemic therapy. Investigator-assessed confirmed ORR was 69% (11/16; 95% CI, 41%-89%), with 7/11 responses ongoing at the time of data cut. The Bayesian estimate of ORR was 69% (95% credible interval, 47%-87%) with a 100% probability that this ORR exceeded the 15% historical RR. Median DOR, PFS, and OS were not estimable due to insufficient progression and death events. Kaplan-Meier estimates of DOR, PFS, and OS at 12 mo were 90%, 79%, and 80%, respectively. The safety population comprised 100 pts enrolled in 7/9 histologies. Among all pts, 92% had an AE. Common AEs of any grade for all histologies were fatigue (38%), pyrexia (37%), and nausea (35%). In the ATC cohort, the most common grade 3/4 events were hyponatremia (19%), pneumonia (13%), and anemia (13%). **Conclusions:** D+T combination therapy significantly improved outcomes in ATC with a favorable safety profile. This regimen represents a clinically meaningful therapeutic advance for pts with advanced/metastatic *BRAF* V600–mutated ATC. Clinical trial information: NCT02034110.

6024 Poster Discussion Session; Displayed in Poster Session (Board #12), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Notch pathway inhibition with LY3039478 in adenoid cystic carcinoma (ACC). *First Author: Caroline Even, Institut Gustave Roussy, Villejuif, France*

Background: ACCs have high levels of Notch-1 receptor expression and activation. LY3039478 (LY) is an orally bioavailable selective Notch inhibitor (Notch 1-4). Here we report on safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of LY in patients (pts) with ACC. **Methods:** Ongoing, multi-part, phase I trial enrolled pts with advanced or metastatic ACC, measurable disease, ECOG ≤1, and baseline tumor tissue. Eligible pts received LY 50 mg three times per week (TIW), on a 28-day cycle until disease progression. Safety assessments were based on CTCAE V4.0. Tumor responses were assessed using RECIST 1.1. Primary objectives are to confirm the recommended phase II dose of LY and document antitumor activity. Secondary objectives are safety and toxicity, PK and progression-free survival (PFS). Exploratory objectives include assessment for PET metabolic responses. **Results:** 22 pts have been enrolled and received LY 50mg TIW (13 men, 9 women; median age 60, range 41-82). All pts had metastatic disease; median treatment duration was 3 cycles (range 1-10) with 6 pts continuing on treatment. One pt had an unconfirmed partial response. Disease control rate (DCR) was 16/22 (73%), of which 4 pts had stable disease ≥ 6 months. In the overall group (n = 22) median PFS (mPFS) was 5.3 months (95% CI: 2.4, NE). mPFS was 7.7 (95% CI: 4.0, NE) for pts in second line (n = 7), while mPFS was 2.4 (95% CI: 1.1, NE) for pts in third line or more (n = 9). In pts without prior systemic therapy (n = 6) mPFS could not be estimated since 4 of those patients were censored. In preliminary analysis, 14 pts were assessed by PET, with 2 (14%) achieving partial metabolic response. Most frequent related adverse events (all grades) occurring in ≥20% of pts included diarrhea (55%), fatigue (45%), vomiting (36%), decreased appetite (27%), dry mouth (27%), and dry skin (23%). Grade 3/4 related treatment-emergent adverse events observed in more than one pt were diarrhea (n = 3) and squamous cell carcinoma of skin (n = 2). PK was assessed in 17 pts, with peak concentrations occurring approximately 2 hours post-dose. Biomarker and histologic analyses of pre and post treatment biopsies will be presented. **Conclusions:** LY showed activity (73% DCR) in ACC with a manageable safety profile. Clinical trial information: NCT01695005.

6025 Poster Session (Board #13), Mon, 1:15 PM-4:45 PM

An open-label, multicohort, phase I/II study to evaluate nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC). *First Author: Jean-Pierre Delord, Toulouse University Cancer Institute IUCT-Oncopole, Toulouse, France*

Background: Treatment options for patients (pts) with R/M NPC are limited to palliative chemotherapy. NPC is often associated with the Epstein–Barr virus (EBV), a potential antigen for immune recognition, and high expression levels of the immune checkpoint receptor programmed death-1 (PD-1) and its major ligand PD-L1. Nivolumab disrupts PD-1–mediated signaling, restoring T-cell antitumor function. **Methods:** In CheckMate 358 (NCT02488759), PD-L1–unselected adults with R/M NPC, ECOG PS of 0–1, and ≤2 prior systemic therapies in the R/M setting were eligible to receive nivolumab 240 mg every 2 weeks until progression or unacceptable toxicity, as part of an ongoing multicohort study of 5 virus-associated cancers. Human papillomavirus-associated NPC and keratinizing squamous cell carcinoma (WHO Type 1) were excluded. Primary endpoints were objective response rate (ORR) and safety; secondary endpoints were duration of response (DoR), progression-free survival (PFS), and overall survival (OS). **Results:** Of 24 treated pts with R/M NPC, median age was 51 years, 88% were male, 62% were white, 88% were European, and 88% had EBV+ tumors. At a median follow-up of 26 weeks (range: 4–40), ORR was 20.8% and appeared to be higher in pts with no prior R/M therapy (Table). The disease control rate (ORR + SD) was 45.8%. Responses were observed regardless of PD-L1 or EBV status. Median PFS was 2.4 mo (95% CI: 1.5, NR); median OS was NR. **Conclusions:** Nivolumab demonstrated clinical activity and a manageable safety profile in R/M NPC, supporting ongoing research with nivolumab in this disease. Updated efficacy and biomarker data will be presented. Clinical trial information: NCT02488759.

Response and safety.

		Prior systemic R/M therapies	
	Response-evaluable pts (N = 24)	0 (n = 5)	≥1 (n = 19)
Best overall response, n (%)			
Complete response	0	0	0
Partial response	5 (20.8)	2 (40.0)	3 (15.8)
Stable disease (SD)	6 (25.0)	2 (40.0)	4 (21.0)
Progressive disease	13 (54.2)	1 (20.0)	12 (63.2)
ORR, % (95% CI)	20.8 (7, 42)	40.0 (5, 85)	15.8 (3, 40)
Time to response, median (range), mo	4.4 (1.7, 5.7)		
DoR, median, mo	NR		
Treatment-related adverse events, %			
Any grade	54.2		
Grade 3–4	8.3		

NR = not reached.

6026 Poster Session (Board #14), Mon, 1:15 PM-4:45 PM

Cost-effectiveness of nivolumab for treatment of platinum-resistant recurrent or metastatic squamous cell carcinoma of the head and neck. *First Author: Kate Carroll, University of California, San Diego Moores Cancer Center, San Diego School of Medicine, La Jolla, CA*

Background: The Checkmate 141 randomized trial found that patients with platinum-refractory, recurrent or metastatic (R/M) squamous-cell carcinoma of the head and neck (SCCHN) treated with nivolumab had significantly longer overall survival than those treated with standard, single-agent therapy. However, nivolumab is more expensive than standard treatment. We conducted a cost-effectiveness analysis of nivolumab for the treatment of R/M SCCHN. **Methods:** We constructed a Markov model to simulate treatment with nivolumab or other single-agent therapy (docetaxel, cetuximab, or methotrexate) for patients with R/M SCCHN. Transition probabilities including disease progression, survival, and toxicity were derived from clinical trial data, while costs (in 2016 US dollars) and health utilities were estimated from the literature. Incremental cost-effectiveness ratios (ICERs), expressed as dollar per quality-adjusted life-year (QALY), were calculated with values less than $100,000/QALY considered cost-effective from a healthcare payer perspective. We conducted one-way and probabilistic sensitivity analyses to examine model uncertainty. **Results:** Our base-case model found that treatment with nivolumab increased overall cost by $59,000 and improved effectiveness by 0.2443 QALYs compared to single-agent therapy, leading to an ICER of $241,100/QALY. In sensitivity analyses, the model was most sensitive to the cost of nivolumab and assumptions about survival. Nivolumab would become cost-effective if the cost per cycle decreased from $13,432 to $5,716. If we assumed that all patients alive at the end of the Checkmate 141 trial were cured of their disease then nivolumab was still not considered cost-effective (ICER $160,000/QALY). Probabilistic sensitivity analysis also demonstrated relative stability of the cost-effectiveness model and found that treatment with nivolumab was cost-effective 0% of the time at a willingness-to-pay threshold of $100,000/QALY. **Conclusions:** While nivolumab significantly improves overall survival, at the current cost it would not be considered a cost-effective treatment option for patients with R/M SCCHN.

6027 Poster Session (Board #15), Mon, 1:15 PM-4:45 PM

Induction gemcitabine cisplatin followed by chemoradiation in locally advanced nasopharyngeal cancer. *First Author: Sadaf Usman, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan*

Background: The current standard of treatment in locally advanced nasopharyngeal cancer is concurrent chemoradiation, however recent addition of induction chemotherapy in the already established regimen has presented an attractive alternative approach. We report on survival with induction Gemcitabine and Cisplatin (GC) followed by chemoradiation (CRT) in the treatment of advanced nasopharyngeal carcinoma. **Methods:** Between 2005 and 2015, 300 patients (M 70%: F 30%) with histologically confirmed nasopharyngeal carcinoma. Histological subtypes WHO I 4% (13) and WHO III 96% (287). AJCC (7^{th} edition) stage was Stage III 28% (85) and Stage IV 72% (215) patients. IC included a 2 drug combination; intravenous gemcitabine 1000 mg/m^2 on day 1 and 8 and cisplatin 75 mg/m^2 on day 1 only. Radiotherapy was given as a phase treatment to a total dose of 70 Gy in 35 fractions. Concurrent three weekly cisplatin (75 mg/m^2) was administered to all patients. **Results:** Median follow up time was 30 months. The 5-year overall survival (OS), loco regional control (LRC) and relapse free survival (RFS) rates were 70% (95% CI 6.43 – 7.52), 69% (95% CI 6.52 – 7.64) and 52% (95% CI 5.25 – 6.34) respectively. One hundred and seven patients failed treatment; local or loco-regional 39% (42), regional 16% (17) and distant 45% (48). **Conclusions:** We conclude that induction gemcitabine and cisplatin followed by chemo-radiation is an effective regimen in management of nasopharyngeal carcinoma, meriting further investigation in randomized clinical trials.

6028 Poster Session (Board #16), Mon, 1:15 PM-4:45 PM

Nimotuzumab combined with cisplatin plus fluorouracil chemotherapy in patients with metastatic nasopharyngeal carcinoma after radical radiotherapy: A multicentre, open-label, phase II clinical trial. *First Author: Chong Zhao, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China*

Background: Cisplatin plus fluorouracil (PF) is main therapy for metastatic nasopharyngeal carcinoma (NPC). However, the efficacy is not satisfactory, especially in patients with metastasis after radical radiotherapy. The purpose of this study was to investigate the efficacy and toxicity of Nimotuzumab combined with PF in patients with metastatic NPC after radical radiotherapy. **Methods:** Patients with untreated metastatic NPC after radical radiotherapy were recruited from 9 hospitals in China with Simon's two-stage design. All patients received Nimotuzumab (200mg/w) and cisplatin (100mg/m^2, day 1) plus fluorouracil (4g/m^2, day 1-4) every 3 weeks until progressive disease (PD) or unacceptable toxicity or a maximum of 6 cycles. If patients had still not progressed at this stage, Nimotuzumab (200mg/w) as monotherapy would be delivered until PD. This study was registered in ClinicalTrials.gov, Number NCT01616849. **Results:** Between Jun, 2012 and April, 2015, 35 patients were enrolled (Table). The objective response rate (ORR) and disease control rate (DCR) were 71.4% and 85.7%, and the median time of progression free survival (PFS) and overall survival (OS) were 6.97 and 11.01 months. The most common toxicities were leukopenia (94.1%), vomiting (97.1%) and nausea (97.1%); the grade 3/4 toxicities were leukopenia (62.9%) and mucositis (20.0%). There was only 1 patient have mild hypotension which related to Nimotuzumab. The ORR, DCR, median time of PFS and OS were 88.9%, 100.0%, 7.29 and 11.47 months in patients who received a total dose of Nimotuzumab $\geq$ 2400mg, respectively. **Conclusions:** Nimotuzumab combined with PF has achieved encouraging efficacy with an acceptable safety profile in metastatic NPC after radical radiotherapy. A phase III randomised study is needed. Clinical trial information: NCT01616849.

Basic information in FAS.

Variable	N
Gender	
male	30
female	5
Age, years	44 (29-67)
Disease status	
DM alone	30
DM and recurrence	5
Number of metastases organs	
1	9
≥2	26
Time from the end of radical radiotherapy to DM, months	18.69 (5.45-150.57)
Dose of Nimotuzumab, mg	2400 (200-6800)
Cycles of PF	4 (1-6)
Efficacy	
CR	1
PR	24
SD	5
PD	3
Unknown	2

6029 Poster Session (Board #17), Mon, 1:15 PM-4:45 PM

Long-term survival in oligometastatic head and neck cancer patients. *First Author: Jonathan Eric Leeman, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Aggressive therapies for patients with oligometastatic disease are increasingly being administered with definitive intent in the context of clinical trials. However, outcomes in oligometastatic head and neck squamous cell carcinoma (HNSCC) patients have not been well characterized. **Methods:** We reviewed outcomes from 1147 patients who received intensity modulated radiotherapy (IMRT) as part of definitive management for stage I-IVB HNSCC from 2001-2013 at our institution. The primary sites included oropharynx (n=735), oral cavity (OCC, n=182), larynx (n=180) and hypopharynx (n=50). Among patients who developed distant metastasis (DM), the the number of clinically or radiographically apparent tumors was assessed. Survival estimates following DM were generated using the Kaplan-Meier method and compared using log-rank testing. Cox proportional hazards models were used for univariate (UVA) and multivariate analyses (MVA). **Results:** A total of 148 (13%) patients developed DM at a median time of 10.7 months (range 0.3-81.2) after IMRT. The median follow-up time following DM was 48 months. 5-year survival following DM was significantly longer in patients with a solitary metastatic lesion compared to multiple lesions (table 1, p=0.001). Of the 19 patients with solitary metastasis, the 14 who received definitive local therapy with either surgery or radiation survived longer than those who did not (5-year survival 55.7% vs 0%, p=0.001), though patients who did not receive local therapy were of poorer performance status. On UVA and MVA, longer survival after DM was associated with presence of a solitary metastatic tumor (MVA hazard ratio 0.31, 95% CI 0.16-0.59, p=0.001). **Conclusions:** An oligometastatic phenotype characterizes HNSCC patients with solitary metastasis, especially when amenable to definitive local therapy. These findings have important implications regarding clinical trial design for HNSCC in the recurrent and oligometastatic setting.

5-year survival following DM according to number of metastatic lesions.

# of metastatic lesions	N	5-year survival following DM (±Std. error)
1	19	39.1% (±12.6%)
2	31	7.9% (±5.3%)
3	20	5.7% (±5.5%)
4	11	0%
5+	67	0%

6030 Poster Session (Board #18), Mon, 1:15 PM-4:45 PM

Premilinary survival results and potential beneficiaries for locally advanced nasopharyngeal carcinoma treated with neoadjuvant chemotherapy followed by concurrent chemoradiotherapy. *First Author: Mei Feng, Sichuan Cancer Hospital, Sichuan, China*

Background: Neoadjuvant is a promising chemotherapy modality for recurrent nasopharyngeal carcinoma (NPC). However, there is still controversy for locally advanced NPC. We study the survival results of locally advanced NPC treated with neoadjuvant chemotherapy followed by concurrent chemoradiotherapy (NACT) retrospectively, and to explore the potential beneficiaries. **Methods:** 147 stage III-IVa+b NPC treated with IMRT were included and divided into two groups. NACT group (76) received 2-3 cycles of neoadjuvant chemotherapy with TP or TPF, and then 2-3 cycles of platinum-based chemoradiotherapy (CCRT). CCRT group (71) received 3 cycles of platinum-based chemoradiotherapy. TNM stage, age and whole blood count before treatment were all collected. The stratified analysis was used for distinguishing the potential beneficiaries. **Results:** median follow-up time was 30 months. For all patients, the 3-year LRRFS, DMFS and OS in NACT and CCRT were 94.5%, 96.8%; 85.8%, 82.8% and 81.6%, 83.4% respectively ($p>$ 0.05). For stage III patients, the 3-year LRRFS, DMFS and OS were 95.2%, 97.3%; 91.4%, 84.6% and 86.3%, 82.1% respectively (p= 0.38, p= 0.15, p= 0.58). Though there was no statistical significance, DMFS in NACT was better than it in CCRT. However, for stage IV, the survival rate had no significant difference. The incidence of grade 3-4 bone marrow suppression was higher in NACT (p= 0.007), and the other toxicities were similar. Univariate analysis showed the percentages of neutrophil and neutrophil-to-lymphocyte ratio (NLR) were significantly correlated with OS (p= 0.031, p= 0.049). N and clinical stage were the adverse prognostic factors for OS (p= 0.025, p= 0.007) and DMFS (p= 0.018, p= 0.001). Clinical stage was the prognostic factors for OS and DMFS in multivariate analyses (p= 0.019, p= 0.01). **Conclusions:** NACT had a comparable survival results and tolerable toxicity with CCRT for locally advanced NPC. Stage III might be the potential beneficiaries from NACT, especially for DMFS. Percentages of neutrophil and NLR might be the new adverse prognostic factor for OS. Clinical stage was still the prognostic factor for OS and DMFS.

6031 Poster Session (Board #19), Mon, 1:15 PM-4:45 PM

Impact of early trials in molecularly-characterized patients (pts) with head and neck cancer (HNC). *First Author: Neus Baste, Hospital Universitari Vall d'Hebron, Department of Oncology, Barcelona, Spain*

Background: Multiple genomic alterations were described in HNC, including squamous cell carcinomas (SCC), salivary gland (SG) and nasopharyngeal (NF) tumors. Tumor molecular profiling (TMP) may increase therapeutic alternatives in early trials for pts with refractory metastatic (met) HNC. We evaluate the impact of matched/unmatched therapy (mT/uT) in HNC with potentially targetable alterations. **Methods:** From 2010-16, 47 met HNC pts were treated in 57 early trials after TMP. Clinical benefit was measured by: time to progression (TTP); clinical benefit rate (CBR: complete response [CR], partial response [PR] and stable disease [SD] > 4months [m]); progression-free survival [PFS] ratio≥1.3 (PFS under molecular therapeutics/PFS upon last prior chemotherapy [pT]). **Results:** Median age was 51 years; median number of pT lines was 1 (0-5). In total, 26 SCC, 11 SG, 8 NF and 2 nasosinusal pts (mostly with lymph nodes and lung met) were treated with small kinases (SK) inhibitors (inh) (50%; main targets PI3K/HER/FGFR), immune-oncology (IO) drugs (40%, PD-1/PD-L1), angiogenesis inh (5%) or chaperone, cytidine analog, RNA polymerase (5%). 14/57 trials were mT including CDKinh (1 *CDKN2A* mutation [mut]), PI3Kinh (5 *PIK3CA* mut, 2 *PTEN* mut), PI3K/MEKinh (1 *NRAS* mut), HERinh (1 *ERBB3*mut), FGFRinh (2 *FGFR1*mRNA high, 1 FGF3/4/19 ligand amplified) and porcupine inh (1 *ZNFR3*mut). Distribution by tumor: IO (16 SCC/5 NF), SKmT (8SG/4SCC/2NF) and SKuT (9SCC/4SG). Responses: 1CR in SCC (IO), 5 PR in SCC (4 IO, 1 FGFRinh), 3 PR in NF (1 cytidin analog, 1 IO, 1 PI3K/MEKinh). Benefit: median TTP 9.33m (CI95% 7-20) with upward trend in NF and SG vs SCC (HR 0.6;p = 0.28), without differences according to target therapies (HR 0.8; p = 0.9); CBR of 58%, without differences by tumor type (p = 0.42) or therapy (SKmT, SKuT, IO; p = 0.5); 60% with PFS ratio≥1.3, significantly higher in SCC and SG (p = 0.016), particularly with IO drug and SKmT, respectively. **Conclusions:** Considering our preselected fit population as bias selection, individualized treatment selection with novel therapeutics based on TMP, especially in NF and SG irrespective of targets (SKmT, SKuT, IO), and in SCC with IO drugs, seems to confer substantial clinical benefit.

6032 Poster Session (Board #20), Mon, 1:15 PM-4:45 PM

A phase 1b/2 study of amcasertib, a first-in-class cancer stemness kinase inhibitor in advanced head and neck cancer. *First Author: Gregory Michael Cote, Massachusetts General Hospital, Boston, MA*

Background: Amcasertib (BBI-503) is an oral first-in-class cancer stemness kinase inhibitor. By targeting multiple serine-threonine stemness kinases, amcasertib inhibits Nanog and other cancer stemness pathways. A phase I clinical trial of amcasertib showed safety and signs of anti-cancer activity in patients (pts) with advanced solid tumors during dose-escalation and RP2D expansion, including pts with advanced head & neck cancer. **Methods:** Pts with advanced, pre-treated head & neck cancers were enrolled. Amcasertib was administered orally, once or twice daily, in continuous 28-day cycles at a starting dose of 10 mg to 300 mg total daily. Adverse events were categorized according to CTCAE v4.03 and tumor imaging was evaluated per RECIST 1.1 guidelines every 8 weeks. **Results:** A total of 21 pts were enrolled, 15 with HNSCC and 6 with salivary or parotid gland cancers. Prior treatments included radiation in 90% (19/21), surgery in 71% (15/21) and prior systemic therapy in 90% (19/21, average 3 prior lines, range 1 to 6). Amcasertib was well tolerated with 43% of pts treated at 300 mg daily (n = 9), 33% at 150 mg BID (n = 7), 19% at 200 mg daily (n = 4), and 5% at 10 mg daily (n = 1). Grade 3 AE included diarrhea (n = 4) and nausea (n = 1). Among all patients who received an evaluation per RECIST (n = 16), the objective responses rate (ORR, proportion with partial response [PR] or complete response [CR] per RECIST) was 13% and the disease control rate (DCR, proportion with stable disease [SD] at 8 weeks, PR or CR) was 50%. At 12 months, in the intent-to-treat population (n = 21) 38% of pts were alive. Median overall survival (mOS) of 7.2 months. **Conclusions:** Clinical safety and encouraging signs of anti-cancer activity were observed in pts with advanced head and neck cancers who have received treatment with amcasertib. Objective response, prolonged disease control, and extended survival have been observed in this pre-treated population with a poor prognosis. Further clinical evaluation of amcasertib in patients with head and neck cancers is warranted. Clinical trial information: NCT01781455.

6033 Poster Session (Board #21), Mon, 1:15 PM-4:45 PM

Treatment patterns in recurrent/metastatic head and neck squamous cell carcinoma in the US. *First Author: Eric S. Nadler, Texas Oncology, Dallas, TX*

Background: Given the most recent FDA approval of cetuximab in 2008 for treatment of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), the objective was to assess utilization of cetuximab and other treatments for R/M HNSCC in real world setting. **Methods:** Adult patients (pts) with R/M HNSCC who initiated systemic therapy between 9/1/2011-12/31/2014 were identified from iKnowMedelectronic health records database (McKesson Specialty Health) supplemented with chart abstraction. Pts were followed through 12/31/2015 to collect data on clinical characteristics, treatments and survival outcomes. **Results:** Among 325 pts with R/M HNSCC, median age was 62 yrs; 82% were male, and 67% had oropharyngeal cancer. The most common first line (1L) regimen consisted of platinum-based combinations (76%; Table 1); 63% received platinum+taxane +/-5FU and only 8% received platinum+cetuximab +/- 5FU. Median overall survival was 13.6 months (range 11.7-16.6). Following 1L therapy, 171 pts (53%) received a 2L regimen; 57 pts (18%) received platinum monotherapy and 8% received 2L platinum+taxane +/- 5FU, while only 12% received cetuximab mono- or platinum+ cetuximab + /- 5FU. Among pts receiving 1L platinum combination, 32% were re-treated with platinum based therapy of which platinum monotherapy (23%) and platinum+taxane +/- 5FU (7%) were most common. **Conclusions:** Despite FDA approval and NCCN guidelines recommending use of cetuximab for palliative treatment of R/M HNSCC, our study demonstrates underutilization in both 1L and 2L settings, underscoring the need to understand reasons for underutilization and the need for newer efficacious treatments.

1L Treatment, n (%)	N	No 2L Treatment	Platinum Mono	Cetuximab Mono	Platinum+ Taxane +/- 5FU	Taxane Mono	Platinum+ Cetuximab +/- 5FU
Overall	325	154 (47)	62 (19)	33 (10)	26 (8)	25 (8)	7 (2)
Platinum-Based Combination	247	118 (48)	57 (23)	29 (12)	18 (7)	12 (5)	5 (2)
Taxane+Platinum+/-5FU	203	95 (47)	56 (28)	27 (13)	12 (6)	3 (2)	5 (3)
Cetuximab+Platinum+/- 5FU	25	14 (56)	0 (0)	0 (0)	3 (12)	6 (24)	0 (0)
1L Monotherapy (Mono)	75	35 (47)	5 (7)	4 (5)	9 (12)	13 (17)	2 (3)
Cetuximab	41	19 (46)	3 (7)	0 (0)	4 (10)	8 (20)	1 (2)
Platinum	17	7 (42)	0 (0)	2 (12)	4 (24)	3 (17)	1 (6)
Taxane	14	7 (50)	1 (7)	2 (14)	1 (7)	2 (14)	0 (0)

6034 Poster Session (Board #22), Mon, 1:15 PM-4:45 PM

A phase I clinical trial of AZD1775 in combination with neoadjuvant weekly cisplatin and docetaxel in borderline resectable head and neck squamous cell carcinoma (HNSCC). *First Author: Eduardo Mendez, Department of Otolaryngology: Head and Neck Surgery, University of Washington, Seattle, WA*

Background: The WEE1 tyrosine kinase regulates G2/M transition and maintains genomic stability. In TP53-deficient tumors (via mutation or HPV inactivation), inhibiting WEE1 with AZD1775 can lead to unrestrained mitosis and cell death. We conducted a Phase I clinical trial of AZD1775 in combination with chemotherapy to define the toxicity profile, establish the maximal tolerated dose (MTD) and assess preliminary efficacy in borderline resectable HNSCC. **Methods:** Stage III/IVB HNSCC deemed borderline resectable by a multidisciplinary team were enrolled in a phase 1, 3 + 3 design to evaluate escalating doses of AZD1775 starting at 125 mg PO BID x 2.5 days alone as lead-in and in combination with cisplatin (25mg/m2) and docetaxel (35 mg/m2) for three additional weeks. Tumors were sequenced with UWOncoPlex (262 cancer genes); HPV status assessed via p16 IHC; toxicities graded with CTCAE v. 4.04; responses measured via RECIST 1.1 and through pathologic assessment when available. Trial is open but primary endpoints were met. **Results:** Eleven patients were screened; 10 enrolled and were evaluable for toxicities. The most common Grade $\geq$ 2 toxicities were diarrhea (4), fatigue (4), neutropenia (3) and nausea (3). The drug-limiting toxicity was Grade 3 diarrhea (2). The MTD was established at 150mg PO BID x 2.5 days, alone and in combination with neoadjuvant cisplatin and docetaxel. Two patients were HPV+/TP53wt, 1 was HPV+/*TP53* mut; 6 were *TP53*mut/HPV-; 1 was TP53 wt/HPV-. Seven out 10 patients had a response. Two patients dropped out after the first week with AZD1775, one due to an allergic reaction to docetaxel and another due to non-compliance. Eight completed neoadjuvant therapy and 7 of those converted to surgery: 2 had pathologic CRs (both HPV+/TP53wt); 4 had PR (all TP53 mutants); 1 (TP53wt/HPV-) had a PR by RECIST, but SD by pathology and 1 had PD. **Conclusions:** AZD1775 is safe and tolerable in combination with neoadjuvant cisplatin and docetaxel. Results show this combination to have promising anti-tumor efficacy in borderline resectable HNSCC with TP53 deficiency, and merits further investigation with the established MTD as the recommended Phase II dose. Clinical trial information: NCT02508246.

6035 Poster Session (Board #23), Mon, 1:15 PM-4:45 PM

The impact of radiotherapy, in addition to chemotherapy, on overall survival in the initial management of patients with newly diagnosed metastatic head and neck squamous cell carcinoma. *First Author: Sujith Baliga, Montefiore Medical Center, Bronx, NY*

Background: The role of radiation therapy (RT) in the upfront management of patients with metastatic head and neck squamous cell carcinoma (HNSCC) is not clearly defined. In this study, we used the National Cancer Database (NCDB) to assess the association between RT use and overall survival (OS) for patients with metastatic HNSCC who received chemotherapy. **Methods:** We analyzed the NCDB to identify patients with newly diagnosed metastatic HNSCC from 2004-2013 who were treated with upfront chemotherapy. Associations between the use of RT and OS were evaluated using the Kaplan Meier method, univariate and multivariate cox regression, propensity score matching, and sequential landmark analysis. Survival outcomes were also compared for patients receiving a biologically effective dose (BED) $\geq$72 Gy_{10} and $<$ 72 Gy_{10}. **Results:** We identified 3,516 patients diagnosed with metastatic HNSCC who were treated with chemotherapy, of which 2,288 (65%) were also treated with RT. The median follow up was 11.9 months. The addition of RT to chemotherapy was associated with prolonged survival (median 13.6 *v* 11.3 months, logrank $p < 0.001$). On multivariate analysis, the use of RT remained associated with prolonged survival (HR = 0.71, 95% CI 0.61-0.82, $p < 0.001$). After propensity score matching, the addition of RT was associated with improved median survival (13.5 *v* 11.2 months) and 5-year (17% *v* 7%) OS compared to chemotherapy alone (log rank, $p < 0{\cdot}001$). Landmark analyses limited to patients who survived at least 3, 6, and 12 months after diagnosis continued to demonstrate improved OS with the addition of RT. Among patients treated with RT, the use of RT schedules with a BED exceeding 72 Gy_{10} was associated with prolonged survival (median 18.0 versus 11.7 months, logrank $p < 0.001$). **Conclusions:** For patients with metastatic HNSCC, the addition of RT to chemotherapy was associated with improved OS in this population based study. These results provide rationale for prospective randomized trials to validate these findings and to determine the optimal radiation therapy dose/fractionation and treatment schedule for these patients.

6036 Poster Session (Board #24), Mon, 1:15 PM-4:45 PM

A phase 1b/2 study of amcasertib, a first-in-class cancer stemness kinase inhibitor, in advanced adenoid cystic carcinoma. *First Author: Gregory Michael Cote, Massachusetts General Hospital, Boston, MA*

Background: Amcasertib (BBI-503) is an oral first-in-class cancer stemness kinase inhibitor. By targeting multiple serine-threonine stemness kinases, amcasertib inhibits Nanog and other cancer stemness pathways. A phase I clinical trial of amcasertib demonstrated safety and signs of anti-cancer activity in patients (pts) with advanced solid tumors. Cancer stemness pathways have been implicated in adenoid cystic carcinoma (ACC). An RP2D expansion cohort was opened for patients with ACC. **Methods:** Pts with metastatic, unresectable ACC for whom systemic therapy was indicated were enrolled. Amcasertib was administered orally, once or twice daily, in continuous 28-day cycles at a starting dose of 110 mg to 300 mg total daily. Adverse events were categorized according to CTCAE v4.03 and tumor imaging was evaluated per RECIST 1.1 guidelines. **Results:** 14 pts with ACC were enrolled. Prior treatments included surgery and radiation in all pts (100%), while 57% (n = 8) had received prior systemic therapy (average 2 prior lines, range 1 to 4). Treatment with amcasertib was well tolerated, with grade 3 diarrhea reported in 1 patient and no related grade 4 AEs. The disease control rate (DCR, proportion with stable disease at 8-weeks, partial response, or complete response per RECIST) was 86% (n = 12) with prolonged disease control (≥ 6 months) achieved in 57% (n = 8) patients. At 12 months, 79% of pts were alive. Median overall survival (mOS) was 28.3 months. **Conclusions:** Clinical safety and encouraging signs of anti-cancer activity were observed in pts with advanced ACC who received treatment with amcasertib. Long term follow-up demonstrates prolonged duration of disease control and that a majority of pts in this cohort have survived beyond 2 years. Further clinical evaluation of amcasertib in pts with ACC is warranted. Clinical trial information: NCT01781455.

6037 Poster Session (Board #25), Mon, 1:15 PM-4:45 PM

A phase II multicenter trial of the multitargeted kinase inhibitor sulfatinib in advanced medullary thyroid cancer (MTC) and radioiodine (RAI)-refractory differentiated thyroid cancer (DTC). *First Author: Jiaying Chen, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Sulfatinib is an oral tyrosine kinase inhibitor targeting Vascular Endothelial Growth Factor Receptor (VEGFR), Fibroblast Growth Factor Receptor 1 (FGFR 1), and Colony Stimulating Factor 1 Receptor (CSF1R). In a proof of concept (PoC) phase II study, sulfatinib showed promising efficacy in patients (pts) with neuroendocrine tumors (NETs). **Methods:** This is an open label, two cohorts phase II study using Simon's two-stage design. In stage I, 15 pts will be enrolled in each cohort (advanced MTC or iodine-refractory DTC), and 10 more pts will be enrolled in a cohort in stage II if at least 2 PR observed in that cohort in stage I. Pts are required to have progressive disease in the past 12 months, but could not have received > 1 prior anti-angiogenesis therapy. Pts are treated with oral sulfatinib 300 mg once daily until disease progression, death, or intolerable toxicity. Primary endpoint is Objective Response Rate (ORR) by investigator per RECIST 1.1. **Results:** As of Dec 31 2016,the studyenrolled 18 pts (MTC: 6, DTC: 12), amongst whom 17 pts were efficacy evaluable. There were a total of 4 confirmed PRs, 1 in the MTC cohort and 3 in the DTC cohort, respectively. The others best response was stable disease (SD). 11 pts (61.1%) had dose interruption due to adverse events (AEs) and 5 pts (27.8%) had dose reduction. Two pts discontinued therapy (1 patient due to disease progression, another due to subject's decision). The most commonly reported AEs were proteinuria 72.2% (Grade 3-4: 22.2%), hypertriglyceridemia 50.0% (Grade 3-4: 0%), hypertension 44.4% (Grade 3-4: 16.7%), blood bilirubin increased 44.4% (Grade 3-4: 5.6%), and diarrhea 33.3% (Grade 3-4: 0%). No Grade 5 AE was reported by the time of data cut-off. **Conclusions:** Sulfatinib appears to be well tolerated in the pts with advanced MTC and RAI refractory DTC. Safety profile seems to be consistent to previous report, with mostly manageable AEs. Efficacy is encouraging in both indications. Further investigation is warranted. Clinical trial information: NCT02614495.

6038 Poster Session (Board #26), Mon, 1:15 PM-4:45 PM

Phase I study of the anti-HGF monoclonal antibody (mAb), ficlatuzumab, and cetuximab in cetuximab-resistant, recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). *First Author: Julie E. Bauman, University of Arizona Cancer Center, Tucson, AZ*

Background: Cetuximab, an anti-EGFR mAb, is approved for R/M HNSCC but only a minority benefits. Activation of cMet, the receptor for hepatocyte growth factor (HGF), overcomes EGFR inhibition in preclinical models and high serum HGF is associated with resistance in patients (pts). We conducted a phase I trial evaluating the combination of cetuximab and ficlatuzumab, an IgG1 anti-HGF mAb, in pts with cetuximab-resistant, R/M HNSCC. **Methods:** In this Narayana k-in-a-row phase I design, cetuximab 500 mg/m^2 was administered every 2 weeks. Ficlatuzumab dose tiers were 10 mg/kg (tier 1) or 20 mg/kg IV every 2 weeks (tier 2), with inter-patient escalation or de-escalation based on cumulative dose-limiting toxicities (DLT). The recommended phase II dose (RP2D) was set at tier 2 if no DLTs were observed after 8 enrolled pts; expansion continued to n = 12. Key eligibility criteria: R/M HNSCC; recurrence within 6 months of cetuximab-radiation or progression during/within 6 months of palliative cetuximab; ECOG PS 0-1. Candidate biomarkers included serum Veristrat, a proteomic classifier in lung cancer where "good" predicts benefit from anti-EGFR therapy and "poor" indicates resistance and poor prognosis. **Results:** From Sept 2015–June 2016, 12 pts were enrolled and treated. Primary site: 1 oral cavity; 3 oropharynx (1 p16+); 2 hypopharynx; 5 larynx; 1 external auditory canal. Platinum-refractory: 11/12. Veristrat: 8 poor; 4 good. Three pts were treated at tier 1 and 9 at tier 2. No DLTs were observed. Grade 3 adverse events included: edema (1), hypoalbuminemia (1), infection (2), thromboembolic event (2). Median PFS and OS at RP2D were 6.0 mos (90% CI = 2.0 mos–not reached) and 8.2 mos (90% CI = 2.7 mos–not reached), respectively. Response rate was 17% (90% CI = 0–28%): 2/12 partial response (PR); 1/3 at 10 mg/kg; 1/9 at 20mg/kg. Clinical benefit rate (PR + stable disease) was 67%. Veristrat was not associated with PFS. **Conclusions:** The RP2D is cetuximab 500 mg/m^2 and ficlatuzumab 20 mg/kg every 2 weeks. This well-tolerated combination demonstrated promising activity in pts with poor prognosis, cetuximab-resistant R/M HNSCC. Phase II testing is justified. Clinical trial information: NCT02277197.

6039 Poster Session (Board #27), Mon, 1:15 PM-4:45 PM

A pilot study of the pan-class I PI3K inhibitor buparlisib in combination with cetuximab in patients with recurrent/metastatic head and neck cancer. *First Author: Ryan J. Brisson, Oakland University William Beaumont School of Medicine, Rochester, MI*

Background: R/M HNC carries a poor prognosis with a median survival of 10-12 months. PI3K pathway aberrations are present in 30% of HNC. This pilot dose-escalation study assesses the safety and tolerability of the PI3K inhibitor buparlisib when given concurrently with cetuximab in R/M HNC, as well as assess efficacy in an expansion cohort. **Methods:** Patients (pts) with R/M HNC who were not amenable to curative intent therapy were enrolled. Pts were given oral buparlisib starting day -7 and daily thereafter. The dose of buparlisib was escalated in a 3+3 design (Level 1: 80mg daily, Level 2: 100 mg daily) followed by a dose expansion cohort. The maximum dose of buparlisib was 100 mg daily. Cetuximab (500mg/m^2) was given intravenously every 14 days starting day 0. Pts continued on treatment until progression of disease. Prior cetuximab failure was allowed. **Results:** Of the 12 pts enrolled, 10 had at least 2 previous treatment regimens (11 with prior cetuximab). 5 pts were HPV+, 4 were HPV-, and 3 had unknown HPV status. 3 pts were treated at the 80 mg dose level while 9 were treated at the 100 mg dose level (3 + 6 patient expansion). Treatment was well tolerated with 2 pts experiencing grade 3 adverse events (AEs) (no grade 4 AEs). The most common AEs were fatigue (83.3%), maculopapular rash (50.0%), and anorexia (50.0%). 3 pts experienced grade 1 anxiety. There were no SAEs. Of the 10 pts who were evaluable for response one patient achieved a PR (10%), and 4 achieved stable disease (40%) per RECIST 1.1. Median overall survival was 280 days (HPV+: 370 days, HPV-:191 days). The study was closed early due to poor enrollment on the expansion cohort as patients opted for concurrently open immunotherapy trials. **Conclusions:** Based on this pilot study, buparlisib plus cetuximab proved to be well-tolerated and showed limited evidence of activity in a heavily pre-treated patient population. Further research is warranted to determine activity of buparlisib in a larger cohort of R/M HNC. Clinical trial information: NCT01816984.

6040 Poster Session (Board #28), Mon, 1:15 PM-4:45 PM

A retrospective cohort study of PD-L1 expression in recurrent and/or metastatic squamous cell carcinoma of the head and neck (SUPREME-HN). *First Author: Sara I. Pai, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) have a poor prognosis. Targeting the PD-1/PD-L1 axis has resulted in clinically meaningful antitumor activity and improved overall survival (OS) in R/M HNSCC patients. Tumoral PD-L1 expression correlates with response to blocking PD-1/PD-L1 antibodies. We investigated the prognostic value of PD-L1 expression in R/M HNSCC patients. **Methods:** Archival tumor samples from R/M HNSCC patients diagnosed between March 2011 and June 2015 at 12 institutions in 6 countries were stained for PD-L1 and clinic-demographic data were abstracted from medical records. Tumoral PD-L1 protein expression was assessed with the validated Ventana SP263 assay and scored as high ($\geq$25% of tumor cells [TC]) or low/negative ($<$ 25% of TC). Extracted data included demographic and tumor characteristics, treatment patterns, and clinical outcomes. Descriptive analyses were conducted and survival estimated by the Kaplan-Meier method. OS was defined from the diagnosis index date of R/M disease to time of death. **Results:** As ofSeptember 26, 2016 (interim analysis), data were available for 143 patients of whom 138 were eligible for analysis. Median age was 62.0 years (range, 28.0−88.0), 76.8% were male, and 84.0% were white. PD-L1 protein expression was high in 43 patients (31.2%), low/negative in 91 (65.9%), and unknown in 4 (2.9%). Median OS (8.2 vs. 8.8 months; P = 0.94) and progression-free survival (PFS) from the start of first-line (6.0 vs. 5.6 months; P = 0.29) or second-line therapy (7.1 vs. 1.8 months; P = 0.11) did not significantly differ between PD-L1 high and low/negative patients, respectively. There were no significant differences in OS based on PD-L1 status within subgroups defined by age, race, tobacco or alcohol use, primary tumor site, performance status, metastatic disease at diagnosis, or treatment with platinum-based chemotherapy. **Conclusions:** Interim analyses indicate that PD-L1 status is not associated with OS or PFS in R/M HNSCC patients.

6041 Poster Session (Board #29), Mon, 1:15 PM-4:45 PM

The negative predictive value (NPV) of FDG-PET/CT in the Head and Neck Squamous Cell Carcinoma (HNSCC) N0 patient, the first report of the ACRIN 6685 trial. *First Author: Brendan C. Stack, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: This study evaluated the negative predictive value for node negativity in HNSCC. **Methods:** Patients were enrolled from 8/10 until 12/16 from 38 centers in the US and 1 center in China. This was a prospective, non-randomized trial. The study was designed to recruit 292 patients; however, 287 were enrolled by study closure. Inclusion criteria were newly diagnosed cT2-T4 SCC patients from the head and neck with one side cN0 who were willing to undergo an elective neck dissection. CN0 was determined by a negative neck CT or MR scan. Exclusions included non-SCC, non-surgical candidates, skin, nasopharynx or sinus primaries. PET/CT imaging reading performed centrally and pathology were analyzed at the neck level (left or right). To estimate confidence intervals, we used a nonparametric bootstrap to account for the correlation of data between sides of neck of the same patient. Correlative data and other image analyses will be reported separately. **Results:** PET/CT scans and pathology were available for 211 (table) N0 sides of neck for review at last interim analysis. NPV estimate with 95% CI for bilateral necks: 0.896 (0.831, 0.950) and specific to the N0 sides: 0.922 (0.862, 0.973). **Conclusions:** FDG PET/CT has high NPV for node negativity in HNSCC. This may obviate the need for elective neck dissection in N0 HNSCC patients. This trial was open about three times longer than planned, and a major obstacle to accrual was the generalized assumption among the oncology community that PET/CT had a high NPV. Therefore, patients sent to study centers for further diagnosis and treatment often had their PET/CT scans performed on non-ACRIN certified equipment. This required investigators to forgo offering the trial or the PET/CT was repeated. Our results may suggest application for pre-operative PET/CT nodal imaging of other primaries/lymphatic basins staged cN0. Funding from the National Cancer Institute through the grants U01 CA079778, U01 CA080098, CA180820, CA180794. Clinical trial information: NCT00983697.

		FDG PET-CT Negative	FDG PET-CT Positive
Pathology	Negative	106	54
Pathology	Positive	9	42

6042 Poster Session (Board #30), Mon, 1:15 PM-4:45 PM

Aspirin use and survival in head and neck squamous cell cancer (HNC) patients. *First Author: Hind Rafei, Department of Medicine, the George Washington University School of Medicine and Health Sciences, Washington, DC*

Background: The phosphatidylinositol-3-kinase (PI3K) signaling pathway is the most common genetic alteration in HNC, particularly in oropharynx cancers (OPC). Up-regulation of the PI3K pathway enhances the production of prostaglandins inhibiting apoptosis in cancer cells. We hypothesized that aspirin (ASA) improves survival in HNC patients (pts) by counteracting the effects of prostaglandins. **Methods:** This is an IRB-approved retrospective cohort study of 584 veterans with HNC treated at the Washington DC Veterans Affairs Medical Center between 1995 and 2015. Charts were reviewed for clinical-pathologic and treatment data; recurrence/distant metastases; cause of death; and for the number, date and dose of ASA prescriptions. Pts who filled more than one prescription, excluding refills, after diagnosis of HNC were considered ASA users. All others were considered non-ASA users. The Kaplan-Meier method and log-rank test were used to compare disease-free survival (DFS) and disease-specific survival (DSS) between users and non-users. **Results:** 332 pts met inclusion criteria. Primary subsites included oropharynx (n = 146), larynx (n = 105), oral cavity (n = 62), and hypopharynx (n = 19). 86 pts were ASA users after diagnosis (25.9%) and more likely to be older (p = 0.002), African American (p = 0.03), never-alcohol users (p = 0.044), and have early stage cancer (I/II; p $<$ 0.0005) compared to non-ASA users. Among all HNC pts, ASA users demonstrated significantly better 5-year (y) DSS (82%) compared to non users (43%; p = 0.009). 5-y DFS was also significantly higher among users (72%) vs non users (39%; p $<$ 0.001). Among the OPC pts, 5-y DSS was higher for ASA users (74%) vs non users (41%; p = 0.024). 5-y DFS was also better for users (72%) vs non users (39%; p = 0.004). For stages III and IV, 5-y DFS was significantly higher among ASA users (64%) vs non users (44%; p = 0.035). 5-y DSS was higher as well in users (69%) vs non users (44%) but p = 0.098. On multivariate analysis, aspirin use remained an independent prognostic factor associated with improved DSS and DFS when accounting for age, race, gender, subsite, stage, tobacco and alcohol use. **Conclusions:** Aspirin use following diagnosis and curative treatment of HNC is associated with improved DSS and DFS.

6043 Poster Session (Board #31), Mon, 1:15 PM-4:45 PM

Predicting response to radical (chemo)radiotherapy (R-CRT) with circulating HPV DNA and tumor DNA (ctDNA) analysis in locally-advanced head and neck squamous cell carcinoma (LAHNC). *First Author: Shreerang Bhide, The Royal Marsden Hospital, Sutton, United Kingdom*

Background: Following R-CRT for human papilloma virus positive (HPV+) and negative (HPV-) LAHNC, patients frequently undergo unnecessary neck dissection (ND) and/or repeated biopsies for abnormal PET-CT findings even in the presence of a complete pathological response (pCR), which causes significant morbidity. We assessed the role of circulating tumor DNA analysis in identifying patients with true residual disease. **Methods:** We prospectively recruited development (DC, n=55) and test (TC, n=33) cohorts of LAHNC patients having R-CRT. For HPV+ tumors we developed a novel amplicon based next generation sequencing assay (HPV-detect) to detect circulating HPV DNA and for HPV- tumors we used personalised droplet digital PCR assays of somatic mutations. Circulating tumor DNA levels at 12 weeks post-R-CRT were correlated to residual disease assessed by PET-CT and surgery. **Results:** In the DC (27 HPV+), baseline HPV-detect demonstrated 100% sensitivity and 93% specificity, confirmed in the TC (20 HPV+). 37 HPV+ patients (DC&TC) had complete samples-set. 36 had a negative HPV-detect at end of treatment, including 6 patients who underwent ND (3) and repeat primary site biopsies (3) for positive PET-CT but had pCR on surgical/biopsy specimen. 1 patient had positive HPV-detect and positive biopsy, indicating 100% agreement for HPV-detect and residual cancer. In a 10 HPV- patients with complete sample-set, there was 90% agreement between ctDNA and residual disease in HPV- tumors (3 ctDNA positive and tumor present, 1 ctDNA negative but tumor present, and 6 negative ctDNA negative tumor) with 80% sensitivity for residual disease and 100% specificity. Combined agreement between ctDNA testing (HPV+ and -) & residual disease was 98% (Table). **Conclusions:** Circulating HPV DNA quantified using HPV-detect and ctDNA identifies patients with residual disease post-R-CRT in LAHNC. Further studies are required to validate these findings.

		HPV detect/ctDNA		
Residual disease		Present	Absent	Total
	Present	4	1	5 (Sensitivity 80%)
	Absent	0	40	40(Specificity 100%)
	Total	4 (Positive predictive value 100%)	41 (Negative predictive value 97%)	45 (Accuracy 98%)

6044 Poster Session (Board #32), Mon, 1:15 PM-4:45 PM

Two-year clinical outcomes of de-intensified chemoradiotherapy for low-risk HPV-associated oropharyngeal squamous cell carcinoma. *First Author: Bhishamjit S. Chera, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: We here-in report 2 year cancer control outcomes from a prospective phase II clinical trial evaluating de-intensified chemoradiotherapy (CRT) for patients with favorable risk, HPV-associated oropharyngeal squamous cell carcinoma (OPSCC). **Methods:** The major inclusion criteria were: T0-T3, N0-N2c, M0, HPV or p16 positive, and minimal smoking history. Treatment was limited to 60 Gy intensity modulated radiotherapy with concurrent weekly intravenous cisplatin (30 mg/m^2). Patients neither received induction chemotherapy nor definitive surgery. The primary study endpoint was pathologic complete response rate (pCR) based on required biopsy of the primary site and dissection of pretreatment positive lymph node regions, regardless of radiographic response. Secondary endpoint measures included 2 year local control (LC), regional control (RC), cause specific survival (CSS), distant metastasis free survival (DMFS), and overall survival (OS), and patient reported symptoms (PRO-CTCAE) and quality of life (EORTC QLQ-C30 & H&N35). **Results:** Forty-four patients enrolled and the median f/u was 36 months (range 5-53 months, 93% with $>/=1$ year, 88% $>/=2$ years). We have previously reported the pCR to be ~ 86%. Two year LC, RC, CSS, DMFS, and OS are the following: 100%, 100%, 100%, 100%, and 95%. All 6 patients who had pathological partial responses are alive with no evidence of disease with a median f/u of 34 months (range 9-48 months). Two patients have died (stroke and glioblastoma). Mean pre and 2-year post EORTC QOL scores were: Global 80/82 (lower worse), Swallowing 11/10 (higher worse), Dry Mouth 16/54, and Sticky Saliva 6/33. 39% of patients required a feeding tube (none permanent) for a median of 15 weeks (5 - 22 weeks). Mean pre and 2 year post PRO-CTCAE (1 to 4 scale, higher worse) scores were: Swallowing 0.4/0.8 and Dry mouth 0.4/1.8. There were no $>/=$ Grade 3 late adverse events. **Conclusions:** The 2-year clinical outcomes with decreased intensity of therapy with 60 Gy of IMRT and weekly low-dose cisplatin are excellent in favorable risk OPSCC with evidence of better preservation of quality of life as compared to standard therapies. Clinical trial information: NCT01530997.

6045 Poster Session (Board #33), Mon, 1:15 PM-4:45 PM

Population assessment of head and neck cancer outcomes by race and HPV status in chance. *First Author: Siddharth Sheth, University of North Carolina, Chapel Hill, NC*

Background: Growing literature suggests that racial disparities exist in patients with head and neck squamous cell carcinoma (HNSCC). Currently, there are many hospital-based cohorts assessing racial disparities, however only a limited number of population-based cohorts exist. This study aims to explore the association between clinical characteristics and patient demographics with overall survival by race and HPV status. **Methods:** Patients were identified from the Carolina Head and Neck Cancer Study (CHANCE), a population based case-control study with enrollment from 2001-2006 in North Carolina. Vital status was determined by linkage with the National Death Index. Survival was considered at 5 years after diagnosis or study enrollment. We used Kaplan-Meyer analyses and Cox proportional hazards regression modeling to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI). **Results:** A total of 1361 HNSCC patients with no baseline metastasis and adequate survival time were identified. Of these, 1010 patients were white while 351 patients were black. Black patients were statistically more likely to be younger at age of diagnosis, have a history of tobacco or alcohol use, be uninsured, and not have completed high school (p-value < 0.001). In an unadjusted cox regression analysis, blacks had 1.50 times (95% CI 1.01-1.57) decreased overall survival than whites. Adjusting for gender, stage of disease, age, treatment, and smoking status, this relationship remained (HR 1.30, CI 1.1-1.6). In a subset analysis of male patients by disease site, there was decreased overall survival in black patients in oral cavity cases ($p < 0.01$). This relationship trended towards significant in pharynx cancer ($p = 0.054$) and was not found in laryngeal cancer. In pharyngeal cases only, there was decreased overall survival in black patients with HPV+ disease ($p = 0.03$) but not in HPV- cases ($p = 0.33$). **Conclusions:** This is the first population-based study that confirms racial disparities in HPV+ HNSCC. We also found worse overall survival prognosis for black patients with oral cavity cancer and a similar trend in pharynx cancer. Further studies are needed to evaluate if this difference is driven by either biological or socioeconomic factors.

6046 Poster Session (Board #34), Mon, 1:15 PM-4:45 PM

HPV status and survival in non-oropharyngeal squamous cell carcinoma of the head and neck. *First Author: Vanessa Wookey, University of Nebraska Medical Center, Omaha, NE*

Background: HPV positive squamous cell carcinoma of the oropharynx and tonsil has been associated with increased survival. However, the prognostic value of HPV status for other primary sites is unclear. We assessed the effect of HPV status on survival in patients with non-oropharyngeal head and neck squamous cell carcinoma at all stages. **Methods:** Data was obtained from the National Cancer Database (NCDB) to determine the effect of HPV status on overall survival (OS) in adults with non-oropharyngeal head and neck squamous cell carcinoma (gum, lip, floor of mouth, tongue (excluding base), hypopharynx and nasopharynx) using SAS software. Pearson's Chi square test was used for comparisons by HPV status. The Kaplan-Meier method was used to estimate OS and differences were compared using a log-rank test. A multivariate Cox proportional hazards regression model analysis was performed to determine effects of individual variables on outcomes. **Results:** Patients with all stages of squamous cell carcinoma of the gum, lip, floor of mouth, tongue (excluding base), hypopharynx and nasopharynx diagnosed from 2010 to 2013 with complete HPV data were included (n = 13,908). In univariate analysis, HPV positivity, female gender, Asian race, primary site (lip, tongue, nasopharynx and hypopharynx), private insurance and any treatment (except for chemotherapy alone) were associated with increased OS, whereas increased age, Black race, higher Charlson-Deyo comorbidity score, hypopharynx primary, and higher AJCC stage were associated with worse OS. After adjustment for covariates, HPV positivity was associated with improved OS (HR 0.83, 95% CI 0.74-0.93; $p < 0.001$). Female gender, gum, lip, nasopharynx primaries, and private insurance on multivariate analysis predicted for improved OS, while age > 70, higher Charlson-Deyo score and higher AJCC stage were associated with worse OS. **Conclusions:** HPV positivity and female gender are good prognostic factors in squamous cell carcinoma of the head and neck, independent of primary site. Trials evaluating de-escalation of treatment should be considered for HPV positive tumors from non-oropharyngeal sites in the head and neck region.

6047 Poster Session (Board #35), Mon, 1:15 PM-4:45 PM

Cellular immune biomarkers to prognosticate for survival to adoptive T-cell therapy in advanced nasopharyngeal cancer. *First Author: Han Chong Toh, Department of Medical Oncology, National Cancer Centre, Singapore, Singapore*

Background: We have published a Phase II clinical trial in 35 advanced incurable stage 4c NPC patients employing upfront first line chemo-immunotherapy of four cycles of gemcitabine and carboplatin, followed by six cycles of adoptive transfer autologous EBV-specific cytotoxic T lymphocytes (CTL). The 2- and 3-year overall survival rates were 62.9 and 37.1% respectively, which represent the best reported survival outcome for first-line treatment of advanced NPC when compared to historical clinical trials. **Methods:** From this Phase II trial, we completed serial multiple deep immune phenotyping analyses including flow cytometry, nanostring, and multiplex ELISA assays. We then investigated how these factors influence and determine successful therapy using 2-year survival rates. **Results:** Longitudinal modular transcriptome analysis of patient PBMCs revealed significant increases in T cell, NK, and B cell modules post chemotherapy within the 2-year survivor group. Administration of CTLs restored expression of lymphocyte transcripts in the non-survivor group at 2-weeks post infusion. However, as immunotherapy proceeded, 2-year survivors displayed significant increases in multiple lymphocyte module associated transcripts. These immune correlates were associated with increased IFN-γ and decreased myeloid chemokine concentrations in peripheral sera during immunotherapy in 2-year survivors. Longitudinal immunophenotyping of patient PBMCs at serial timepoints showed that 2-year survivors displayed significant decreased amounts of monocytic myeloid-derived suppressor cells (mMDSCs), compared to non-survivors after chemotherapy, which subsequently determined successful CTL immunotherapy survival benefit. **Conclusions:** This is the first report in human cancer patients that successful adoptive T cell immunotherapy correlates with lower mMDSCs following chemotherapeutic preconditioning. We have also identified potential prognostic immune biomarkers that effectively predicts efficacy of CTL immunotherapy, following upfront combination chemotherapy, and thus survival. Lymphodepletion with chemotherapy appears to be vital for adoptive T cell therapy efficacy.

6048 Poster Session (Board #36), Mon, 1:15 PM-4:45 PM

The impact of HPV infection on survival of patients with non-oropharyngeal head and neck cancer. *First Author: Samer Alsidawi, Mayo Clinic, Rochester, MN*

Background: The role of Human Papilloma Virus (HPV) infection in non-oropharyngeal squamous cell carcinoma (non-OPSCC) of the head and neck is unknown. Current available studies have yielded conflicting results due to limited number of patients. We present a large analysis from the National Cancer Database (NCDB) evaluating HPV-positive non-OPSCC. **Methods:** Using the NCDB registry, we included adults diagnosed with non-OPSCC from 2004-2012 with available HPV status. A cohort of patients with OPSCC was analyzed for HPV prevalence comparison. Survival analysis was performed using Kaplan-Meier method and stratified using HPV-status. The prognostic effect of variables was studied using Cox proportional hazards models. The JMP software was used for statistical analysis. **Results:** A total of 8726 non-OPSCC patients were identified and primary sites included the oral cavity (50%), larynx (41%) and hypopharynx (9%). 11% of non-OPSCC patients had evidence of infection with high-risk HPV strains compared to 61% of OPSCC patients. HPV-positive non-OPSCC patients presented at slightly younger age, had more advanced stage and higher tumor grade compared to HPV-negative patients ($P < 0.01$). HPV-positive non-OPSCC patients had better survival than HPV-negative patients (HR 0.82, 95% CI 0.72-0.93, $P < 0.01$) and this was most pronounced in patients with locally advanced disease (5-year survival 50% versus 40%, HR 0.69, 95% CI 0.6-0.8, $P < 0.01$). A univariate and multivariate analysis were performed adjusting for age, sex, race, stage, primary site, Charlson/Deyo comorbidity score, financial income, tumor grade, surgery, radiation and chemotherapy administration. Smoking history was unavailable. HPV positivity was an independent predictor of better survival in non-OPSCC in multivariate analysis (HR 0.69, 95% CI 0.59-0.8, $P < 0.01$). **Conclusions:** HPV infection is seen in a subset of patients with non-OPSCC head and neck cancer and these present with more advanced tumors. The survival of patients with HPV-positive non-OPSCC is significantly better than HPV-negative tumors. Routine HPV testing and enrollment in treatment de-intensification clinical trials similar to OPSCC might be appropriate for this patient population.

6049 Poster Session (Board #37), Mon, 1:15 PM-4:45 PM

Correlation of constitutive PD-1 resistance in HNC with GM-CSF expression and presence of myeloid derived suppressor cells (MDSCs). *First Author: Tanguy Y. Seiwert, University of Chicago, Chicago, IL*

Background: PD-1 checkpoint blockade is active in head and neck squamous cell carcinomas (HNC) with a response rate of ~18% and significant impact on survival. However, only a subset of patients benefits (Seiwert, Lancet Oncol). Biomarkers such as PD-L1 IHC and the Interferon-Gamma gene expression profile (INF-G GEP) identify inflamed tumors with a higher chance of response (~35-40%). However, it remains unclear why the majority of INF-G inflamed tumors still do not respond, or how to overcome constitutive resistance. **Methods:** 50 anti-PD-1 treated recurrent/metastatic HNC patients were included. Tumor RNA was analyzed using a 638-gene immune panel on the Nanostring nCounter. HPV status was assessed by HPV E6/E7 mRNA. T-cell inflamed phenotype was calculated using the 6-gene INF-G GEP (geometric mean) using both a low (6) and a high cutpoint. Differential gene expression was determined between inflamed-benefitting (IB) patients (defined as OS $\geq$ 250days), and inflamed-non-benefitting (INB) patients. Candidate biomarkers were evaluated in the entire cohort. **Results:** CD8 correlated highly with INF-G GEP ($R = 0.80$), suggesting T cell-driven inflammation. Comparing inflamed benefitting with inflamed non-benefitting tumors, the most differentially expressed gene was CSF-2, encoding GM-CSF, with 4-fold higher expression in inflamed non-benefitting (INB) tumors (with both cutpoints). In the overall anti-PD-1 treated cohort of 50 patients, CSF-2/GM-CSF correlated strongly with poor overall survival ($P = 0.02$), outperforming both HPV status, or PD-L1 expression in cox PH multivariate analysis. GM-CSF expression has been linked to myeloid derived suppressor cells (MDSC); MDSC marker CD34, as well as JAK2/IL10 were significantly elevated in inflamed non-benefitting (INB) tumors. There was no difference in M2 macrophage marker CD163 between the two groups. **Conclusions:** Constitutive resistance to PD-1 checkpoint blockade in inflamed HNC associates with expression of GM-CSF and Myeloid Derived Suppressor Cell (MDSC) markers. Strategies to deplete MDSCs, such as chemotherapy, should be considered in combination or sequentially with anti-PD-1.

6050 Poster Session (Board #38), Mon, 1:15 PM-4:45 PM

Characterization of potential predictive biomarkers of response to nivolumab in CheckMate 141 in patients with squamous cell carcinoma of the head and neck (SCCHN). *First Author: Fernando Concha-Benavente, University of Pittsburgh Medical Center and University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: Nivolumab, an anti-programmed death-1 (PD-1) monoclonal antibody, demonstrated longer median overall survival (7.5 vs 5.1 months) and improved response (13.3% vs 5.8%) versus investigator choice chemotherapy (ICC) in patients with recurrent SCCHN after platinum failure in CheckMate 141 (NCT02105636), a randomized, open-label Phase 3 trial. We screened peripheral blood lymphocytes (PBL) to identify biomarkers which may predict response to nivolumab. **Methods:** Paired baseline (day 1) and on treatment (day 43) PBL samples ($n = 36$; 24 nivolumab; 12 ICC) were analyzed using multicolor flow cytometry and a non-competing anti-PD-1 antibody. Results were correlated with clinical outcome: responders (complete/partial response) and non-responders (stable or progressive disease). **Results:** Levels of CD8+ T cells at baseline and on treatment were higher in nivolumab responders compared to non-responders (23% vs 13%; $P < 0.05$). Interestingly, PD-1+ CD8+ and PD-1+ CTLA-4+ CD8+ effector T cells (likely exhausted T cells) decreased about 2-fold following nivolumab in both responders and non-responders ($P < 0.05$), whereas, the decrease in CTLA-4+ CD8+ effector T cells following nivolumab was significant in responders only (8% vs 5%; $P < 0.05$). Levels of PD-1+ TIM-3+ CD8+ effector cells decreased following nivolumab in non-responders only (11% vs 7%; $P < 0.05$), a similar non-significant reduction was observed in responders. Levels of PD-1+ Tregs were lower in responders than non-responders at baseline (19% vs 33%; $P < 0.01$), and following nivolumab (12% vs 20%; $P < 0.001$). As in T-effector cell populations, PD-1+ Tregs decreased about 1.6-fold after nivolumab in both responders and non-responders ($P < 0.01$). Interestingly, baseline Ki67+ Treg levels were lower in non-responders (28% vs 17%; $P < 0.05$). **Conclusions:** Response to nivolumab may be associated with higher levels of CD8+ T cells and CTLA-4+ CD8+ effector T cells, and lower PD-1+ CD8+ effector T cells and PD-1+ Tregs at baseline. Targeting both PD-1 and CTLA-4 axes is warranted in SCCHN to overcome suppressive signals in CD8+ effector T cells and in Treg cells expressing both checkpoint receptors. Clinical trial information: NCT02105636.

6051 Poster Session (Board #39), Mon, 1:15 PM-4:45 PM

Association of mannitol (MAN) with cisplatin (CIS)-induced nephrotoxicity (NTX) and cumulative CIS dose (CCD). *First Author: Sri Ramalingam, Medical College of Wisconsin, Milwaukee, WI*

Background: CIS is widely used in cancer therapy with CCD linked to survival outcome. CCD, however, is constrained by side effects—particularly NTX (incidence 20-30%). MAN is widely used to prevent CIS NTX despite low level of evidence. Herein, we took advantage of a national shortage of MAN to examine renoprotective effects of MAN in CIS treated patients. **Methods:** Between 2006-2012, 704 consecutive pts undergoing CIS therapy, with or without MAN, were analyzed. Pt characteristics, oncologic diagnosis, treatment, and renal function data were collected. The primary objective was to compare clinically significant NTX, as defined by $>$ 25% reduction in glomerular filtration rate (GFR) from baseline, between the treatment groups. Cox proportional hazards regression was used to model the hazard of NTX as a function of CIS dose. **Results:** Of 704 pts, 442 were treated with MAN and 262 without. The median age was 58.9 years. Age ($p = 0.83$), gender ($p = 0.77$), and race ($p = 0.056$) were similar between groups whereas baseline GFR (MAN 91.2 $\pm$ 22; CIS 86.3 $\pm$ 24; $p = 0.005$) and diagnoses ($p < 0.001$) differed. The distribution of diagnoses was: head and neck (25.9%), genitourinary (26.0%), lung (14.3%), gastrointestinal (10.4%), lymphoma (4.5%), and other (18.9%). The mean CIS dose (mg) per cycle in MAN versus CIS only group was 126.1 $\pm$ 58 and 109.3 $\pm$ 58 respectively ($p < 0.001$). The CCD (mg) was higher in the MAN compared to the CIS only group (469.8 $\pm$ 295 versus 299.0 $\pm$ 241; $p < 0.001$). After adjusting for baseline GFR, age, gender, race, and diagnoses, the MAN group experienced lower risk of $>$ 25% decrease in GFR at any given CCD (HR: 0.68, CI: 0.51-0.91, $p = 0.01$). Females (HR: 1.72, CI: 1.28-2.32; $p = 0.0003$), older pts (HR: 1.24, CI: 1.10-1.40; $p = 0.0003$), and Hispanic pts (HR: 2.39, 1.04-5.50; $p = 0.04$) were more likely to sustain $>$ 25% reduction in GFR. **Conclusions:** MAN enhances CCD by protecting against CIS-induced NTX. Pts with MAN experienced a lower risk of clinically significant acute kidney injury (AKI) and received a higher average CIS dose per cycle and CCD. Women, older pts, and Hispanic pts had a higher risk of AKI. Future investigation is warranted to examine whether MAN-associated CCD effects translate into survival advantages.

6052 Poster Session (Board #40), Mon, 1:15 PM-4:45 PM

Molecular signatures of class II HLA and p-16 status as an immune-based classification of OPSCC relying on known predictors of sensitivity to PD-1 blockade. *First Author: Nabil F. Saba, Winship Cancer Institute, Atlanta, GA*

Background: PD-1 inhibitors are known to have significant clinical activity in head and neck squamous cell cancer (SCCHN); there is, however, no selection criterion for SCCHN patients who may benefit from PD-1 inhibition. Utilizing RNA-seq analysis we explored a set of human genes encoding leukocyte antigens (HLAs) as part of a 37-gene panel predictive of response in melanoma patients to PD-1 inhibitors (Chen et al, Cancer Discov. 2016 Aug;6(8):827-37). We investigated whether this panel could define an immune-based classification of oropharyngeal squamous cell carcinoma (OPSCC). **Methods:** We have applied a minimal mutation and copy number content (151 genes) using an Agilent Clearseq DNA and an extensive Illumina Truseq RNA panel providing key information on gene fusions, differential gene expression, coding mutation and metagenomics on 47 SCCHN FFPE samples including 27 OPSCC. We performed an unsupervised hierarchical clustering of the samples. Two clusters with high and low expression were noted. Fisher's exact test was performed to determine if the samples in each clusters were associated with p16 as a surrogate marker for HPV status. The same procedure was repeated on Level 3 transcriptome data from the TCGA via GDC data portal. **Results:** A set of fourteen immune related HLA antigen genes were identified within the 37-gene panel predictive to response to PD-1 inhibitors in p16+ versus - OPSCC ($p = 0.015$).We applied the same set of immune related HLA genes on the 103 patient samples from TCGA with known p16 status. When applied on all samples, there was no correlation between the HLA gene expression and p16 status ($p = 0.1366$); however, when restricted to OPSCC patients there was a high correlation with p16 status ($p = 0.0047$). **Conclusions:** We have identified a set of immune related HLA type II genes that are over-expressed in p16 positive OPSCC. This opens the door for further evaluation of these genes to better understand the immune related factors affecting the biology of HPV-associated OPSCC and its response to PD-1 inhibitors. (This research was supported by a grant NCI R21 CA182661-01A1to NFS and GZC).

6053 Poster Session (Board #41), Mon, 1:15 PM-4:45 PM

IDO1 as a mechanism of adaptive immune resistance to anti-PD1 monotherapy in HNSCC. *First Author: Lori J Wirth, Massachusetts General Hospital, Boston, MA*

Background: Patients with recurrent/metastatic human papillomavirus-associated head and neck squamous cell carcinoma (HPV-HNSCC) demonstrate improved response rates to anti-PD-1 blockade, which may be attributed to the inherent inflammation associated with the local expression of foreign, highly immunogenic viral antigens. However, these response rates are at best 25%, suggesting there may be immune resistance networks that are limiting clinical responses to anti-PD-1 therapy. To address this question, we investigated other potential immune checkpoint pathways that may be upregulated in PD-L1 expressing HPV-HNSCCs. **Methods:** Using a custom microarray of 59 immune-related genes, we compared the gene expression profile of laser-captured micro-dissected PD-L1 (+) and (-) immune fronts in HPV-HNSCCs. Gene expression was validated using quantitative PCR (qPCR) and protein expression geographically localized using quantitative multiplex biomarker imaging in a separate cohort of HPV-HNSCCs. Furthermore, we assayed pre- and post-treatment biopsies from anti-PD-1 treated patients and correlated gene expression with clinical responses. **Results:** Of the immune-related genes, IDO1 was increased 65-fold in 10 PD-L1(+) as compared to 5 PD-L1(-) HPV-HNSCCs ($p = 0.004$). qPCR confirmed upregulated expression of IDO1 and quantitative immunofluorescence demonstrated that PD-L1 and IDO1 geographically co-localized within the tumor microenvironment in a validation cohort of 25 HPV-HNSCC patients. In anti-PD1 treated patients, IDO1 expression increased up to two-fold and correlated with disease progression in HNSCC patients. **Conclusions:** IDO1 is an immune checkpoint molecule that modulates T cell activity through the depletion of L-tryptophan. We propose that IDO1 is an adaptive immune resistance pathway to anti-PD-1 monotherapy. The results provide rationale for combinatorial therapies targeting the IDO1 and PD-1:PD-L1 networks in HNSCC patients.

6054 Poster Session (Board #42), Mon, 1:15 PM-4:45 PM

Association of DRB1 and DRBQ haplotype 04:01~03:01 with HPV positive head and neck squamous cell carcinoma. *First Author: Arun Khattri, The University of Chicago, Chicago, IL*

Background: The incidence of human papilloma virus (HPV) associated oropharyngeal head and neck cancer (HNC) is increasing rapidly in the US, Europe, and Asia. HPV16 is etiologic in 90-95% of HPV+ HNC. Sexual transmission and inability to clear infection leading to viral genome integration or chronic presence of episomal HPV16 DNA are precursors to HPV+ HNC carcinogenesis. However it remains unclear why a majority of HPV16 exposed individuals are able to clear the initial infection and avoid the risk of cancer. We hypothesized that difference in the ability eradicate infection may be mediated by certain HLA haplotypes. **Methods:** HPV(+) HNC patients from the TCGA cohort were HLA-typed based on available exome sequencing data. HLA typing was performed using the ATHLATES algorithm. We compared the distribution of alleles and haplotypes of classical HLA genes (A, C, B, DRB1 and DQB1) among HPV(+) HNC patients with those found in HPV(-) patients. Furthermore we evaluated enrichment of candidate alleles compared to publically available data in Caucasian non-cancer individuals. **Results:** Out of 528 HNC samples in the TCGA cohort, 450 were of Caucasian ancestry. The DRB1~DQB1 haplotype 04:01~03:01 was significantly increased in HPV(+) HNSCC patients compared to normal, non-cancer individuals (p-value = 0.0045, OR = 2.52, 95% CI = 1.2–5.03). This was not the case for HPV(-) HNC patients. The number of African American samples in TCGA was comparably small (N = 48, with N = 5 being HPV+) however the frequency of DRB1~DQB1 haplotype 04:01~03:01 in the general African American population is significantly lower. **Conclusions:** DRB1~DQB1 haplotype 04:01~03:01 associates with an elevated risk for HPV+ HNC. Similar findings were reported 17 years ago for cervical cancer (Br J Cancer, 82(7), 1348–1352), and further validate our findings across tumor types. Mechanistic studies to understand potential DRB1~DQB1 haplotype 04:01~03:01 HPV specific immune dysfunction, as well as evaluation in different risk and racial populations are indicated.

6055 Poster Session (Board #43), Mon, 1:15 PM-4:45 PM

Cell-free DNA for treatment monitoring and outcome predictor in head and neck cancer. *First Author: Julia Beck, Chronix Biomedical, Göttingen, Germany*

Background: Copy number instability (CNI) signatures of cancers can be readily detected by Next Generation Sequencing of plasma cell-free DNA (cfDNA). HPV detected in oropharyngeal carcinomas is currently the only prognostic biomarker available. We report here CNI scores for disease monitoring of Head and Neck Cancers (HNC) with potential predictive value for personalized therapeutic options. **Methods:** A total of 132 plasma samples were collected from 54 HNC patients under informed consent and IRB approval. cfDNA was extracted from plasma, ~20M paired-end NGS mappable reads (reference: HG19) per sample were generated and CNI scores were calculated by read counting statistics. After unblinding CNI scores were evaluated as diagnostic parameter for association with disease characteristics and progression. Survival analysis was conducted after dichotomization of baseline CNI scores at a value of 31 corresponding to the 97.5thpercentile of a normal reference group (RG, n = 141). **Results:** CNI scores above the 97.5th RG percentile were detected in 40 out of 54 (74%) treatment naïve baseline samples. 29 patients with tumors $\leq$ T3 (62%, n = 42) and 11 out of 12 (92%) with T4 tumors had CNI scores $>$ 31, with significantly higher CNI scores ($p = 0.04$) seen for T4 tumors. Higher CNI scores were also found in patients with tumor lymph node invasion (n = 37; median: 381, Q25-Q75: 57-1573) compared to negative lymph nodes (pN0, n = 17; 27, 19-64, p= 0.0004). A steep decline of CNI scores was detected after surgical resection, with increasing CNI scores in later disease progression. The pre-operative CNI scores were a stronger predictor of time to recurrence ($p = 7*10^{-5}$) than the pN status ($p = 0.05$) (Cox regression). High baseline CNIs ($>$ 31) strongly correlated with time to recurrence (Kaplan-Meier log-rank $p = 0.018$) with a median of 20 months and median overall survival of 30 months in the high CNI group, neither reached in the low CNI-score group (60 m follow-up). **Conclusions:** Chromosomal instability within HNC was quantified from plasma cfDNA as CNI score. The CNI score may serve as better predictor for the time to recurrence interval than pN status. The data suggests that cfDNA analysis as CNI score may serve as real-time marker of treatment efficacy and outcome.

6056 Poster Session (Board #44), Mon, 1:15 PM-4:45 PM

Poor-prognosis nasopharyngeal carcinoma as defined by a molecularly distinct subgroup and prediction by a miRNA expression signature. *First Author: Lan Zhao, City University of Hong Kong, Hong Kong, Hong Kong*

Background: Nasopharyngeal carcinoma (NPC) is a highly invasive and metastatic cancer, with diverse molecular characteristics and clinical outcomes. Our aim in this study is to dissect the molecular heterogeneity of NPC, followed by construction of a prognostic model for prediction of distant metastasis. **Methods:** For molecular subtyping of NPC using miRNA expression data, we selected 86 stage II (AJCC 7th Edition) NPC patients from GSE32960 as training cohort. The remaining 226 NPC patients from GSE32960 and 246 NPC patients from GSE70970 were used as two validation cohorts. Consensus clustering was employed for unsupervised classification of the training cohort. Classifier was built using support vector machine (SVM), and was validated in the two validation cohorts. Univariate and multivariate Cox regression analyses were employed for feature selection and constructing a prognostic model for predicting high-risk distant metastasis, respectively. **Results:** We identified three NPC subtypes (NPC1, 2, and 3) that are molecularly distinct and clinically relevant. NPC1 (~45%) is enriched for cell cycle related pathways, and patients classified to NPC1 have an intermediate survival; NPC3 (~19%) is enriched for immune related pathways, and has good clinical outcomes. More importantly, NPC2 (~36%) is associated with poor prognosis, and is characterized by upregulation of epithelial-mesenchymal transition (EMT). Out of the total 25 differentially expressed miRNAs in NPC2, miR-142, miR-26a, miR-141 and let-7i have significant prognostic power ($p < 0.05$), as determined by univariate Cox regression analysis. For identification of high-risk distant metastasis, we built a multivariate Cox regression model using the selected 4 miRNAs. Our model can robustly stratify NPC patients into high- and low- risk groups both in GSE32960 (HR 3.1, 95% CI 1.8-5.4, p = 1.2e-05) and GSE70970 (HR 2.2, 95% CI 1.1-4.5, p = 0.022) cohorts. **Conclusions:** We proposed for the first time that NPC can be stratified into three subtypes. Using a panel of 4 miRNAs, we established a prognostic model that can robustly stratify NPC patients into high- and low- risk groups of distant metastasis.

6057 Poster Session (Board #45), Mon, 1:15 PM-4:45 PM

FGFR3 correlation with mutant p53 and its prognostic value in oropharyngeal squamous cell carcinoma (OPSCC). *First Author: Zhuo Georgia Chen, Winship Cancer Institute, Atlanta, GA*

Background: Fibroblast growth factor receptor 3 (FGFR3) is expressed in squamous cell carcinoma of the head and neck (SCCHN) including oropharyngeal squamous cell carcinoma (OPSCC) and is a potential therapeutic target. Information on its prognostic value and its correlation with other relevant cancer related proteins is limited. **Methods:** We performed immunohistochemistry (IHC) analyses of p16, mutant p53 (mp53), and FGFR3 on 221 retrospectively collected OPSCC tissue samples. mp53, and FGFR3 were semi-quantified as weighted index [WI = % positive x intensity (0. 1+, 2+, and 3+)]. Correlations of FGFR3 WI with p16 status, and mp53 WI were analyzed. Association of FGFR3 with disease-free survival (DFS) or overall survival (OS) was assessed. **Results:** A total of 144/221 (65%) were p16 +, 93/172 (54%) had mp53, and 140/221 (63%) expressed FGFR3. FGFR3 was highly correlated with mp53 ($p < 0.001$), which was true in both p16 + and – OPSCC ($p < 0.0001$ and $p = 0.0006$, respectively).mp53 level was significantly lower in p16 positive *versus* p16 negative group ($p < 0.0001$). Univariate analysis revealed an association of p16 negative and high mp53 with worse OS ($p < 0.001$ and $p < 0.001$, respectively) and DFS ($p < 0.001$ and $p = 0.004$, respectively). FGFR3 was associated with worse OS and DFS ($p = 0.014$ and $p = 0.047$, respectively). On multivariable analysis FGFR3 was associated with worse DFS ($p = 0.005$), but not OS. Kaplan-Meier plot using medians of both FGFR3 and mp53 as the cut-off values showed that higher FGFR3 and mp53 correlated to worst DFS (p = 0.025) and OS (p = 0.009). **Conclusions:** Our results suggest that FGFR3 is associated with mp53 and p16 – OPSCC and correlates with worse clinical outcome. The biologic relation of FGFR3 and mp53 in OPSCC deserves further investigation. (This research was supported by a grant NCI R21 CA182661-01A1to NFS and GZC).

6058 Poster Session (Board #46), Mon, 1:15 PM-4:45 PM

Intact APM and PD-1:PD-L1 pathway upregulation in HIV-infected head and neck cancer patients. *First Author: Sara I. Pai, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: HIV-infected individuals have a higher incidence of oral infection with human papillomavirus (HPV) and possibly a higher incidence of head and neck cancer (HNC). Whether this observation reflects defects in the ability of this Òimmune-compromisedÓ patient population to mount sufficient tumor specific immune responses and/or reflects activation of immune escape mechanisms is not known. To address this question, we investigated the expression of HLA class I antigen processing machinery (APM) components and PD-1:PD-L1 pathway activation in HIV(+) HNC patients. **Methods:** 62 HIV(+) HNC patients diagnosed between 1991-2011 from five tertiary care referral centers in the United States and matched HIV (-) HNC controls were identified. HLA class I APM component, PD-1, and PD-Ll expression were analyzed by immunohistochemical staining. Clinical data was abstracted from the medical records. **Results:** 44 of 62 (71%) HIV(+) HNC cases were matched based on gender, age (< 10 years), and anatomic sub-site to HIV(-) HNC patients. There was no significant difference between the cases and controls in HLA-A, HLA-B/C, LMP2, and TAP1, as well as PD-1 and PD-L1 expression. Overall, 62% of all subjects had high PD-1 expression and 82% of the subjects expressed PD-L1. HLA-A, HLA-B/C, and LMP2 expression was significantly correlated with moderate to high PD-1 expression in the HIV(+) HNC cases (p = 0.004, p = 0.026, and p = 0.006, respectively) but not in the HIV(-) controls. Similarly, HLA-A expression was also significantly associated with PD-L1 expression only in the HIV(+) HNC cases (p = 0.029). **Conclusions:** No defects were detected in the expression of the HLA class I APM components tested. PD-1:PD-L1 pathway was found to be upregulated in both HIV(+) and HIV(-) HNC patients. Our data suggest that recently approved anti-PD-1 immunotherapy should not exclude HIV(+) patients.

6059 Poster Session (Board #47), Mon, 1:15 PM-4:45 PM

Comprehensive targeted next-generation sequencing to reveal limited clonal evolution after concurrent chemoradiation in patients with squamous cell carcinoma of the head and neck. *First Author: Inge Tinhofer, Department of Radiooncology and Radiotherapy, Charité Unversity Hospital and German Cancer Research Center Heidelberg (DKFZ)/German Cancer Consortium (DKTK), Berlin, Germany*

Background: Recent next-generation sequencing (NGS) studies revealed a wide mutational spectrum in SCCHN. However, little is known about spatial intratumoral heterogeneity and temporal clonal evolution. Precise understanding of the genomic architecture of primary and recurrent/metastatic (R/M) tumors will be crucial for the development of personalized treatment and molecular biomarkers. **Methods:** In this pilot study, paired tumor samples (primary, R/M lesions) from 10 patients with locally advanced SCCHN who progressed after concurrent chemoradiation (CTRX) were included. Mutational profiling was performed by NGS targeting the exonic regions of 327 genes. Only somatic mutant variants with a difference of $\geq$0.15 in allele frequency (AF) between primary and R/M tumors were considered for further analysis. **Results:** Median time to progression was 6.2 months (range: 2.5-30.2). Overall, the difference in mutational patterns of primary and R/M tissue was very small. On average, one mutant variant (range: 0-2) was selectively detected in only one of the paired samples or differed in AF for $\geq$0.15. Nonetheless, clonal selection of mutant variants previously linked to disease progression was observed in 8 of 10 cases. In line with their gain of function, an increase in AF of *TP53* missense mutations (R175H, R248Q) in the recurrent tumor - suggestive of the selection of treatment-resistant mutant *TP53* subclones - was observed in two patients. Further variants with increased mutant AF in recurrent tumors were found in *ADCY2*, *CDKN2A*, *FGFR3*, *MET*, *NOTCH1, PIK3CA* and *TGFBR2*. **Conclusions:** We here provide first evidence that treatment-induced clonal selection after CRTX frequently occurs in SCCHN but is limited to only few gene alterations associated with an aggressive phenotype. This result is surprising given CRTX being a DNA-damaging regimen with inherent risk of de-novo mutagenesis and abundant time for clonal tumor evolution. Further investigations of spatial intratumoral heterogeneity and clonal evolution in larger patient cohorts are required for improving our understanding of treatment resistance and disease progression in SCCHN.

6060 Poster Session (Board #48), Mon, 1:15 PM-4:45 PM

CDKN2A copy number loss in HPV- and HPV+ head and neck cancer to indicate poor prognosis: An integrated genomic and clinical TCGA analysis. *First Author: William S. Chen, Yale School of Medicine, New Haven, CT*

Background: HPV infection is associated with high p16 expression and relatively good prognosis in head and neck cancers. Analysis of CDKN2A, the gene that encodes the p16 tumor suppressor protein, may further elucidate the association between HPV status and prognosis in head and neck squamous cell carcinomas (HNSCCs). We aimed to identify whether CDKN2A copy number loss was associated with poor survival in HNSCCs stratified by HPV status. **Methods:** We analyzed The Cancer Genome Atlas (TCGA) head and neck cancer data, integrating genomic measurements with clinical metadata. Patients 85 years old or younger with a primary tumor in the oral cavity, oropharynx, hypopharynx, or larynx were included. Defining CDKN2A copy number loss as a relative log2 copy number ratio < -0.6, CDKN2A mRNA and p16 protein expression levels were compared to confirm significant differences in gene transcription and translation between the copy number loss and non-copy number loss patient groups. Overall survival (OS) and disease-free survival (DFS) were evaluated to characterize prognostic differences between genomic groups. **Results:** 397 patients negative for HPV (HPV−) and 91 patients positive for HPV (HPV+) HNSCC were identified. 139 HPV− patients and 9 HPV+ patients demonstrated CDKN2A copy number loss. The CDKN2A copy number loss group expressed significantly lower levels of CDKN2A mRNA and p16 protein than did the non-copy number loss group in both HPV+ and HPV− disease. Median OS for HPV− patients with and without CDKN2A copy number loss was 21.8 months and 46.0 months ($P = 0.02$). Median DFS was 12.0 and 19.4 months respectively ($P < 0.05$). Median OS for HPV+ patients with and without CDKN2A copy number loss was 12.7 months and 57.4 months ($P = 0.004$) and median DFS was 7.0 and 36.6 months respectively ($P = 0.02$). **Conclusions:** CDKN2A copy number loss was associated with low CDKN2A mRNA and p16 protein expression, with poor prognosis in terms of disease-free and overall survival.

6061 Poster Session (Board #49), Mon, 1:15 PM-4:45 PM

PTEN and cetuximab resistance in head and neck squamous cell carcinoma (HNSCC). *First Author: Alexandre Andre B. A. Da Costa, A.C. Camargo Cancer Center, São Paulo, Brazil*

Background: Platinum-based chemotherapy in association to cetuximab is the standart first-line treatment for metastatic HNSCC. There is no established biomarker for cetuximab efficacy in HNSCC. We have previously shown that PTEN loss of expression is a bad prognostic factor for patients treated with platinum-based chemotherapy and cetuximab. The aim of the present study was evaluate the prognostic impact of PTEN loss of expression in patients treated with or without cetuximab and to evaluate its predictive value to cetuximab benefit. **Methods:** One hundred and nineteen patients with metastatic or locally recurrent HNSCC were included. Clinical data on treatment and outcomes was retroespectively colected from medical charts. Tissue micro-array was constructed to evaluate PTEN protein expression through immunohistochemistry. Citoplasmatic staining was evaluated using H-score. Tumors with H-score < 10 were considered to present PTEN loss of expression. **Results:** From the 119 patients 72 were treated with chemotherapy plus cetuximab while 47 were treated with chemotherapy alone. Median overall survival (mOS) was 9.2 months and median progression free survival (PFS) was 4.6 months. Patients treated with cetuximab compared to those who were not treated with cetuximab had a mOS of 11.4 vs 7.0 months ($p = 0.770$) and a median PFS of 6.2 vs 3.0 months ($p = 0.249$). Patients with PTEN loss of expression had a worse OS and PFS with mOS of 5.8 vs 10.5 months ($p = 0.002$) months and mPFS of 3.2 vs 5.2 ($p = 0.015$). On multivariate analysis including PTEN loss of expression and ECOG performance status both remained independently associated to survival with HR 2.25 (CI95% 1.28-3.97, $p = 0.005$) for PTEN loss of expression and a HR 1.63 (CI95% 1.07-2.50, $p = 0.023$) for ECOG. Negative prognostic impact of PTEN loss of expression was seen only in the cetuximab treated patients (mOS 7.3 vs 13.0 months; $p = 0.002$) but not in the chemotherapy only group (mOS 3.2 vs 7.5 months; $p = 0.051$). Interaction test for treatment group and PTEN loss of expression showed a $p = 0.418$. **Conclusions:** The present study confirms PTEN as a prognostic factor for metastatic HNSCC and suggests PTEN expression should be studied in larger cohorts to evaluate its predictive value to cetuximab response.

6063 Poster Session (Board #51), Mon, 1:15 PM-4:45 PM

A phase II randomized, multicentric clinical trail comparing recombinant human endostatin plus intensity-modulated radiotherapy versus concurrent chemoradiotherapy in locally advanced low-risk nasopharyngeal carcinoma. *First Author: Min Kang, Department of Radiation Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China*

Background: A prospective, randomized, and multicentric phase II study was performed to evaluate the short-term efficacy and safety of Endostar plus intensity-modulated radiotherapy (IMRT) versus concurrent chemoradiotherapy(CCRT) in locally advanced low-risk nasopharyngeal carcinoma (NPC). **Methods:** From September 2014 to August 2016, 120 patients with low-risk NPC at stages III-IVa from 9 centers were randomly divided into experimental group (Endostar plus radiotherapy (ERT); n = 60) and control group (CCRT; n = 60). ERT patients were given Endostar (7.5 mg/m^2/day) by continuous intravenous infusion (CIV) from 5 days before radiotherapy for consecutive 10 days for 2 cycles with an interval of 14 days. Then, ERT patients received 2 cycles of 10 days of maintenance treatment with Endostar after radiotherapy. The CCRT patients were given cisplatin (100 mg/m^2) on days 1, 22, and 43 for 3 cycles. Immediate and 3-month efficacy and adverse effects were evaluated between the two groups. ClinicalTrials registration number was NCT02237924. **Results:** All patients were eligible for toxicity and response analysis. Regarding immediate efficacy, the complete response(CR) rates were 45.0% for ERT arm and 33.3% for CCRT arm in nasopharynx ($P = 0.190$), and 43.3% for ERT arm and 36.7% for CCRT arm in regional nodes ($P = 0.456$). Three months after RT, the CR rates were 71.2% for ERT arm and 60.0% for CCRT arm in nasopharynx ($P = 0.151$), and 74.6% for ERT arm and 63.3% for CCRT arm in regional nodes ($P = 0.172$). The rate and severity of leukopenia, hemoglobin reduction and thrombocytopenia in ERT arm were significantly lower than CCRT arm ($P < 0.01$). The occurrence rates of Xerostomia, oral mucositis, nausea / vomiting, constipation and weight loss in ERT arm were significantly lower than those in CCRT arm ($P < 0.01$). **Conclusions:** The present study demonstrates that ERT has similar short-term efficacy on locally advanced low-risk NPC compared with CCRT, but the acute adverse effects of ERT are fewer, and the compliance and tolerability of patients are better. Clinical trial information: NCT02237924.

6064 Poster Session (Board #52), Mon, 1:15 PM-4:45 PM

Multimodality risk adapted therapy with induction carboplatin/paclitaxel/lapatinib for SCCHN amenable to transoral surgery. *First Author: Jared Weiss, University of North Carolina Hospitals, Chapel Hill, NC*

Background: Induction chemotherapy in SCCHN has mostly been studied prior to XRT where proof of improved survival is lacking. Regimens using weekly platinum, taxane and targeted therapy have resulted in high RR. Attempts are frequently made to intensify or de-intensify, but few have adapted therapy by response. **Methods:** Patients with transorally resectable, treatment naïve SCCHN and node positivity or $T > 3$ were treated weekly 6 times with Carboplatin AUC 2, paclitaxel 135mg/m2 and daily lapatinib 1000mg followed by transoral resection. Subjects with pN0/1 received no radiation; those with close margins, ECE, pN2a-b, PNI/LVSI were treated with weekly cisplatin 30mg/m2 and XRT with involved-field XRT allowed while those with pN2c/3 were treated with cisplatin 100mg/m2 Q3W and standard XRT. Primary endpoint was clinical RR (cRR) following induction chemotherapy. **Results:** Primary sites: oropharynx (OP) (30), supraglottic larynx (5), oral cavity (4) and hypophyarnx (1). Of OP patients, 17 were HPV low risk. Grade 3/4 toxicity during induction: decreased WBC (7), fatigue (3), diarrhea (2), febrile neutropenia (2), neuropathy (2), rash (2) and 1 each of ALT and AST increased, hyperglycemia, hypotension, nausea, PPDE. 39/40 proceeded to surgical resection (1 patient refused for non-study reasons). 29/39 subjects who were projected to require XRT were able to avoid it. 8/10 subjects with study-defined indication for adjuvant XRT received it. cRR 37/40, pRR 14/40. Clinical and pathologic responses correlated poorly (see table). With median FU of 1.7 years, there has been no recurrence or death. Mean VRQOL was 91.7 before induction, 92.3 before surgery and 92.3 1 year post surgery. Mean MDADI was 82.8 before induction, 85.9 before surgery and 84.5 1 year post surgery. **Conclusions:** The regimen led to excellent feasibility of surgical resection, high cRR and a real pCR. cR predicted poorly for pR. Most patients were able to avoid XRT. Speech and swallowing function were preserved. NCT01612351. Clinical trial information: NCT01612351.

Clinical Response, n	pCR
cSD 3	2/3
cPR 20	5/20
cCR 17	7/17
Clinical Response at primary site, n	pCR at primary
cSD 6	3/6
cPR 9	5/9
cCR 19	8/19
Clinical Response in neck, n	pCR in neck
cSD 3	2/3
cPR 12	7/12
cCR 17	10/17

6065 Poster Session (Board #53), Mon, 1:15 PM-4:45 PM

LIHNCS: Lugol's Iodine in Head and Neck Cancer Surgery—A multi-centre, randomised, controlled trial assessing the effectiveness of Lugol's Iodine to assist excision of moderate dysplasia, severe dysplasia and carcinoma in-situ at mucosal resection margin of oral and oropharyngeal squamous cell carcinoma. *First Author: James Anthony McCaul, Regional Maxillofacial Unit, Queen Elizabeth University Hospital, Glasgow, United Kingdom*

Background: Oral cavity and oropharynx cancer are increasing worldwide but survival has not significantly improved over the last thirty years. Presence of dysplasia or carcinoma in-situ at surgical margins following resection of squamous carcinoma (SCC) of the head and neck is associated with increased local recurrence and reduced survival. While carcinoma can usually be distinguished from normal mucosa, dysplasia is less readily distinguished at operation. We describe outcomes of LIHNCS, a RCT assessing effectiveness of Lugol's iodine staining for visualization and excision of margin dysplasia at primary surgery. **Methods:** Patients planned for curative surgical resection of oral cavity/ oropharynx SCC were recruited. Participants were randomised 1:1 into either a standard surgical treatment arm or surgical treatment including Lugol's iodine staining according to defined SOP. Randomisation was stratified by centre and surgeon using computer-generated random permuted blocks. Data monitors, pathologists and external reviewers were blinded to treatment allocations. Chief investigator, surgeons and other health care professionals were blinded to results. Primary endpoint is presence of carcinoma or dysplasia at mucosal margins. **Results:** Sixty-five surgeons in 24 centres recruited and LIHNCS was powered for 300 cases. Following successful recruitment, extension was granted for progression to 409, including 300 T1 and T2 cases. Patient acceptance was 89%. Median follow up is 36.5 months and 118 patients have died to date. Significantly fewer patients in the Lugols arm required further mucosal resection after primary surgery ($p = 0.005$). In as treated analysis dysplasia is reduced at resection margins for T1 and T2 tumours ($p = 0.04$). **Conclusions:** Lugol's iodine visualisation of dysplasia at curative surgical resection of oral and oropharynx SCC is associated with reduced requitement for further mucosal resection and appears to result in reduced dysplasia at mucosal resection margins. Clinical trial information: ISRCTN03712770.

6066 Poster Session (Board #54), Mon, 1:15 PM-4:45 PM

Optima: A phase II dose and volume de-escalation trial for high- and low-risk HPV+ oropharynx cancers. *First Author: James Melotek, University of Chicago, Chicago, IL*

Background: In this prospective phase II de-escalation study, we used induction chemotherapy to identify favorable HPV+ oropharyngeal cancer (OPC) pts, including those with high-risk tumors, and applied significantly lower radiation or chemoradiation doses than previously reported. **Methods:** Pts with HPV+ OPC were classified as low-risk ($\leq$T3, $\leq$N2B, $\leq$10 PYH) or high-risk (T4 or $\geq$N2C or $>$ 10 PYH). Pts received 3 cycles of carboplatin (AUC 6, D1) and nab-paclitaxel (100 mg/m2, D1/8/15). 1) Low-risk pts with $\geq$50% response received low-dose radiotherapy alone to 50Gy (RT50). 2) Low-risk pts with 30-50% response OR high-risk pts with $\geq$50% response received low-dose chemoradiotherapy to 45Gy (CRT45). 3) All other (= poor response) pts received regular-dose CRT (CRT75). All pts also received de-escalated RT volumes limited to the first echelon of uninvolved nodes. CRT consisted of paclitaxel, 5-FU, hydroxyurea, and 1.5Gy twice daily RT every other week. Primary site biopsy and neck dissection were performed only after de-escalated treatment (RT50, CRT45) for pathologic confirmation. The primary endpoint was 2-year PFS. Secondary endpoints included pathologic complete response (pCR) rate and toxicity. **Results:** 62 pts were enrolled. 28 pts (45.2%) were low-risk and 34 pts (54.8%) were high-risk. 71.4% of low-risk pts received RT50 and 21.4% received CRT45. 70.6% of high-risk pts received CRT45. The pCR rate was 94.4% after RT50 and 92.3% after CRT45. Median follow-up is 1 year. The 2-year PFS and OS were both 100% for low-risk pts, and 91.6% and 97.0% for high-risk pts. Significant decrease in the rates of grade $\geq$3 mucositis (15.8% RT50, 46.4% CRT45, 60.0% CRT75, $p = .033$) and grade $\geq$3 dermatitis (0% RT50, 21.4% CRT45, 30.0% CRT75, $p = .056$) were observed. PEG-tube dependency was improved at 3 months (0% RT50, 14.8% CRT45, 70.0% CRT75, $p < .001$) and 6 months (0% RT50, 3.7% CRT45, 20.0% CRT75, $p = .066$) post-treatment. **Conclusions:** Favorable response to induction chemotherapy appears to be a powerful biomarker for dose and volume de-escalation with 50Gy RT or 45Gy CRT. Outstanding survival and high pCR rates suggest that completion neck dissection may not be necessary. Toxicity and functional outcomes are significantly improved. Clinical trial information: NCT02258659.

6067 Poster Session (Board #55), Mon, 1:15 PM-4:45 PM

Resource utilization in patients with head and neck cancer: Analysis of CCTG HN6 (NCT00820248). *First Author: Ketan Ghate, Queen's University/ Cancer Centre of SE Ontario, Kingston, ON, Canada*

Background: As new treatments for head and neck cancer arise, further information is required regarding resource utilization. The Canadian Cancer Trials Group HN.6 study included collected resource utilization data prospectively on patients with locally advanced squamous cell carcinoma of the head and neck treated with cisplatin or panitumumab plus radiotherapy (RT). **Methods:** The HN.6 phase III trial enrolled 320 patients across Canada between 2008-2011. The economic analysis was conducted from the societal perspective. Resource utilization was collected prospectively for 3 categories: outpatient, hospitalization and institutionalization (end of life care) at baseline, 8 weeks, every 3 months(mo) for 2 years and every 4 mo until 3 years. Lost productivity questionnaires were collected in the last week of RT. Descriptive statistics were used to summarize the outcomes. Categorical variables were reported by percentage and continuous variables were reported by mean and standard deviation. **Results:** Of 320 pts randomized, resource utilization and lost productivity data were available for 317 (99%) and 285 (89%) pts, respectively. Eighty nine pts required 130 emergency room visits (mean 1.46$\pm$0.85). There were 696 (mean 3.74$\pm$3.22) office visits among 186 pts and 367 (mean 3.95$\pm$6.43) outpatient visits among 93 pts. Surgeons, radiation oncologists and emergency room physicians were the top three providers of outpatient care with 234 (mean 2.05$\pm$1.54), 137 (mean 1.67$\pm$1.19) and 118 (mean 1.4$\pm$0.78) visits for 114, 82 and 84 pts, respectively. CT scans (286), lab tests (418), x-rays (182) and other tests (400) were conducted in 136, 180, 120 and 194 pts, respectively. Three pts were institutionalized for end of life care (mean 28 days$\pm$26.06), and 214 pts were hospitalized (mean 14.5 days$\pm$28.8). One hundred and thirteen (41%) pts reported a change in work status at the end of RT. **Conclusions:** Radical treatment for locally advanced SCCHN is resource intensive. Tracking resources utilized prospectively in clinical trial settings and reporting this information consists of an efficient way to inform health resource allocation decisions. Clinical trial information: NCT00820248.

6069 Poster Session (Board #57), Mon, 1:15 PM-4:45 PM

Standard of care vs reduced-dose chemoradiation after induction chemotherapy in HPV+ oropharyngeal carcinoma patients. *First Author: Hope Rainey, Mount Sinai School of Medicine, New York, NY*

Background: Locally advanced Human Papillomavirus (HPV) + oropharyngeal carcinoma (OPC) has a significantly better response, locoregional control and survival compared to non HPVOPC. Standard-dose chemoradiotherapy (sdCRT) results in significant side effects, leading to acute and life-threatening late morbidity. We studied whether reduced dose chemoradiation (rdCRT) after induction chemotherapy (IC) resulted in equivalent progression-free survival (PFS) compared to sdCRT + IC with decreased late morbidity. **Methods:** Patients with locally advanced OPC and $<$ 20 pack years (py) smoking history were tested for p16 and then HPV by type-specific PCR. After 3 cycles of docetaxel, cisplatin and fluorouracil (TPF) IC all HPV+/p16+ subjects underwent clinical and radiographic evaluation. Clinical responders were randomized to either sdCRT (70Gy) or rdCRT (56Gy) with weekly carboplatin (AUC 1.5) at a 1:2 ratio. The primary endpoint was 2 year PFS; the secondary endpoint was 2 year overall survival (OS). Toxicity, late morbidity and swallowing were monitored. **Results:** 23 patients were enrolled and 20 randomized, 8 to sdCRT and 12 to rdCRT; 2 were HPV- and 1 refused further therapy after IC and were not randomized. Median age was 56.5 yrs (range 36-78); 30% were African-American, 10% were Hispanic, 5% were female; 16 were HPV 16+ and 4 were other high risk (HR) variants; 60% never smoked, 25% were $<$ 10 py, and 15% were 10-20 py; 70% had high risk features: T4, N2c, or N3. Clinical response to TPF was 100%; 70% had a clinical complete response. As of February 1, patients have been followed for a median of 37.5 months (range 21.7 – 49.5). 2 year PFS/OS for sdCRT and rdCRT are 87.5% vs 83.3% (log-rank test $p = 0.85$), respectively. All 3 failures were local or regional and 2 of 3 occurred in non HPV16 HR variants. **Conclusions:** HPV+ OPC patients who received rdCRT after TPF IC had similar PFS/OS compared to those receiving sdCRT. These results uphold the potential clinical benefit of radiation dose reduction as a treatment option with comparable survival to the standard radiation dose. A Phase III trial comparing IC plus rdCRT to sdCRT alone or with IC is warranted in this population. Non-HPV16 HR variants may have a worse outcome. Clinical trial information: NCT01706939.

6070 Poster Session (Board #58), Mon, 1:15 PM-4:45 PM

Impact of p16 expression on induction taxotere-cisplatin-5 FU (TPF) followed by cetuximab-radiotherapy in N2b-N3 head and neck squamous cell carcinoma (HNSCC): Results of GORTEC 2007-02 phase III randomized trial. *First Author: Yungan Tao, Gustave Roussy Cancer Campus, Villejuif, France*

Background: TPF is a reference induction chemotherapy regimen in non-operated locally advanced (LA) HNSCC. GORTEC 2007-02 phase III randomized trial was restricted to HNSCC patients with large nodal spread (N2b-N3). Results showed no benefit of 3 cycles of induction TPF followed by cetuximab-radiotherapy (RT), as compared to concurrent chemoradiotherapy (CRT) (Geoffrois *et al ASCO 2016*). **Methods:** Patients were randomized to receive concurrent CRT (arm A) or induction TPF followed by cetuximab-RT (arm B). RT was 70 Gy/35F/7 weeks. Concurrent chemotherapy was 3 cycles of carboplatin-5FU as previously described (Calais JNCI 1999). About 2/3 of patients had oropharyngeal cancers (OPC) and HPV status was determined in these patients using p16 expression as a surrogate (immunohistochemistry). Smoking status was also collected. Primary endpoint was progression free survival (PFS). **Results:** Between May 2009 and Aug 2013, 360 eligible patients were randomized including 231 (64%) OPC. Overall, p16 expression could be assessed in 172 / 231 OPC patients (74%) with 84 in arm A and 88 in arm B. 26 patients were found p16+ in arm A (31%) and 19 in arm B (22%). Only 8 out 45 (18%) p16+ patients were non-smokers showing that the large majority of OPC patients randomized were p16- (127/172) and smokers (117/129). A significant improvement in PFS was found in p16+ compared to p16- OPC ($p < 0.0001$). The absence of benefit in PFS associated with TPF + cetux-RT compared with CRT was suggested both in p16+ (HR: 0.78, 95% CI: 0.28 – 2.20) and in p16- OPC (HR: 1.28, 95% CI: 0.84 – 1.93), and the interaction between p16 and treatment modality was not significant ($p = 0.35$). A significant benefit was observed in favor of arm B regarding distant metastasis, but this effect was not different between the p16+ and p16- OPC, while there was no benefit of TPF + cetux-RT compared with CRT for loco-regional control, regardless of p16 status. **Conclusions:** The OPC p16 subpopulations were small. No benefit of induction TPF chemotherapy followed by cetuximab-RT compared with CRT in OPC patients regardless of p16 status. Clinical trial information: NCT01233843.

6071 Poster Session (Board #59), Mon, 1:15 PM-4:45 PM

A multicenter phase II trial of docetaxel, cisplatin and cetuximab (TPE) followed by cetuximab concurrent with radiotherapy in patients with local advanced squamous cell carcinoma of the head and neck (ECRIPS study). *First Author: Sadamoto Zenda, National Cancer Center East, Chiba, China*

Background: Induction chemotherapy is a treatment option for locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). However, Docetaxel, Cisplatin, and 5-FU (TPF) followed by Cisplatin with radiotherapy is currently not recommended due to toxicity concerns. The aim of this phase II study was to assess the feasibility of Docetaxel, Cisplatin, and Cetuximab (TPE) followed by Cetuximab with concurrent radiotherapy for LA-SCCHN. **Methods:** Patients were eligible if they had histologically proven SCC of oropharynx, hypopharynx or larynx, a PS of 0-1, adequate organ function, and no distant metastasis. Induction chemotherapy consisted of Cisplatin 75mg/m^2 and Docetaxel 75mg/m^2 on day1 and the induction regimen was repeated every 3 weeks up to a total of 3 courses. Cetuximab was administered at an initial dose of 400mg/m^2 followed by 250mg/m^2 weekly until the end of radiotherapy. Radiotherapy (70Gy/35fr/7w) was started after last administration of Docetaxel. Primary endpoint was the rate of treatment completion. The planned sample size was 55 with one-sided alpha of 0.025 and the power of more than 90% based on the expected and threshold treatment completion rates of 65% and 40%. **Results:** Between August 2013 and October 2015, 54 patients with a median age of 58 years were eligible and had the study treatment. There were 50 males, hypopharynx/oropharynx/larynx cancer of 28/19/7 cases, and 48 Stage IV disease. Response rate at induction chemotherapy was 72% while that after radiotherapy was 76% . Of 54 patients, 50 (93%) received > 2 courses of induction chemotherapy, and 41 (76%) had the full dose of radiotherapy. The rate of treatment completion was thus 76% (95%CI, 62–87%). The frequency of grade 3-4 neutropenia, febrile neutropenia, and allergy/infusion reaction was 93%, 39%, and 11%, respectively. One treatment-related death was observed. **Conclusions:** Induction TPE followed by Cetuximab with concurrent radiotherapy was feasible with a promising efficacy. A phase III study to evaluate this treatment strategy is warranted. Clinical trial information: UMIN000009928.

6072 Poster Session (Board #60), Mon, 1:15 PM-4:45 PM

Prognostic factors associated with benefit to post-operative chemotherapy: A National Cancer Data Base analysis. *First Author: Jessica Lyn Geiger, Cleveland Clinic, Cleveland, OH*

Background: Addition of chemotherapy to adjuvant radiation (RT) confers an OS benefit and is recommended in HNSCC patients with nodal extracapsular extension (ECE) and positive surgical margins based on pooled data. The purpose of this study is to retrospectively evaluate a larger patient data set in an attempt to confirm this observation and to assess current patterns of practice. **Methods:** The National Cancer Data Base (NCDB) was queried to identify patients with HNSCC who were treated with primary definitive surgery followed by adjuvant RT between 2004 and 2012. For patients treated with surgery and post-operative RT with or without chemotherapy, the effect of the systemic therapy on OS was explored using multivariable Cox proportional hazards modeling and stratified by patient and disease factors. **Results:** 6,351 patients were identified meeting study criteria; 3157 patients (49.7%) received adjuvant RT alone, and 3194 patients (50.3%) received adjuvant chemo-radiotherapy (CRT). An increase in chemotherapy usage was observed over time (6% of patients in 2004; 16% in 2012). No difference was seen in OS by use of CRT (median OS 8.3 years in patients without CRT vs. 9.4 years in patients with CRT, $p = 0.0893$). On multivariate analysis OS was improved in younger patients, patients with less co-morbidity, oropharynx, lower T and lower N. OS was also improved in patients given chemotherapy if either ECE or positive surgical margins were present (HR 1.166, $p = 0.0438$) but not in those with negative surgical margins and no ECE (HR 1.037, $p = 0.5888$). Nonetheless, chemotherapy was given to 38% of post-operative patients without these risk factors and not given to 35% of patients with risk factors. **Conclusions:** This NCDB analysis confirms an OS benefit with addition of chemotherapy to post-operative RT in HNSCC patients with ECE or positive surgical margins but not in patients without these risk factors, consistent with current guidelines. National practice patterns, however, do not mirror these recommendations. These results are subject to limitations of retrospective analysis of a large database and further studies are needed to better elucidate high risk factors benefiting from intensifying adjuvant therapy.

6073 Poster Session (Board #61), Mon, 1:15 PM-4:45 PM

Immunogenicity results using human papillomavirus (HPV) specific DNA vaccine, INO-3112 (HPV16/HPV18 plasmids + IL-12) in HPV+ head and neck squamous cell carcinoma (HNSCCa). *First Author: Charu Aggarwal, Abramson Cancer Center, Philadelphia, PA*

Background: Oropharyngeal HNSCCa is frequently associated with HPV. We hypothesize that immunotherapy with INO-3112 will generate immune responses in patients (pts) with HPV+ HNSCCa. **Methods:** This Phase I/IIa trial included pts with p16+ locally advanced HNSCCa, ECOG PS 0-1. INO-3112 was delivered IM along with electroporation with the CELLECTRA device, Q3 weeks x 4 doses. Cohort 1 (C1) pts received INO-3112 pre and post-surgery; Cohort 2 (C2) pts received INO-3112 post cisplatin-based definitive chemoradiation. 1° and 2° endpoints were safety and immune responses. Pre- and post INO-3112 tissue samples (C1) were assessed for tumor infiltrating lymphocytes (TILs). Peripheral immune responses were assessed by ELISA for HPV16/18 specific antibody levels, and by IFNɣ ELISpot for antigen specific response, at each dose visit and q3 months (mos). **Results:** As of 08/2016, 22 pts were treated, completing accrual. C1: $n = 6$, C2: $n = 16$; 20 male, median age 57.5 years (32-76); base of tongue = 10, tonsil = 12; never smoker = 10. All pts are alive, median follow up is 15.9 mos (1-26). INO-3112 was well-tolerated with no related Grade 3-5 AEs. In 5 C1 pts post immunotherapy, increase in CD8+ infiltration into tumor was noted in 2 pts (1.6-3.6 fold) and decrease in FoxP3+ was noted in the other 3 (1.8-2.1 fold). This resulted in positive shift in CD8+/FoxP3+ ratio in neoplastic tissue in 4/5 pts. Peak mean/median antibody responses to HPV16 E7 and HPV18 E7 antigens for 19 evaluable pts were 1:1235/1:150 and 1:2853/1:450, respectively. As compared to baseline, 18 evaluable pts showed elevated HPV16/HPV18 specific T cell activity (by IFNɣ ELISpot), with peak mean/median responses of 179.99/68.33 SFU per 10^6 PBMC (HPV16) and 107.18/53.3 SFU per 10^6 PBMC (HPV18). Persistent cellular responses > 100 SFU/10^6PBMC were noted out to 12 mos. 3 pts have progressed; 1 pt received Nivolumab for progressive disease, and remains in CR. **Conclusions:** These data show that INO-3112 generates HPV-specific peripheral humoral and cellular immune responses that may persist out to 12 months and influences the composition of CD8+ and FoxP3+ immune infiltration into tumor tissue in HPV+ HNSCCa. Clinical trial information: NCT02163057.

6074 Poster Session (Board #62), Mon, 1:15 PM-4:45 PM

Assessment of established patient reported outcomes (PROs) instruments measuring toxicities and quality of life (QOL) for patients (pts) with head and neck cancer (HNC) treated on ECOG 1308 and 2399 studies. *First Author: Anthony Cmelak, Vanderbilt University Ingram Cancer Center, Nashville, TN*

Background: HPV HNC pts are younger and have a higher cure rate than smoking-related pts, and therefore carry treatment toxicities longer. Dose deintensification and conformal RT may result in decreased toxicity. We report the impact of these techniques on patient outcomes in E2399 and E1308 as measured through PROs. **Methods:** Longitudinal data on acute and late toxicities were recorded prospectively at baseline, post-treatment, and at 6, 12, 24 and 30 months in HPV+ pts on E1308 and HIV+/- pts on E2399 using the following measures: *E1308*: FACT-HN, KATZ Index of Independence (ADL), Brief Fatigue Index (BFI), Instrumental Activities of Daily Living (IADL), and the Vanderbilt Head and Neck Symptom Survey Version 2 (VHNSS V2); on *E2399*: FACT-HN. We correlated acute and late toxicities with de-escalation of RT dose (69.3Gy to 54Gy) on E1308, and with IMRT (E1308) vs. conformal RT (E2399). **Results:** 38 pts on E1308 completed 12 mo VHNSS V2; 32 received low dose IMRT and 6 standard dose, and 56 E2399 pts completed 12 mo FACT-HN. Items from the VHNSS V2 showed that difficulty eating solids (40% vs. 89%, $p = 0.011$) and improved nutrition (10% vs 44%, $p = 0.025$) were statistically improved at 12 months by lowering IMRT dose from 69.3Gy to 54Gy. The FACT-HN showed an improvement in eating solids at 12 mo when comparing low dose IMRT vs. 3DRT (65% vs. 33% had no or minimal solid food problems, $p = 0.057$). No other statistically significant reductions in toxicity were noted on any of the other PRO instruments. **Conclusions:** Both FACT-HN and VHNSS V2 demonstrated an improvement in eating solids by reducing IMRT dose. FACT-HN demonstrated that IMRT is associated with an improvement in eating solids when compared to 3DRT. Analyses are exploratory and need to be validated using randomized data.Future studies should stress accurate and complete PRO data. The KATZ, BFI, and IADL were not sensitive to detecting differences in toxicities from IMRT dose reduction on E1308. The VHNSS V2 and FACT-HN instruments corroborated specific toxicities both by RT technique as well as IMRT dose, and will therefore be utilized in future ECOG-ACRIN HNC studies. Clinical trial information: NCT01084083.

6075 Poster Session (Board #63), Mon, 1:15 PM-4:45 PM

Cost-effectiveness of prophylactic antibiotics to prevent pneumonia in patients treated with chemoradiotherapy (CRT) for locally advanced head and neck carcinoma (LAHNC). *First Author: Janneke Ham, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Recently, we reported about a prospective randomized study (PANTAP-study) investigating the effect of prophylactic antibiotics in LAHNC pts treated with CRT. We did not show a reduction in pneumonias, but did find a significant decrease in the number of hospitalizations. Detailed quality of life (QoL) results have been reported elsewhere. Now we present the results of the cost-effectiveness analysis. **Methods:** A multicenter study was performed in LAHNC pts treated with CRT, i.e.cisplatin weekly or 3-weekly combined with radiotherapy for 42 or 49 days. The standard treatment group (STG) received no prophylactic antibiotics; the intervention group (IG) received prophylactic antibiotics, i.e. amoxicillin/clavulanic acid, from day 29 until 14 days after completion of CRT. QoL questionnaires, including EQ-5D, QLQ-C30, EORTC Head&Neck35 and PSSHN, were taken before start of CRT, before start of antibiotics, at the end of CRT and at the end of follow up. Costs of hospitalization, prophylactic antibiotics, pain medication and anti-emetics were taken into account for the cost-effectiveness analysis. **Results:** A total of 94 pts were randomized; 48 pts to the STG and 47 pts to the IG. Between the STG and IG we found a difference per patient in costs of hospitalization of €2076 and €682 ($p = 0.03$), respectively, but not in the costs for pain medication per patient €78 and €46, respectively, ($p = 0.382$). The total costs of hospitalization in combination with prophylactic antibiotics, pain medication and anti-emetics were €2462 and €1037 ($p = 0.046$) in the STG and IG respectively, leading to a difference in total costs per patient of €1425 in favor of the IG. There were no significant differences in QoL between the groups. **Conclusions:** Prophylactic antibiotics during CRT for LAHNC did not reduce the rate of pneumonias, but reduced the number of hospitalizations in the IG, which led to a significant reduction in costs. Given the lack of adverse clinical effects, the same QoL, the cost savings and the impact of costs of hospitalization on health care globally, we recommend the use of prophylactic antibiotics in LAHNC pts receiving CRT. Clinical trial information: NCT01598402.

6076 Poster Session (Board #64), Mon, 1:15 PM-4:45 PM

A personalized approach using hypoxia resolution to guide curative-intent radiation dose-reduction to 30 Gy: A novel de-escalation paradigm for HPV-associated oropharynx cancers (OPC). *First Author: Nadeem Riaz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: We conducted a pilot study using functional imaging to guide reduction in radiation (RT) to 30Gy with concurrent chemotherapy in patients with HPV+ OPC. **Methods:** 19 patients were enrolled prospectively from 7/2015-10/2016. Primary tumors were excised and analyzed for DNA repair foci *ex-vivo*. A pre-RT dynamic ^{18}F-FMISO (fluoromisonidazole) PET was then used to assess tumor hypoxia (defined as > 1.2 tumor to muscle SUV ratio) in cervical lymph nodes. Patients without hypoxia on baseline or repeat scan done 5-10 days after initiation of chemoRT received 30Gy (57% reduction) over 3 weeks to the tumor bed and neck with 2 cycles of concurrent chemotherapy (high-dose cisplatin or carboplatin/5-FU). Patients with persistent hypoxia received the standard dose of 70Gy over 7 weeks with chemo. Neck dissection (ND) was done 4-months post chemoRT. Weekly DWI MRI, ctDNA, whole exome & RNA sequencing were performed. **Results:** 19 patients (11 tonsil, 5 BoT, 3 unknown primaries) were enrolled. Staging: 11 T1, 5 T2, 3 Tx; 5 N1, 3 N2a, 11 N2b; all M0. On pre-RT ^{18}F-FMISO scans, 13 were positive and 6 were negative for hypoxia. Of the 12 intra-treatment ^{18}F-FMISO scans (1 not done due to intermittent illness, this patient received 70Gy), 3 were positive and these patients received 70Gy chemoRT. 15 patients were de-escalated to 30Gy. To date, analysis showed complete pathologic response in 8 of 9 patients (all 15 expected to have ND by April 2017. The one positive case received only 1 cycle of cisplatin. To date, 18 of 19 patients (95%-6 pending ND) remain disease free. Correlative analysis with sequencing, DNA repair foci, ctDNA, and results from pathologic and intra-treatment imaging response will be presented. **Conclusions:** This is the first report of apersonalized approach to a major decrease in RT dosing for definitive treatment of HPV+ oropharyngeal carcinoma guided by patient-specific imaging-based treatment response. De-escalation to 30Gy informed by intra-treatment imaging for hypoxia appears feasible, safe and efficacious. A multi-center trial to validate these pilot results is planned. Clinical trial information: NCT00606294.

6077 Poster Session (Board #65), Mon, 1:15 PM-4:45 PM

Disparities in supportive therapy for head and neck cancer and impact on missed radiation days and weight loss. *First Author: Stephen Ramey, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL*

Background: National guidelines emphasize the importance of speech and swallowing (SS) and nutrition services (NS) for head and neck cancer patients (pts). This study evaluates influences of demographic and treatment factors on receipt of SS and NS at a safety-net hospital (SH) and an adjacent private hospital (PH). It also examines associations between lack of these services and negative outcomes. **Methods:** This retrospective analysis included non-metastatic laryngeal or oropharyngeal cancer pts treated with radiotherapy (RT) at a PH or SH. Univariate (UVA) and multivariable (MVA) analyses utilized linear regression, logistic regression, and zero-inflated Poisson regression. Covariates included race, ethnicity, preferred language, insurance status, immigration status, gender, age, treating hospital, comorbidity score, primary treatment modalities, time to treatment initiation (TTI), and stage. Potential negative outcomes of not receiving SS and/or NS were analyzed only among pts treated with chemoradiation (CRT). **Results:** Of 239 pts (PH = 138 pts; SH = 56 pts), 28.6% of SH pts received SS pre-RT vs 54.1% at the PH ($p < 0.001$). Receipt of pre-RT NS did not differ significantly between SH (14.3%) and PH (19.7%) but was low at both. On MVA, SH care (OR 0.29; $p = 0.029$) and longer TTI (OR 0.99; $p = 0.033$) were associated with decreased pre-RT SS. In contrast, surgery before RT (OR 10.1; $p = 0.002$) and surgery before CRT (OR 10.7; $p = 0.001$) vs RT alone were associated with increased pre-RT SS. No covariates were significantly associated with receipt of NS on MVA. For pts receiving CRT, pre-RT SS was associated with less weight loss during RT (mean difference = 2%; $p = 0.036$). Receiving both pre-RT SS and NS was associated with fewer missed RT days (RR 0.49; $p = 0.004$). Receipt of SS and/or NS were not associated with gastric tube placement, emergency room visits, or non-chemotherapy admission days during or within 90 days of CRT. **Conclusions:** SS was received less often at a SH vs a PH. NS were delivered at a low level at both centers. Lack of supportive services was associated with increased missed RT days and increased weight loss during CRT. Quality metrics to establish supportive care benchmarks may help reduce disparities.

6078 Poster Session (Board #66), Mon, 1:15 PM-4:45 PM

Phase II study: Induction chemotherapy & transoral surgery as definitive tx for locally advanced oropharyngeal squamous cell carcinoma (OPSCC)—A novel approach. *First Author: Robert S. Siegel, George Washington University School of Medicine, Washington, DC*

Background: The standard of care for OPSCC includes chemoradiation (CRT) or surgery with adjuvant radiation (RT). However, RT is associated with significant life long morbidity. We assessed the efficacy of a two-drug induction regimen, followed by transoral robotic assisted surgery (TORS) & neck dissection for locally advanced OPSCC. **Methods:** This is an IRB approved single-arm phase II study for untreated stage III or IVA OPSCC patients (pts) with an ECOG < 2 and GFR > 50 cc. Induction chemotherapy consisted of cisplatin 75 mg/m2 and taxotere 75 mg/m2 every 21 days for 3 cycles. Tumor shrinkage was examined after each cycle. If the primary tumor was $> 80\%$ smaller, pts underwent TORS and neck dissection(s). At post-op visits, flexible laryngoscopy, blood work, and imaging with PET/CT and/or MRI were done. Short and long term toxicity, progression-free survival (PFS) and overall survival (OS), and quality of life (QOL) were evaluated. **Results:** Nineteenpts were treated and 14 are available for analysis. Thirteen were male, 12 were Caucasian, 2 were African-American, and 13 were HPV+. Median age at diagnosis was 57. Tumors involved the tonsil (11 pts) and base of tongue (3 pts). Three pts were stage III, and 11 were stage IVA. Tumor size was reduced on average by 58%, 84% and 92% after the 1st, 2^{nd} and 3^{rd} induction cycles respectively. Pathologic complete remission of primary disease occurred in 11 pts and in 7 pts with cervical lymph node disease. Four pts were given dose-reduced chemo and one pt was changed to carboplatin per protocol because of renal dysfunction. In addition, adverse events included three patients with grade I fatigue, neuropathy or nausea. Pre vs post tx QOL scores were not significantly different. At a mean follow-up (f/u) of 13 months (range 2.5 to 19.7), 13 pts are alive and well. Three pts recurred, and were treated with salvage CRT. One pt died of metastatic disease. **Conclusions:** Cisplatin + Taxotere is an effective induction tx for OPSCC, Induction tx followed by transoral & neck resections without RT is a promising tx model for OPSCC. It appears effective while avoiding adverse effects of RT. Longer f/u is required to assess its true efficacy. Clinical trial information: NCT02760667.

6079 Poster Session (Board #67), Mon, 1:15 PM-4:45 PM

Treatment outcomes of 257 patients with locally advanced nasopharyngeal carcinoma treated with nimotuzumab plus intensity-modulated radiotherapy with or without chemotherapy: A single institution experience. *First Author: Wang Fang Zheng, Zhejiang Cancer Hospital, Hangzhou, China*

Background: To report the long-term outcome and toxicitie of locally advanced nasopharyngeal carcinoma (NPC) treated with nimotuzumab plus intensity- modulated radiotherapy (IMRT) with or without chemotherapy. **Methods:** From October 2009 to March 2014, 257 newly histology-proven, non-metastatic NPC patients were retrospectively enrolled. They are aged 10-76 years. The distribution of disease was stage III in 150 (58.4%), stage IV A in 88 (34.2%), and stage IV B in 19 (7.4%). All the patients received the treatment of nimotuzumab plus IMRT, and 239 cases were used for cisplatin-based chemotherapy. Acute and late radiation-related toxicities were graded according to the Acute and Late Radiation Morbidity Scoring Criteria of Radiation Therapy Oncology Group. The accumulated survival was calculated according to the Kaplan-Meier method. Log-rank test was used to compare the survival difference. Multivariate analysis was performed using Cox's proportional hazard model. **Results:** All patients had completed the combined treatment. With a median follow-up of 48 months (range, 13–94 months), the estimated 3-year and 5-year overall survival rates were 92.6% and 86.2%, respectively. Univariate analysis showed that age, T stage, clinical stage and neoadjvant chemotherapy were related with OS. Multivariate analysis indicated that age and clinical stage were independent prognosticators. The median cycle for nimotuzumab addition was 12 weeks. The incidence of grade 3–4 acute mucositis and leukocytopenia were 10.9% and 9.3%, respectively, with no cases of skin rash and infusion reaction. Xerostomia was the most common late complication, and the degree of dry mouth in most survivors was mild-to-moderate at the last follow-up time. **Conclusions:** Nimotuzumab plus IMRT with or without chemotherapy showed promising outcomes in terms of loco-regional control and survival, without increasing the incidence of radiation-related toxicities for patients.

6080 Poster Session (Board #68), Mon, 1:15 PM-4:45 PM

A phase 1 trial of NBTXR3 nanoparticles activated by intensity-modulated radiation therapy (IMRT) in the treatment of advanced-stage head and neck squamous cell carcinoma (HNSCC). *First Author: Christophe Le Tourneau, Institut Curie, Paris, France*

Background: Functionalized hafnium oxide nanoparticles (NBTXR3) have been developed as selective radioenhancers, which may represent a breakthrough approach for the local treatment of solid tumors. The high electron density of the nanoparticles, when exposed to radiotherapy (RT), allow the absorption/deposition of a high radiation dose within the tumor cells, to physically kill the cells and possibly improve outcome. A phase I trial was implemented for the treatment of locally advanced HNSCC in patients (pts) older than 65 years who cannot receive cisplatin. **Methods:** Pts received a single intratumor (IT) injection of NBTXR3, volume dose levels escalated at 5%, 10%, 15% and 22% of baseline tumor volume, followed by RT (IMRT, 70Gy/ 35 fractions / 7 weeks). Primary endpoints included feasibility of the IT implantation and safety. Secondary endpoints included IT residency of NBTXR3 using CT scan and RECIST 1.1 response. **Results:** Enrollment was completed for volume 5%, 10%, and 15% (11 pts) and 1 patient at volume dose level 22%. Feasibility of the IT injection was confirmed. The treatment was easily administered, was safe with no SAE, or early DLT, which allowed the pts for completion of the planned RT schedule. Adverse events related to the injection procedure included grade 1-2 injection pain (1 pt), and tumor hemorrhage (1 pt). Results demonstrated that a single injection of NBTXR3 provides adequate bioavailability of NBTXR3 IT over seven weeks of RT. No leakage of NBTXR3 to the adjoining healthy tissues was observed. Preliminary results of antitumor activity according to RECIST 1.1 are presented below: 11 evaluable pts, 10 showed complete or partial response (RECIST 1.1) including, 1/5 complete response at dose levels $\leq 10\%$ and 3/6 complete responses at dose levels $> 10\%$ Follow up results with duration of response and tolerance will be disclosed. **Conclusions:** Injection of NBTXR3 was safe and well tolerated. All pts received the planned RT. Clinical trial information: NCT01946867.

6081 Poster Session (Board #69), Mon, 1:15 PM-4:45 PM

Phase Ib study of cetuximab + BYL719 + IMRT in stage III-IVB head and neck squamous cell carcinoma (HNSCC). *First Author: Lara Dunn, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Activation of the PI3K/mTOR signaling pathway is common in HNSCC. PI3K inhibitors have been shown to enhance radiosensitivity. BYL719 is an α-specific PI3K inhibitor that is synergistic and efficacious when combined with cetuximab, an FDA-approved radiosensitizing agent in HNSCC. This study evaluates the addition of BYL719 to cetuximab and radiation in the treatment of locally advanced HNSCC. **Methods:** This is a single-institution, phase I study. Patients with Stage III-IVB HNSCC received cetuximab 400 mg/m^2 IV loading dose prior to intensity modulated radiation therapy (IMRT), followed by 250 mg/m^2 weekly infusions during IMRT. BYL719 was given orally during IMRT in 3 dose levels (DLs): 1) 200 mg, 2) 250 mg, and 3) 300 mg per day in a standard 3 + 3 dose escalation design. **Results:** 11 patients are evaluable; median age-60 years (36-73); Stage III-1, IVA-9, IVB-1; oropharynx primary-9, unknown primary-2; HPV-positive -10. 8 patients completed treatment. 3 patients were treated on DL 1 and 2 without a dose limiting toxicity (DLT). Both patients on DL 3 experienced a DLT of grade 3 mucositis. Related adverse events (AEs) of any grade experienced by all 8 patients include: mucositis, weight loss, and hyperglycemia. Related grade 3 and 4 AEs in at least 2 patients include: mucositis (4), dysphagia (4), and decreased lymphocyte count (2). An additional 3 patients have been enrolled onto DL 2 and are undergoing treatment. All other patients had a complete response (CR) on post-treatment PET (from 6/2015 - 9/2016) and remain free of disease. Of 6 patients with mutational analysis, 1 had an activating *PIK3CA* mutation associated with a rapid response on serial intra-treatment MRIs. **Conclusions:** BYL719 administered at DLs 200 mg or 250 mg oral daily with cetuximab and IMRT resulted in expected AEs of radiation-based treatment with cetuximab and tolerable class-related AEs of PI3K inhibitors. BYL719 300 mg oral daily exceeds the maximum tolerated dose; the phase II recommended dose is pending completion of expansion of DL 2. All patients who completed treatment had a CR. Further evaluation of the addition of BYL719 to the platinum-sparing regimen of cetuximab + IMRT in the treatment of locally advanced HNSCC is warranted. Clinical trial information: NCT02282371.

6082 Poster Session (Board #70), Mon, 1:15 PM-4:45 PM

Institutional treatment volume and outcomes in salivary gland cancer. *First Author: Conor Ernst Steuer, Winship Cancer Institute, Atlanta, GA*

Background: Salivary gland cancer (SGC) is a rare malignancy and has been understudied in the literature. Given the rarity of SGC, we sought to compare outcomes of SGC within high volume (HV) and low volume (LV) centers, utilizing the National Cancer Database (NCDB). **Methods:** The NCDB was queried from 2004 to 2014 for SGC using ICD-O-3 codes for the 4 most common histologies: (mucoepidermoid carcinoma (ME), adenoid cystic carcinoma (AdCC), acinic cell carcinoma(ACC), and adenocarcinoma NOS (A)) for consistency. The number of cases treated at each facility was calculated, and the threshold for distinguishing high volume vs. low volume was determined using the 80th percentile of the number of cases treated per facility. Patient characteristics were compared using chi-squared tests and ANOVA. Overall survival was estimated using the Kaplan-Meier method, and was compared using log-rank tests. Statistical analyses were performed using SAS 9.4. **Results:** There were 31,189 SG patients overall; 16,373 were either ME, AdCC, ACC, or A and were included in the analysis. There were 6534 patients treated in LV (41%) and 9839 in HV (59%). HV centers were more likely to be academic and integrated network cancer programs ($p < .001$). The median age for LV vs. HV was 61y vs. 58y ($p < .001$), 49% vs. 47% male ($p = .007$), and 84% vs. 80% White ($p < .001$), respectively. Patients presented with slightly more advanced disease at HV, with 24.4% having stage 3-4 disease, vs 23% in LV ($p = .004$). The majority of patients underwent surgical resection (57% LV vs. 64% HV). HV had more negative margins (59% vs 55%, $p < .001$), more neck dissections (72% vs. 64%, $p < .001$), and longer hospital stays (mean 2.21d vs 1.55d, $p < .001$). More patients in LV received radiation than HV (55% vs. 52%, $p < .001$), but there was no difference in chemotherapy use ($p = 0.650$). Patients had better survival (m1 disease excluded) in HV as compared to LV (5-year OS HV 77.4% vs LV 75.5%, HR 0.89, $p = 0.002$). **Conclusions:** Our results indicate that survival of SGC is affected by institutional treatment volume and the significant differences in treatment at LV vs. HV institutions urges for the need of better standardization of care.

6083 Poster Session (Board #71), Mon, 1:15 PM-4:45 PM

RNAseq analysis of the sorafenib phase III DECISION trial in differentiated thyroid cancer (DTC): Correlation with clinical outcome. *First Author: Jaume Capdevila, Vall d'Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain*

Background: In DECISION, sorafenib significantly impacted progression-free survival (PFS) and response rate (RR) in radioactive-iodine refractory DTC. The aim of this biomarker study was to identify RNA expression profiles related with PFS, overall survival (OS) and RR and to describe the expression profiles of DTC histologies. **Methods:** Of the 417 patients in the trial, 247 had sufficient formalin fixed paraffin embedded archival tumor material for RNAseq. We generated on average 77 million paired-end reads for each sample on HiSeq2000 (Illumina). RNAseq reads were mapped against the human reference genome (GRCh38) with STAR (v2.5.1b) using ENCODE parameters. 125 samples had sufficient quality to be included in the analysis. **Results:** The analysis subset included 68 sorafenib and 57 placebo patients (PFS 10.3 vs 7.4 months, HR: 0.62 CI 95% 0.38-0.99, $p = 0.046$). Unsupervised clustering using the 100 most variable genes identified 3 groups: BRAF-like (included most of the BRAF-mutated tumors), RAS-like (included most of the RAS mutated tumors) and non-BRAF-non-RAS-like group (included most wild-type tumors). These groups, based on the mutational profile, can be correlated with tumor type: the papillary BRAF-mutant, the follicular wild-type, and a third group with papillary, follicular and poorly differentiated with predominant RAS mutations. A Student t-test comparing papillary and follicular histologies revealed a signature of 283 genes with significantly different expression that, within the papillary tumors, identifies a subset with an expression profile more similar to follicular. No RNA signatures correlating with benefit from sorafenib were identified. **Conclusions:** While papillary and follicular thyroid cancers have significantly different RNA expression profiles, a subset of papillary has been identified with an expression profile more similar to follicular. In addition, a unified RAS-like expression profile spans subsets of papillary, follicular, and poorly differentiated thyroid cancers, suggesting that tumor biology can be similar across histologies. Clinical trial information: NCT00984282.

6084 Poster Session (Board #72), Mon, 1:15 PM-4:45 PM

Interim baseline characteristics from RIFTOS MKI, a global non-interventional study assessing the use of multikinase inhibitors (MKIs) in the treatment of patients with asymptomatic radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC). *First Author: Marcia S. Brose, Abramson Cancer Center, Philadelphia, PA*

Background: RIFTOS MKI was designed to compare the time to symptomatic progression from study entry in patients with RAI-R DTC for whom there was a decision to treat or not to treat with an MKI in the real-life setting. Here, we report interim baseline characteristics for the first 274 patients enrolled in the study. **Methods:** RIFTOS MKI is a non-interventional study enrolling patients with asymptomatic RAI-R DTC. The decision to initiate MKIs at study entry was at the discretion of the treating physician. Final analysis will be performed once 700 patients have been enrolled and the last enrolled patient has been followed for 24 months. **Results:** Of 274 patients, the median duration of observation was 169.5 days. Patients have been enrolled from USA (n = 74), Japan (n = 55), Europe (n = 80), and rest of the world (n = 65); 54% were female and the median age was 68 years. Most patients had an ECOG performance status of 0 or 1 (97%) and distant metastases (81%). The most frequent histology was papillary (73%). The median time from initial diagnosis of DTC to study entry was 7 years. RAI refractoriness was mainly due to lack of RAI uptake (60%), primarily in Japan (80%). Japan also had the shortest median time from RAI classification to initial visit (2 months) vs other regions, and the average dose per RAI treatment and median cumulative activity of RAI were lower in Japanese patients (3.4 and 3.7 GBq, respectively) (Table). **Conclusions:** The RIFTOS MKI study is the largest non-interventional study in RAI-R DTC. The regional differences in treatment history observed in the RIFTOS MKI study reflect differences in accessibility and treatment practice. The study is ongoing. Clinical trial information: NCT02303444.

	USA	Japan	Europe	Rest of the world	Total
	n = 67	n = 34	n = 73	n = 65	n = 239
Median cumulative activity of RAI, GBq (mCi)	7.8 (210.8)	3.7 (100)	13.0 (351.4)	13.3 (359.5)	9.3 (248.6)
Average activity of RAI, GBq (mCi)	5.5 (148.6)	3.4 (91.9)	4.6 (124.3)	4.7 (127.0)	4.6 (124.3)
	n = 68	n = 55	n = 80	n = 65	n = 268
Median time from RAI classification to initial visit, months	16.40	2.00	25.10	4.30	10.75

6085 Poster Session (Board #73), Mon, 1:15 PM-4:45 PM

Combination of dabrafenib (DAB). *First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: BRAFV600E mutations (BRAFm) are the most common mutations in thyroid cancer. BRAF inhibitors are active in BRAFm melanoma, but there is less activity noted in BRAFm thyroid cancer. Preclinically, BRAF inhibitors inhibit BRAFm thyroid cancers only transiently due to activation of HER2/HER3, driven by a neuregulin-dependent autocrine loop. The addition of LAP, a HER2/HER3 kinase inhibitor, sensitizes the cell to growth suppression by BRAF inhibitors (Cancer Discov 5(3):520, 2013). A phase I study evaluating the combination of DAB, a BRAF inhibitor, and LAP was initiated to evaluate the safety and pharmacodynamic changes the combination. **Methods:** Eligibility included thyroid cancers with the presence of a BRAFV600E mutation. Any prior treatment was allowed. All patients received DAB 150 mg bid starting 2 weeks prior to LAP. Doses of daily lapatinib were escalated in a standard 3+3 design at (1) 750 mg; (2) 1250 mg; (3) 1500 mg. Toxicities, including Dose Limiting Toxicities (DLT), were noted only after both drugs were started. Patients (pts) removed before the start of LAP were not included in the analysis. Biopsies were done at baseline, after the start of DAB, and after the start of both DAB and LAP. Responses were defined using RECIST 1.1. **Results:** 15 evaluable pts were enrolled on the phase I portion of the study. Gender – 10/15 (67%) male; median age – 63 years; histology – differentiated thyroid cancer (DTC) 13 (87%), anaplastic thyroid cancer (ATC) 2 (13%); brain metastases – 4/15 (27%); prior tyrosine kinase inhibitor – 9/15 (54%). There was one DLT - Grade 5 event unlikely related to drugs in a pt with ATC. Grade 4 toxicities – 0. Grade 3 toxicities –lymphocytes (1). The partial response rate is 60%. The response rate in the DTC group is 69% (0% in ATC). One other pt came off treatment due to withdrawal of consent. Median progression-free survival is 15 months (range, 2-34+ months). Median follow up is 15 months. Translational studies are pending. **Conclusions:** The combination of DAB 150 mg bid and LAP 1500 mg daily was safe and well-tolerated. Furthermore, significant activity was noted, especially at the top dose level. Further investigation with this regimen is warranted. Clinical trial information: NCT01947023.

Dose level	#	DLT	Response rate	# with ATC
1-LAP 750mg	6	1	50%	1
2-LAP 1250mg	3	0	33%	1
3-LAP 1500mg	6	0	83%	0

6086 Poster Session (Board #74), Mon, 1:15 PM-4:45 PM

Targeted therapy for advanced salivary cancer with HER2 or hedgehog alterations: Interim data from MyPathway. *First Author: Razelle Kurzrock, Moores Cancer Center, University of California San Diego School of Medicine, San Diego, CA*

Background: Salivary gland cancers comprise <1% of cancers. Advanced cases have a 40% 5-year survival rate. Due to their rarity, no standard treatment guidelines exist. However, salivary duct carcinomas have morphological and gene expression profiles similar to breast cancers, and 20–40% of this subset have HER2 alterations. MyPathway (NCT02091141) is an ongoing, phase 2, multi-basket study evaluating the efficacy of targeted treatments in nonindicated tumor types with alterations in the HER2, BRAF, Hedgehog (Hh), or EGFR pathways. We present interim data for patients with salivary cancer. **Methods:** Patients had advanced salivary cancer with HER2 (amplification, overexpression, and/or mutation) or Hh (SMO or PTCH-1) alterations, locally assessed by gene sequencing, FISH, or IHC, as applicable. Patients received standard doses of pertuzumab + trastuzumab or vismodegib, respectively, until disease progression or unacceptable toxicity. The primary endpoint is investigator-assessed objective response rate (ORR) by RECIST v1.1. **Results:** As of Nov 30, 2016, 8 patients had been treated for salivary cancer, all carcinomas (7 had HER2 alterations; 1 had an Hh alteration). One HER2 patient without a post-baseline tumor assessment by data cut-off was not evaluable for efficacy. Characteristics and outcomes are shown (Table). Of 6 patients with a complete response (CR) or partial response (PR), 5 patients were still receiving study treatment by the data cut-off, with a median time on treatment of 4.6 months (range 1.4–12.5). There were no new safety signals. **Conclusions:** Six of 7 patients (86%) with advanced salivary carcinoma achieved CR or PR by targeting HER2 (n=5) or Hh (n=1) alterations. These promising results merit study of these treatments in additional patients. Accrual to MyPathway is ongoing. Clinical trial information: NCT02091141.

	HER2 (n=7)[a]	Hh (n=1)[b]
Median age, years	59 (range 47–80)	65
Male, n	6 (86%)	1
Prior lines of treatment, median	1 (range 0–3)	0
Objective response[c], n	5 (1 CR, 4 PR) ORR: 83% (95% CI 36–100)[d]	1 (PR)

[a]Six patients had HER2 amplification/overexpression (1 patient with PR also had HER2 mutations [D769H/L755F]). The unevaluable patient had a HER2 mutation (S310F); [b]PTCH-1 (Q400*); [c]CR + PR; [d]In 6 evaluable patients.

6087 Poster Session (Board #75), Mon, 1:15 PM-4:45 PM

***NTRK1-3* point mutations in poor prognosis thyroid cancers.** *First Author: Nicole M. Iniguez-Ariza, Mayo Clinic, Rochester, MN*

Background: *NTRK1-3* fusions, identified in pediatric radiation-associated thyroid cancers, are low frequency oncogenic drivers that can trigger constitutive activation of TrK1-3 tyrosine kinase domains with responsively heightened downstream signaling through RAS-MAPK, PI3K-AKT, and/or PLCγ-PKC. *NTRK* point mutations are rare and of largely uninvestigated oncogenic potential, but some appear oncogenic. **Methods:** Advanced thyroid cancer (TC) patients (pts) requiring systemic therapy at Mayo Clinic sites underwent tumor genetic interrogation using Foundation One analyses with the goal of informing salvage therapeutic strategies. In this IRB-approved study, data from pts with TCs bearing *NTRK* point mutations were retrospectively analyzed, as this occurrence was unexpected but potentially of prognostic and/or therapeutic relevance. **Results:** Five of 55 pts (9%) with advanced TCs subject to Foundation One tumor interrogation had *NTRK1-3* point mutations (allele frequency, AF, 15-49%); none had fusions. All 5 tumors had microsatellite stability; 4/5 had low tumor mutation burden (2-5 mutations/megabase). *NTRK* mutations in 3 anaplastic TC (ATC) pts (15% prevalence) were: *NTRK3* I749M (AF 15%; overall survival, OS, 15 mos), *NTRK1* R744H (AF not available; OS 9.5 mos), and *NTRK1* R583H (AF 20.1%; OS > 4.9 mos); *NTRK2* S167Y (AF 49%; OS > 51 mos) or *NTRK1* R6W (AF 42%; OS > 60 mos) were found in one papillary (PTC) and one Hürthle cell (HCC) TC pt respectively (summary table below). **Conclusions:** *NTRK* point mutations, but not fusions, were unexpectedly identified in 9% of assessed advanced TCs - but remarkably in 15% of ATCs. Mutated NTRKs, along with oncogenic p53 and TERT, may contribute to TC progression, especially in ATC, consequent to downstream activation of MAPK and PI3K-AKT pathways. We posit that *NTRK* point mutations may have therapeutic implications for treatment of refractory disease.

Male 67	ATC	*NTRK3* I749M	*TERT* promoter -124C > T *TP53* S215N *NF1* T1052fs*8 *RB1* Q702* *EP300* W1115* *KEAP1* Q402*
Female 63	ATC	*NTRK1* R744H	*TERT* Promoter-146C > T TP53 E285K
Male 60	ATC	*NTRK1* R583H	*TERT* promoter -124C > T *TP53* H214fs*2, P278T *KEAP1* G333S
Female 66	PTC	*NTRK2* S167Y	*BRAF* V600E
Female 52	HCC	*NTRK1* R6W	*TERT* promoter 124C > T *KRAS* G12A

6088 Poster Session (Board #76), Mon, 1:15 PM-4:45 PM

Comprehensive genomic profiling of parathyroid carcinoma. *First Author: Hyunseok Kang, The Sidney Kimmel Comprehensive Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore, MD*

Background: Parathyroid carcinoma (PC) is a rare endocrine malignancy, which can cause life-threatening hypercalcemia. Initial surgery is often noncurative, and adjunctive radiotherapy and previous chemotherapies have not been shown to be effective. Previous studies identified recurring mutations in *CDC73* and *PRUNE2*in a limited number of patients. We queried whether comprehensive genomic profiling (CGP) would have potential to discover novel targets of therapy. **Methods:** DNA was extracted from 40 microns of FFPE sections from 13 consecutive cases of relapsed/metastatic PC. CGP was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 672x for up to 315 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. Genomic alterations (GA) included base substitutions (SUB), INDELs, copy number alterations (CNA) and fusions/rearrangements. Clinically relevant GA (CRGA) were defined as GA linked to drugs on the market or under evaluation in mechanism driven clinical trials. **Results:** Total of 13 specimens were identified from 7 male and 6 female patients. The mean age of the patients in this study was 54 years (range 38 to 76 years). All (100%) cases were Stage IV at the time of CGP. Tumor mutation burden was generally low - median mutation load per mega base was 1.8. There were 58 total GA (4.5 GA/sample) and 10 CRGA (0.8 CRGA/sample). The most frequent GA were non-CRGA mutations in *TP53* (31%) and *CDC73* (31%). *MEN1* mutations were identified in 23% of cases. Frequent alterations in genes controlling cell cycle progression at G1 including *CDKN1B*, *CDKN2A*, *CDKN2B* and *CDKN2C* were identified (30%). The most frequent CRGA involved *PTEN* (23%), NF1 (23%) and *KDR* (15%). No alterations in *BRAF* or *RET*were identified. A patient with KDR mutation treated with cabozantinib experienced > 50% drop in PTH level and radiographic partial response in 3 months. **Conclusions:** CGP identified previously unreported TP53 mutations in PCs and potentially actionable genomic alterations including *PTEN*, *NF1* and *KDR*. Clinical benefit and response observed in a patient treated with VEGFR targeted therapy suggest that patients with this rare tumor may be candidates for targeted therapies.

6089 Poster Session (Board #77), Mon, 1:15 PM-4:45 PM

Association of activating NOTCH1 mutations in adenoid cystic carcinoma with shorter progression-free survival to systemic therapy. *First Author: Renata Ferrarotto, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We previously reported that activating *NOTCH1* mutations occurs in approximately 20% of ACCs and drive a phenotype with solid histology, liver and bone metastases, poor prognosis, and potential responsiveness to Notch1 inhibitors; however the impact of *NOTCH1*mutations on responsiveness to systemic therapy in ACC is unknown. The aim of this study was to evaluate the ORR and median PFS (mPFS) to systemic therapy in patients with metastatic ACC according to their Notch1 status. **Methods:** We identified 20 ACC patients with measurable disease that underwent treatment at MDACC and had tumor molecular profile. A radiologist blinded to the patient's *NOTCH1*status performed review of all images. Measurement of target lesions was captured by a quantitative imaging analysis tool for ORR assessment by RECIST 1.1. PFS was estimated by Kaplan-Meier method. Comparisons of PFS between groups were performed using log-rank test. P≤0.05 was considered statistically significant. **Results:** Out of 20 patients, 4 (20%) were *NOTCH1* mutant. Notch1 pathway activation status by immunohistochemistry (NICD) was available for 15 patients, 10 were positive. The median number of therapy lines was 2 (range 1-6). Best ORR among 49 treatment plans across all lines of systemic therapy including chemotherapy (15), anti-EGFR (10), anti-VEGFR (11), and others (13) was PR in 2 (4%), SD in 29 (59%), and PD in 18 (37%). During first line treatment, patients with *NOTCH1* mutations had significantly shorter mPFS compared to *NOTCH1* wild-type (2.97 vs. 6.92 months, P = 0.02). The PFS rate at 3 months was 25% for *NOTCH1*-mutants vs. 81% for wild-type. A trend towards shorter PFS was seen in NICD positive vs. negative (3.58 vs. 6.74 months, P = 0.2). **Conclusions:** *NOTCH1* mutations in ACC are associated with shorter PFS during first-line treatment. Validation of these findings is warranted in larger patient cohorts.

TPS6090 **Poster Session (Board #78a), Mon, 1:15 PM-4:45 PM**

KEYNOTE-412: Pembrolizumab (pembro) in combination with chemoradiation versus chemoradiation alone in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). *First Author: Jean-Pascal H. Machiels, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

Background: Approximately half of patients (pts) with HNSCC are diagnosed with locally advanced disease and treated with surgery or concomitant chemoradiotherapy (CRT) with cisplatin. Unfortunately, disease recurs in 40% to 60% of patients. The PD-l inhibitor pembro is approved for recurrent/metastatic HNSCC. CRT has immunomodulatory effects; preclinical data suggest that efficacy can be improved by adding pembro. The phase 3 KEYNOTE-412 trial (NCT03040999) will explore if CRT + pembro can improve outcomes of pts with LA-HNSCC. **Methods:** Adult pts with newly diagnosed, pathologically proven, treatment-naive LA-HNSCC will be enrolled. Study population will include p16-negative HNSCC (any T3-T4 or any N2a-N3 [AJCC 7th edition]) and p16-positive oropharyngeal cancer (any T4 or any N3). Other eligibility criteria: measurable disease per RECIST v1.1 by blinded independent central review (BICR), provision of tumor sample for biomarker analyses, ECOG PS 0 or 1, and eligible for definitive CRT but not considered for primary surgery. Pts will be randomly assigned 1:1 to receive either pembro 200 mg every 3 weeks (Q3W) plus CRT, which includes radiotherapy (RT; accelerated [70 Gy, six 2 Gy fractions/wk] or standard [70 Gy, five 2 Gy fractions/week] fractionation) plus cisplatin 100 mg/m^2 Q3W for 3 cycles only, or placebo Q3W plus CRT. Pts will be stratified by RT regimen, tumor site/p16 status, and disease stage. Treatment will continue until centrally confirmed disease progression, unacceptable AEs, decision to withdraw by pt or investigator, or completion of 17 doses of pembro/placebo. Disease status will be evaluated by CT or MRI 12 weeks after end of CRT, every 4 months during the next 2 years, and then every 6 months during years 3-5. Pts will be evaluated for neck dissection at 12 weeks after CRT. AEs will be monitored and graded using CTCAE v4.0 throughout the trial and for 30 days (90 days for serious AEs) after end of treatment. Primary efficacy end point is event-free survival per RECIST v1.1 by BICR. Key secondary end points: overall survival, quality of life, and safety and tolerability of pembro. Approximately 780 pts will be enrolled. Clinical trial information: NCT03040999.

TPS6091 **Poster Session (Board #78b), Mon, 1:15 PM-4:45 PM**

Phase III randomised controlled trial (RCT) comparing alternative regimens for escalating treatment of intermediate and high-risk oropharyngeal cancer (CompARE). *First Author: Hisham Mohamed Mehanna, University of Birmingham, Birmingham, United Kingdom*

Background: Patients with intermediate and high-risk oropharyngeal cancer (OPC) have poorer response to standard treatment and poorer overall survival compared to low-risk OPC. The CompARE trial is designed to test alternative approaches to intensification of treatment for these patients to improve survival. **Methods:** CompARE is a pragmatic phase III open-label multicenter RCT with an adaptive multi-arm multi-stage design. Eligible OPC patients include those with; HPV negative, T1-T4, N1-N3 or T3-4, N0 or HPV positive current smokers (or $\geq$ 10 pack years previous smoking history) with T1-T4, N2b-N3. The primary outcome measure is overall survival. Secondary outcome measures include quality of life, toxicity, swallowing outcomes, feeding tube incidence, surgical complications and cost-effectiveness. The trial is powered to detect a hazard ratio of 0.69 (an improvement of 10% in OS at 3-years) requiring 128 control events. It is estimated that the study will take 6.5 years to recruit sufficient patients to experience the number of events needed. Planned interim futility analyses using event-free survival (EFS) will be performed when 70 and 114 control EFS events have occurred. Current treatment arms are; (1) control: standard treatment of 3-weekly cisplatin 100mg/m^2 or weekly 40mg/m^2 with Intensity Modulated Radiotherapy (IMRT) using 70Gy in 35F +/- neck dissection determined by clinical and radiological assessment 3-months post treatment. (3) IMRT 64Gy in 25F + cisplatin 100mg/m^2 day 1 of week 1 and week 5 or weekly 40mg/m^2+/- neck dissection as per standard treatment. (4) Resection of primary + selective neck dissection followed by standard treatment. (5) One cycle of induction durvalumab 1500mg followed by standard treatment then durvalumab 1500mg every four weeks for a total of 6 months. Recruitment to arm (2) involving induction chemotherapy from the original protocol is suspended. Since July 2015, 42 patients have been randomised with 16 sites open to recruitment. The Data Monitoring Committee last reviewed progress and conduct of the trial in September 2016 and recommended continuation. ISRCTN Number: 41478539, CRUK CRUK/13/026 Clinical trial information: 41478539.

TPS6092 **Poster Session (Board #79a), Mon, 1:15 PM-4:45 PM**

An open-label, single-arm, multi-institutional phase II trial of avelumab for recurrent, metastatic nasopharyngeal carcinoma. *First Author: Assuntina Gesualda Sacco, University of California San Diego Moores Cancer Center, La Jolla, CA*

Background: The majority of patients with nasopharyngeal carcinoma (NPC) present with locally advanced disease, with a predilection for early systemic dissemination. For patients who develop recurrent and/or metastatic (R/M) NPC, survival is poor. Following first-line platinum-based regimens, there is no well-defined paradigm for subsequent therapies. Inhibition of PD-L1 with Avelumab is an attractive strategy because Epstein-Barr virus (EBV), the primary causative agent in NPC pathogenesis, universally upregulates PD-L1 expression; proposed mechanisms of upregulation include immune resistance via innate (EBV-induced latent membrane protein-1) and adaptive (Interferon-gamma) mechanisms; increased PD-L1 expression is an independent poor prognostic factor for disease-free survival. **Methods:** Patients with histologically/cytologically confirmed, EBV-related NPC not amenable to curative intent therapy who received $\geq$1 prior line of systemic therapy for R/M disease are eligible. Patients must be at least 18 years old, ECOG 0-2, willing to undergo tumor biopsy, have adequate organ and marrow function, and no prior therapy with PD-1/PD-L1 inhibitors. 39 patients will be enrolled across 6 sites. Patients will receive Avelumab 10 mg/kg IV on days 1 and 15 of each 28-day cycle. Treatment will continue until disease progression, unacceptable toxicity, investigator/patient decision. A newly obtained tumor specimen is required at enrollment; optional biopsy at time of progression. EBV plasma DNA titers will be evaluated at baseline, during treatment and at progression, using an EBV BamHI-W DNA PCR. Blood samples at baseline and 12 weeks after treatment initiation will be obtained for correlatives. Primary endpoint is overall response rate (ORR; complete and partial responses) at 6 months per RECIST. A two-stage design will reject H_0 (ORR 15%) if the observed ORR is $\geq$30%, α 0.1, β 0.8, required sample size n = 39. Secondary endpoints include duration of response, progression-free and overall survival. Correlative analyses will evaluate PD-L1 expression, T and B-cell subsets, frequency and clonality. The study has accrued 2 of planned 39 patients. NCT02875613. Clinical trial information: NCT02875613.

TPS6093 **Poster Session (Board #79b), Mon, 1:15 PM-4:45 PM**

JAVELIN head and neck 100: A phase 3 trial of avelumab in combination with chemoradiotherapy (CRT) vs CRT for 1st-line treatment of locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). *First Author: Nancy Y. Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cisplatin + radiotherapy is a standard-of-care treatment for patients (pts) with LA SCCHN. Combining avelumab (fully human IgG1 anti–PD-L1 antibody) and CRT may synergistically activate multiple immune-mediated mechanisms to effect a robust and durable antitumor response and improve long-term disease control. **Methods:** JAVELIN Head and Neck 100 (NCT02952586) is a global, multicenter, randomized, double-blind, phase 3 trial of avelumab + cisplatin-based CRT vs placebo + CRT as 1st-line treatment for pts with LA SCCHN. The primary objective is to demonstrate superiority of avelumab + CRT in prolonging progression-free survival (PFS) vs CRT alone. Eligible pts have LA SCCHN of the oral cavity, oropharynx, larynx, or hypopharynx; HPV− or non-oropharyngeal HPV+ disease of stage III, IVa, or IVb; or HPV+ oropharyngeal disease T4, N2c, or N3. Pts must be candidates for cisplatin-based CRT. Other eligibility criteria include ECOG PS $\leq$1 and no prior systemic treatment for advanced disease. Approximately 640 pts will be randomized 1:1 to receive avelumab 10 mg/kg (1-hour IV) + CRT (intensity-modulated RT [70 Gy/35 fractions] + cisplatin 100 mg/m^2 [x3]) or placebo + CRT. There will be 3 treatment phases: lead-in (single dose of avelumab or placebo), CRT (concurrent avelumab or placebo + CRT for 7 weeks), and maintenance (avelumab or placebo Q2W for 12 months). The rationale for this design is to induce an immune response during lead-in and CRT phases, followed by maintenance treatment to prolong and support immune memory development. The primary endpoint is PFS per modified RECIST v1.1. Secondary efficacy endpoints include overall survival, objective response, locoregional failure, distant metastatic failure, and duration of response. Other endpoints include safety, pharmacokinetics, immunogenicity, pt-reported outcomes, and biomarker assessments. Treatment will continue for 12 months following initiation of the maintenance phase or until progressive disease, unacceptable toxicity, or any other protocol-defined criterion for withdrawal occurs. Enrollment in this phase 3 trial began in November 2016. Clinical trial information: NCT02952586.

TPS6094 **Poster Session (Board #80a), Mon, 1:15 PM-4:45 PM**

Anti-PD-L1 durvalumab combined with cetuximab and radiotherapy in locally advanced squamous cell carcinoma of the head and neck: A phase II study. *First Author: Pierluigi Bonomo, University of Florence, Florence, Italy*

Background: Head and neck squamous cell carcinoma (HNSCC) is characterized by prominent immune escape mechanisms. Potentially, the blockade of immune check points such as the PD-1/PD-L1 axis may stimulate the host T-cell activation against tumor cells and favor the FcγRIIIa-mediated, Cetuximab (CTX) induced antibody dependent cellular cytoxicity (ADCC). Durvalumab (DUR) is a humanized monoclonal IgG1, anti-PD-L1 antibody with promising activity in recurrent/metastatic HNSCC (NCT01693562). The aim of our study is to test the hypothesis that a restored ability of the host immune system via blockade of the PD1/PD-L1 axis through DUR may enhance the antitumor activity of both CTX and radiotherapy (RT) in locally advanced HNSCC, a setting with unmet needs for effective treatment options. **Methods:** In this open-label, multi-center, single-arm, phase II study, enrolled patients will receive RT (69.9 Gy/2.12 Gy fx in 33 fractions over 7 weeks) with concurrent CTX (400 mg/m^2 1 week before RT start followed by 250 mg/m^2 q1w) and DUR (1500 mg q4w starting from RT-CTX week 1) followed by adjuvant DUR (to a maximum of 6 months after completion of RT-CTX). Primary endpoint of the study is 2-year progression-free survival (PFS). Assuming a 2-year PFS of 66% based on historical data from RTOG study 0129, the experimental regimen is hypothesized to yield a 12% absolute increase at 2 years, corresponding to a hazard ratio of 0.6 ($\alpha = 0.1$, power is 0.80 when the 2-year PFS is 78%). The required sample size with this design is 69 patients. A safety run-in is planned after the enrollment of first 12, 24 and 36 patients. Patients affected by high-risk ($>$ N2a or $>$ T3, any N) larynx, hypopharynx and HPV negative oropharynx or HPV-positive oropharynx ($>$ N2b, $>$ 10 pack/years) will be eligible. To avoid potential RT-induced chronic loco-regional immunosuppression, protocol-indications will be undertaken to restrict target volumes to sites of gross disease and subclinical high risk lymph node basins excluding areas deemed at very low risk of disease spread. For this purpose, dose-painting intensity modulated radiotherapy (IMRT) is mandatory for this study. Clinical trial information: 2016-004668-20.

TPS6095 **Poster Session (Board #80b), Mon, 1:15 PM-4:45 PM**

A randomized, double-blind phase II study of pembrolizumab versus placebo in patients with head and neck cancers at high risk for recurrence or low-volume residual disease: The PATHWay Study. *First Author: Joshua Bauml, University of Pennsylvania, Philadelphia, PA*

Background: Head and neck squamous cell carcinoma (HNSCC) is a major medical problem worldwide. While some patients may be cured with a combination of surgery, radiation, and systemic therapies, a significant percentage of patients will have recurrent and incurable disease. Despite our epidemiologic understanding of which patients are likely to recur, there are no consolidative therapies that have been shown to improve outcomes in this high-risk population. Pembrolizumab is a PD-1 inhibitor that has shown significant single agent activity in recurrent/metastatic HNSCC after treatment with other systemic therapies. While drug development of pembrolizumab is ongoing in Phase III studies in the 2nd and 1stline recurrent/metastatic disease settings, the ultimately the biggest potential impact based on patient volume and survival will potentially be in the curative intent setting. This randomized study is intended to explore the incorporation of pembrolizumab into the treatment of patients with locally advanced HNSCC at high risk for recurrence. **Methods:** Eligible patients must have HNSCC, completed therapy with definitive intent, and have an estimated risk of recurrence ≥40-50% (including tumors with extensive lymphadenopathy, extracervical lymphadenopathy, indeterminate residual local or distant mass after treatment, non-responders to induction chemotherapy, incomplete definitive therapy, receipt of salvage therapies, or oligometastatic disease treated definitively). Patients will be randomized to 1 year of either pembrolizumab 200 mg or placebo, administered intravenously day 1 of each 3-week cycle. The primary hypothesis of the study is that the addition of pembrolizumab will improve the 2-year progression-free survival (PFS) rate, compared to placebo. A sample size of 90 (45 patients per treatment arm, assuming 10% loss of follow up in N = 100 patient trial) will achieve 92.7% power at alpha = 0.10 (one-sided) to detect a difference between 50% and 72.5% PFS at 2 years. Approximately 51 events are required to detect such a difference. Patient screening and enrollment are expected to begin spring 2017.

TPS6096 **Poster Session (Board #81a), Mon, 1:15 PM-4:45 PM**

Phase ɯ (window) preoperative study of olaparib with cisplatin or with durvalumab or alone or no treatment in patients with histologically proven head and neck squamous cell carcinoma who are candidates for surgery (OPHELIA). *First Author: Amanda Psyrri, University General Hospital Attikon, National and Kapodistrian University of Athens, Athens, Greece*

Background: Novel agents are often investigated in unselected end-stage cancer patients and their efficacy is evaluated by the classical RECIST criteria making unlikely to fully exploit the antitumor potential of these targeted agents. Olaparib (O) is a potent inhibitor of PARP especially active in tumors that have homologous recombination DNA repair pathway deficiencies. Durvalumab (D) is a selective, high-affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, overcoming PD-L1-mediated inhibition of T-cell activation. There is substantial evidence that tumor cells use PARP to repair platinum-induced DNA damage and thus escape apoptosis. In addition, O may complement the antitumor activity of D by increasing DNA damage through repair inhibition. **Methods:** OPHELIA is an open-label randomized multicenter phase II (window) trial in patients (pts) with head and neck squamous cell carcinoma (HNSCC). Treatment-naive HNSCC pts selected for primary curative study are randomized 3:3:3:1 in 4 neoadjuvant treatment groups: D 1500 mg on day 1 followed by O 600mg daily for 21-28 days (12 pts), cisplatin 60 mg/m^2 on day 1 followed by O 75mg daily for 5 days (12 pts), monotherapy with O 600mg daily for 21-28 days (12 pts) and no treatment (5 pts). Preoperative therapy is discontinued 24 to 36 hours before surgery. Tumor biopsies, CT scans, PET and blood specimens are obtained at diagnosis and at surgery. Primary endpoint is the change in the tumor Ki-67 before and after treatment. Secondary endpoints are objective response rate according to RECIST 1.1 criteria, pathologic complete response rate and metabolic response rate assessed by FDG-PET/CT scan. Exploratory endpoints will include tumor and blood biomarkers. Translational correlates will be tested in tumor tissue, plasma and germline DNA and will include mutations in genes associated with DNA repair assessed by next generation sequencing and circulating tumor cells (CTCs) evaluated for DNA repair biomarkers and PD-L1. Trial is open to enrollment. Clinical trial information: NCT02882308.

TPS6097 **Poster Session (Board #81b), Mon, 1:15 PM-4:45 PM**

A randomized phase II study of chemoradiation (CRT) +/- nivolumab (Nivo) with sequential safety evaluations of Nivo +/- lirilumab (Liri) or ipilumumab (Ipi) concomitant with (C) RT in intermediate (IR) and high-risk (HR) head and neck squamous cell carcinoma (HNSCC) (RTOG 3504, NCT02764593). *First Author: Maura L. Gillison, Ohio State University, Columbus, OH*

Background: Nivolumab (Nivo), a monoclonal antibody to the programmed death-1 (PD-1) immune checkpoint receptor, improved overall survival (OS) for patients (pts) with platinum-refractory, recurrent/metastatic HNSCC compared with standard therapy. A placebo controlled phase IIR trial was designed to investigate the hypothesis that Nivo added to platinum-based CRT will improve progression free survival (PFS) for pts with newly diagnosed IR/HR HNSCC. **Methods:** Eligibility includes IR HNSCC (p16+, oropharynx T1-2N2b-N3/T3-4N0-3, $>$ 10 pack-years (pys) or T4N0-N3, T1-3N3 ≤ 10 pys) and HR HNSCC (oral cavity, larynx, hypopharynx, or p16(-) oropharynx, stage T1-2N2a-N3 or T3-4N0-3). After safety evaluation in 8 evaluable pts, 176 pts will be randomized (1:1) to cisplatin (40 mg/m^2/week X 7) with radiation (IMRT, 70 Gy in 7 weeks) +/- Nivo/placebo (240 mgs q14 days X 5, then 480 mgs q28 X3). Primary endpoint is PFS. Secondary endpoints include OS, acute and chronic toxicity, quality of life and biomarkers (tumor PD-L1 expression; E6/7 seroreactivity and frequency of functional circulating and intraumoral T cells). Parallel with Phase IIR are sequential safety evaluations (see Table) in platinum eligible and ineligible ($>$ 70 years; ≥3 grade neuropathy; ≥2 hearing loss; or CrCl $<$ 60 ml/min) cohorts (N = 10-20) of Nivo +/- Liri (anti-KIR) or Ipi (anti-CTLA4) concomitant with RT alone, cisplatin-RT or cetuximab-RT platforms followed by 3 months of adjuvant immunotherapy. The primary endpoint is safety and feasibility. With 8 evaluable pts, the probability of treatment assessed as toxic is $>$ 78% when the true toxicity rate is $>$ 45% and treatment assessed tolerable is $>$ 80% if the true toxicity rate is $<$ 20%. Clinical trial information: NCT02764593.

Cohort	Cisplatin Eligible	Immunotherapy	Chemotherapy	RT IMRT 70 Gy/7 weeks
1	Yes (Y)	Nivo	Weekly cis	Y
2	Y	Nivo	High dose cis	Y
3	Y	Nivo	Cetuximab	Y
4	Y	Nivo + Liri	High dose cis	Y
5	Y	Nivo + Ipi	High dose cis	Y
A	No (N)	Nivo	–	Y
B	N	Nivo	Cetuximab	Y
C	N	Nivo + Liri	–	Y
D	N	Nivo + Ipi	–	Y

TPS6098 **Poster Session (Board #82a), Mon, 1:15 PM-4:45 PM**

Phase II trial of ribociclib and everolimus in p16 low anaplastic thyroid cancer (ATC). *First Author: Bernard Tawfik, University of Texas Southwestern Medical Center, Dallas, TX*

Background: ATC is a rare thyroid cancer with a highly aggressive clinical course. Median OS is 3-4 months and 90% of patients die within 1 year of the diagnosis. There are no effective treatment options in metastatic disease. Targeted therapies to ALK and BRAF are occasionally associated with dramatic responses. Retinoblastoma (Rb) inhibits cell cycle progression and is inactivated by CDK 4/6, which is the target for ribociclib. Nearly all differentiated thyroid cancers are Rb negative, conversely nearly 100% of ATC expresses intact Rb which may be crucial for rapid cell cycle progression. Ribociclib is a CDK 4/6 inhibitors that slows cell cycle progression and DNA replication in tumors with functional Rb. The p16 protein similarly inhibits CDK4/6; if p16 levels are high Rb is phosphorylated and thus inactive. p16 is low in ATC, and from our comprehensive genomic analysis 30% of ATC lacks the p16 gene *CDKN2a*. Most ATC demonstrates PI3K/Akt/mTOR abnormalities, this pathway represents an attractive target in ATC. The mTOR inhibitor everolimus has shown promising efficacy in ATC cell lines, especially in those with TSC2 mutation whose wild type negatively regulates mTOR. **Methods:** The combination of everolimus and ribociclib targets mutations/abnormalities that are frequently seen in ATC, and is tolerable based on Phase I/II trial results in the latest arm of the biomarker/oncogene driven ATC Master Protocol . This open-label trial treats metastatic Rb+ ATC patients with p16-/*CDKN2a*-. Treatment is ribociclib 400 mg + everolimus 5 mg QD. The primary endpoint is the overall response rate; secondary endpoints are PFS, OS, safety and toxicity. Exploratory objectives include if tissue biomarkers or mutations noted on Next Generation Sequencing correlate for enhanced/impaired response to combination therapy. Simon's two-stage design will be used with the null hypothesis that the true response rate is 5%, this will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If no response in these 9 patients, the study will be stopped. Otherwise, 21 additional patients will be accrued for a total of 30. Clinical trial information: NCT02289144.

TPS6099 **Poster Session (Board #82b), Mon, 1:15 PM-4:45 PM**

A phase II study of pembrolizumab and docetaxel for aggressive RAI refractory thyroid carcinomas or salivary gland cancers: The iPRIME study. *First Author: Tanguy Y. Seiwert, University of Chicago, Chicago, IL*

Background: Both aggressive, radioactive iodine refractory thyroid cancers as well as high-grade salivary gland cancers respond poorly to chemotherapy, and there is no widely used standard of care. Targeted thearpies as well as cytotoxic chemotherapy (e.g. doxorubicin, or taxanes) are commonly used, but are only modestly effective. Both salivary gland and thyroid cancers have been shown to have tumor infiltrating lymphocytes, tumor inflammation, and PD-L1 expression (*Ayers, AACR 2015*). Early data with anti-PD-1 immunotherapy using pembrolizumab (Keynote 28) show activity in ≤10a% of patients in a biomarker selected population (Keynote 28 thyroid and salivary gland cohorts). However, most patients are not PD-L1 positive and were not eligible. Recently synergy of anti-PD-1 checkpoint blockade with cytotoxic chemotherapy was reported in several studies (e.g. Langer et al, Keynote 21G). Mechanistically chemotherapy may increase tumor inflammation, and eradicate immusupressive myeloid derived suppressor cells (MDSCs). Data suggest a significant increase in the response rate e. g. in KN21G from 29% to 55%. Furthermore the depths of responses and durability improve, including patients with PD-L1 negative tumors. **Methods:** We hypothesize that the combination of PD-1 checkpoint blockade and cytotoxic chemotherapy will show synergistic activity in aggressive thyroid cancers and salivary gland cancers. Eligible patients will have radioactive iodine refractory, aggressive thyroid cancer (cohort A, N = 25 pts), or progressive salivary gland cancers (cohort B, N = 25 pts). There will be no PD-L1 or other biomarker selection. Patients must have progressed on prior therapy. Patients will receive docetaxel at a dose of 75mg/m2 Q21 days as well as pembrolizumab 200mg flat-dose Q21 days intravenously. The primary outcome of this study is response rate. The addition of pembrolizumab to chemotherapy will increase the response rate from 20% (H0) to 40% (H1). A simon two-stage design will be used for each cohort (cohorts A and B) with an estimate 81% power in each arm. Patient screening and enrollment are expected to begin mid 2017. Clinical trial information: pending.

6500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Primary outcomes analysis of a multicenter randomized controlled trial of an interactive decision tool for patients with breast cancer. *First Author: Sarah T. Hawley, University of Michigan Medical School, Ann Arbor, MI*

Background: High quality treatment decisions require that patients are well informed about treatment and that their values are considered. Yet studies show that patient knowledge about breast cancer treatment trade-offs is low and appraisal of decision-making is not optimal. **Methods:** We conducted a randomized controlled trial (RCT) of a tailored, comprehensive (locoregional and systemic treatment) and interactive decision tool (iCanDecide), compared with static online information. 537 newly diagnosed, early stage breast cancer patients were enrolled at the first visit in 22 surgical practices. Participants were surveyed 5 weeks (N = 496; RR 92%) post enrollment after locoregional treatment decision-making. The primary outcome was a high quality decision, including two components: high knowledge about treatment options and a values concordant treatment decision. The main secondary outcome was preparation for decision making. We evaluated the distribution of participants in each arm, and conducted logistic regression modeling to assess the association between the intervention and the outcomes controlling for patient characteristics and strength of treatment preference at enrollment. **Results:** Significantly more intervention than control patients had high knowledge (60% vs. 42%, $p < 0.001$), although the majority of both groups reported values concordant treatment (~84%). Intervention patients also reported feeling prepared for decision making significantly more often than controls (45% vs. 32%, $P < 0.01$). Patients randomized to the interactive intervention had higher knowledge (OR: 2.2; 95% CI 1.2-4.0) and preparation for decision making (OR: 1.5; 95% CI 1.1-1.4), even after adjusting for age, education, race, stage and clinical site. **Conclusions:** In this large RCT, a tailored, interactive treatment decision tool for breast cancer improved knowledge and prepared patients for complicated decision making, more than access to static online information. Future work to further integrate such tools into the clinical workflow is needed. Clinical trial information: NCT01840163.

6501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Cognitive technology addressing optimal cancer clinical trial matching and protocol feasibility in a community cancer practice. *First Author: J. Thaddeus Beck, Highlands Oncology Group, Rogers, AR*

Background: IBM Watson for Clinical Trial Matching (CTM) is a cognitive computing solution that uses natural language processing (NLP) to help increase the efficiency and accuracy of the clinical trial matching process. This solution helps providers locate suitable protocols for their patients by reading the trial criteria and matching it to the structured and unstructured patient characteristics when integrated with the Electronic Medical Record (EMR). It is also designed to determine which sites have the most viable patient population and identify inclusion and exclusion criteria that limit enrollment. **Methods:** This project was a collaboration among Highlands Oncology Group (HOG), Novartis and IBM Watson Health to explore the use of CTM in a community oncology practice. HOG is in Northeast Arkansas and has 15 physicians and 310 staff members working across 3 sites. During the 16-week pilot period, data from 2,620 visits by lung and breast cancer patients were processed by the CTM system. Using NLP capabilities, CTM read the clinical trial protocols provided by Novartis, and evaluated the patient data against the protocols' inclusion and exclusion criteria. Watson excluded ineligible patients, determined those that needed further screening, and assisted in that process. Feedback on the user experience was also obtained. **Results:** In an initial pre-screening test, the HOG clinical trial coordinator (CTC) took 1 hour and 50 minutes to process 90 patients against 3 breast cancer protocols. Conversely, when the CTM screening solution was used, it took 24 minutes. This represents a significant reduction in time of 86 minutes or 78%. Watson excluded 94% of the patients automatically, providing criteria level evidence regarding the reason for exclusion, thus reducing the screening workload dramatically. **Conclusions:** IBM Watson CTM can help expedite the screening of patient charts for clinical trial eligibility and therefore may also help determine the feasibility of protocols to optimize site selection and enable higher and more efficient trial accruals.

6502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Global impact of a clinical informatics system: Scalable delivery of on-time access to evidence-based multidisciplinary expert treatment decisions for all cancers. *First Author: Rajendra A. Badwe, Department of Surgical Oncology, Breast Disease Management Group, Tata Memorial Centre (TMC), Mumbai, India*

Background: There is a scarcity of expert oncologists in the world. Patients in nonurban areas have poor access to evidence-based treatment decisions and worse outcomes. In India, there are ~1600 experts for 1.8 Million patients. Created in May 2014, "TMC NCG Navya Online" is an expert opinion service based on an informatics system. We prospectively study its real-world impact. **Methods:** Navya exhaustively searches and outputs evidence and experience based treatment options for an individual patient. Its accuracy was validated in trials at TMC (one of the world's largest tertiary care centers) and UCLA-OVMC. Navya's patient data summary and treatment options are rapidly reviewed and vetted (1-2 minutes) on mobile by experts from TMC and NCG, (consortium of 104 cancer centers in India). Expert decisions are converted into a simple language report for patients. System generated evidence based information on diagnostics, regimens, side effects etc are also provided. To prospectively assess impact, from July to December 2016, all patients were asked via phone follow-up: 1. If report was shared with treating provider, 2. Final treatments delivered. **Results:** 9361patients from 22 developing countries registered with TMC NCG Navya Online. 3402 expert decisions were provided and converted into 2614 simple language reports. 5229 patients received system generated evidence based information. Median time to deliver a report was 24 hours. The prospective sample was 582 decisions with a 75% (n = 436) follow-up rate. 74% of reports were shared with treating providers. 73% of TMC NCG Navya's decisions, (n = 306), were the final treatments delivered. Common reasons for non-implementation included decline in ECOG status and not testing biomarkers (ER/PR etc). **Conclusions:** Expert oncologists use Navya to provide rapid online opinions to patients across 22 developing countries. Patients shared the expert opinions with their providers and received evidence-based treatments. Expanding the reach and impact of such a service to nonurban USA and the world, can maximize outcomes for patients without ready access to expertise.

6503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Impact of the timing of hepatitis B virus (HBV) identification and anti-HBV therapy initiation on the risk of adverse liver outcomes in patients receiving cancer therapy. *First Author: Jessica Hwang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients with cancer and hepatitis B virus (HBV) infection receiving cancer therapy are at risk for HBV reactivation. We aimed to determine the impact of early vs. late HBV identification and early vs. late/no anti-HBV therapy on adverse liver outcomes of patients with cancer with chronic (HBsAg+/anti-HBc+) or past (HBsAg-/anti-HBc+) HBV infection. **Methods:** We retrospectively studied adult patients with solid or hematologic malignancies who received chemotherapy during 2004-2011. Adverse liver-related events included hepatitis flares, liver failure, and death. Time-to-event analysis was used to determine incidence, and multivariable hazard models to determine predictors of outcomes. *Early* was defined as at the initiation of cancer therapy and *late* as after therapy initiation. **Results:** There were 18,688 study patients (80.4% had solid tumors). Among patients with hematologic malignancies, 89.6% had HBV testing of which 90.4% was early. Among patients with solid tumors, 10.8% had HBV testing of which 46.4% was early. Prevalence of chronic HBV was 1.1% (52/4905) and past HBV was 7.1% (350/4905). Among patients with chronic HBV with hematologic or solid malignancy, those identified late had 2.95 times (1.45-6.01) higher risk of liver failure than those identified early. Among chronic HBV patients, 59% (23/39) with early testing had early initiation of anti-HBV therapy, while all of those tested late had late/no initiation of anti-HBV therapy. Predictors of liver failure were male sex, chronic HBV, and late HBV identification for patients with solid tumors, and allogeneic SCT for patients with hematologic malignancies. **Conclusions:** Early HBV identification correlated with early anti-HBV therapy initiation and reduced risk of liver failure after chemotherapy in chronic HBV patients with solid tumors or hematologic malignancies as well as patients with past HBV and solid tumors.

6504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Post-discharge transitions of care for hospitalized patients with advanced cancer. *First Author: Daniel E Lage, Harvard Medical School, Boston, MA*

Background: Patients with advanced cancer experience frequent hospitalizations and burdensome transitions of care post-discharge. We examined predictors of discharge location for patients with advanced cancer. **Methods:** We prospectively enrolled patients with advanced cancer with unplanned hospitalizations from 9/14 to 3/16. Upon admission, we used the Edmonton Symptom Assessment Scale and Patient Health Questionnaire-4 to assess physical and psychological symptoms, respectively. We used logistic regression models to identify predictors of discharge to location other than home, including post-acute care (PAC) [skilled nursing facility or long term acute care hospital] or hospice [any setting]. We used Cox regression models adjusted for clinical variables to assess the relationship between discharge location and survival. **Results:** Out of 932 patients, 726 (77.9%) were discharged home, 118 (12.7%) to PAC and 88 (9.4%) to hospice. Compared with patients discharged home, those discharged to PAC or hospice had higher symptom burden, including dyspnea, constipation, low appetite, drowsiness, fatigue, depression, and anxiety (all $p < 0.05$). Patients discharged to PAC or hospice vs. home were more likely to be older (OR 1.03, $p < 0.0001$), live alone (OR 1.95, 95% CI: 1.25-3.02, $p < 0.003$), have impaired mobility (OR 5.08, 95% CI: 3.46-7.45, $p < 0.0001$), longer length of stay (OR 1.15, 95% CI: 1.11-1.20, $p < 0.0001$), higher ESAS physical symptoms (OR 1.02, 95% CI: 1.003-1.032, $p < 0.017$), and higher PHQ-2 depression symptoms (OR 1.13, 95% CI: 1.01-1.25, $p < 0.027$). Patients discharged to hospice vs. PAC were more likely to receive palliative care consultation (OR 4.44, 95% CI: 2.12 to 9.29, $p < 0.0001$) and have shorter length of stay (OR 0.84, 95% CI: 0.77 to 0.91, $p < 0.0001$). Compared with patients discharged home, those discharged to PAC had lower survival (HR 1.53, 95% CI 1.22-1.93, $p < 0.0001$). **Conclusions:** Patients with advanced cancer discharged to PAC or hospice have substantial physical and psychological symptom burden and poor physical function. Patients discharged to PAC also have inferior survival compared with those discharged home. They may benefit from targeted interventions to improve their quality of life and care.

6505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

The role of chronic disease in the costs of potentially preventable emergency department use during treatment: A regional study. *First Author: Laura Elizabeth Panattoni, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The Centers for Medicare and Medicaid Services (CMS) released a quality metric for potentially preventable chemotherapy-associated emergency department (ED) use, effective in 2020. This metric excludes diagnoses with emerging evidence for outpatient management, such as proactive symptom management (PSM) and those for ambulatory care sensitive chronic conditions. Little is known about the intersection between potentially preventable ED visits due to cancer vs. other chronic disease. This study characterized the number and costs of ED visits during treatment. **Methods:** Western Washington cancer registry records from 2011- 2015 were linked with claims from two commercial insurers. Patients with newly diagnosed solid tumors undergoing initial treatment with chemotherapy or radiation were eligible. ED use was tracked one year post treatment initiation. ED diagnosis codes for fields 1-10 from the CMS metric and the PSM literature were labeled "Potentially Preventable" (Pp). Codes from the Agency for Healthcare Research and Quality's Prevention Quality Indicators (PQI) for Chronic Conditions were labeled "Potentially Preventable-Chronic Disease" (PpChronic). Costs were adjusted to $2016. **Results:** Of the 7,053 eligible patients, 2,543 (36.1%) visited the ED (median # visits [IQR]: 1 [1-2]). The most commonly listed codes included Pain (1,054 visits) and Dyspnea (279 visits) for Pp, Hypertension-PQI (652 visits) and COPD-PQI (206 visits) for PpChronic, and Diabetes (247 visits) and Hyperlipidemia (181 visits) for the other codes. Spending on ED visits including both potentially preventable cancer and chronic disease diagnoses totalled $706,552 (20% of ED costs). **Conclusions:** One fifth of ED costs potentially resulted from simultaneous poor cancer symptom and chronic disease management. Future research should explore the role of chronic illness in categorizing which ED visits are potentially preventable during cancer treatment.

Diagnoses Codes	*Visits*	*Total Cost*
Pp + PpChronic + others	542 (19.1%)	20%
Pp + *no* PpChronic + others	1,260 (44.4%)	53%
***no* Pp + PpChronic + others**	259 (9.1%)	6%
***no* Pp + *no* PpChronic + others**	778 (27.4%)	21%
Total	**2,839**	**$3,529,523**

6506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Analysis of reimbursement (R) for next generation sequencing (NGS) on patients' tumors in the context of a personalized medicine program. *First Author: Thomas D. Brown, Swedish Cancer Institute, Seattle, WA*

Background: R policies for NGS testing vary widely among private and public insurers. While drug costs are the greatest challenge in personalized or precision medicine, cost and R are substantial barriers to genomic profiling with NGS. We examined variation in coverage and R for a cohort of cancer patients (pts) treated at a tertiary oncology center. **Methods:** An Institutional Review Board approved prospective registration protocol was activated with the objective of establishing a centralized longitudinal clinical, molecular phenotypic, and research data repository for pts diagnosed with cancer. Based on provider assessment of medical necessity, mutations in 68 cancer associated genes were analyzed. Evaluation of R for NGS was performed from Sept, 2014 through Jan, 2017, with use of CPT code 81455. R was analyzed based on: payer type; pt age; localized vs. metastatic disease; and actionability of data. **Results:** 588 pts with evaluable analytic cases, and NGS testing, with R results shown in the table below. For groups with >= 10 pts: R frequency was highest in managed care programs, either private or Medicare, and least frequent in non-HMO Medicare ($p<.001$). In pts receiving R, payments by private HMOs were highest ($p<.02$). NGS results with labelled drug indications were associated with less frequent R (26% vs. 35%; $p<.05$), and lower payments (mean of $358 vs. $567; $p<.02$) compared to other NGS results. Younger age was associated with more frequent R (38% in pts <60 years, 24% in pts >= 60 years; $p<.005$). Neither cancer diagnosis nor stage were significantly associated with R. **Conclusions:** One third of pts received some R for NGS testing. R was more frequent and higher in managed care programs, both private and Medicare. R was more likely for younger age pts, while actionable NGS results were associated with lower R. These data demonstrate the need for rational, transparent, and consistent R policies, along with a value-based R model for NGS across all payer groups.

	Private		Medicare					
	Non-HMO	HMO	Non-HMO	HMO	Medicaid	Self-Pay	Tricare	VA
# pts	256	72	147	48	51	7	6	1
# pts with R	85 (33%)	36(50%)	7 (5%)	35 (73%)	30 (59%)	0 (0%)	0 (0%)	1 (100%)
R if paid (mean)	$1,448	$2,134	$1,211	$1,590	$1,341	$0	$0	$4,000

6507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Implementation of precision oncology in the Veterans Health Administration (VHA). *First Author: Michael J. Kelley, Department of Veterans Affairs, Durham, NC*

Background: VHA is the US's largest integrated healthcare system providing care to over 6 million Veterans (~40% in rural areas). Precision Oncology offers the promise of effective, low-toxicity targeted therapies tailored to individual tumor genomics but is unequally available to patients in the US. As part of the Cancer Moonshot, VHA is implementing a system-wide Precision Oncology Program (POP) including patients in rural areas, where specialty oncology care has historically had limited availability. **Methods:** Patients tested with multigene NGS tumor sequencing through 1 of 2 contracted vendors were identified from POP records and cancer characteristics were extracted from POP and medical records. Drug use data was obtained from the VA Corporate Data Warehouse. NGS testing results and annotations were extracted from POP records. **Results:** A total of 978 tumor samples were sent for NGS testing since program inception in 2015. The most common diagnoses are lung (464: adeno 314, squamous 107), GI (87), LN (75), liver (56), H&N (52), and prostate (43). The rate of sample test requests increased rapidly after national implementation in July 2016 (mean 23 samples/month prior to implementation to mean 126 samples/month 3 months later) as did the number of participating facilities (mean 8/month to 27/month). Sequencing success rate increased from 68% to 71% over the same interval while mean turn around time remained similar at 19.7 and 19.1 d, respectively. NGS results are available for a cohort of 344 patients including: lung 200 (adeno 138, squamous 51), skin 28, LN 20, liver 19, GI 16. 979 variants were found including TP53 278, KRAS 106, STK11, APC 38, PIK3CA 38, and CDKN2A 37. 228 patients had actionable results (on-label drug 24, off-label drug 165, clinical trial 213). To date, 8 patients received a recommended drug outside a clinical trial between 11 and 288 d after testing (median 82 d); 4 additional patients had received an NGS-recommended drug prior to testing. **Conclusions:** Implementation of tumor NGS testing as part of Precision Oncology Program in a US distributed healthcare system is feasible. Further program implementation and provision of appropriate targeted drugs both on and off study will be necessary to impact patient outcomes.

6508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Utilization of consultative molecular tumor board in community setting. *First Author: Carol J. Farhangfar, Levine Cancer Institute, Charlotte, NC*

Background: Physicians in the community have a broad range of experience using genomics data to inform treatment decisions. They typically have a heavier patient load than found in academic centers and treat a variety of tumor types. Genomic data has been reportedly used less than anticipated, even when results were actionable. Monthly didactic molecular tumor boards have been implemented in a number of cancer centers to try to fill gaps in knowledge. **Methods:** A weekly virtual consultative molecular tumor board (MTB) was implemented (Mar 2016) at an academic hybrid, multi-site community-based cancer institute to provide rapid molecularly-driven treatment guidance to physicians, augment genomics education, provide supporting documents for off-label use and clinical trials. A baseline survey was performed prior to first MTB. MTB assessments were summarized and provided to treating physician. Data was abstracted from the electronic medical records and clinical trials management system. Descriptive statistics were utilized to summarize utilization of MTB and treatment recommendations. **Results:** Genomics testing with a large panel (~600 genes) was requested for 809 patients (Jun 2015-Feb 2017). The MTB received 81 requests for review from 32 physicians from 14 locations. Most commonly reviewed disease sites were lung, ovary, pancreatic, colon, breast and head and neck cancers; 37% of reviews requested were for rare tumors. Median time to review request was 15 days from receipt of results. MTB recommendations were followed in 70% of cases, 16% continued current/other therapy, 11% declined rapidly (hospice/died), and 3% of patients decided against recommendations. Forty-four (44) percent were screened for recommended clinical trials; 26% went on study. **Conclusions:** Implementation of a weekly virtual consultative MTB facilitates molecularly-driven treatment decisions in community setting, especially in rare tumor types and enhances clinical trial accruals.

6509 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM

Do the American Society of Clinical Oncology (ASCO) Value Framework and the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale measure the same construct of clinical benefit? *First Author: Sierra Cheng, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada*

Background: Whether the American Society of Clinical Oncology (ASCO) Value Framework and the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) measure similar constructs of clinical benefit is unclear. It is also unclear how they relate to quality-adjusted life-years (QALYs) and funding recommendations in the UK and Canada. **Methods:** Randomized clinical trials (RCTs) of oncology drug approvals by the Food and Drug Administration, European Medicines Agency and Health Canada between January 2006 and August 2015 were identified and scored using the ASCO version 1 (v1) framework (August 10, 2015), ASCO version 2 (v2) framework (May 31, 2016) and ESMO-MCBS (May 30, 2015) by at least two independent reviewers. Spearman correlation coefficients were calculated to assess construct (between frameworks) and criterion validity (against incremental QALYs from the National Institute of Clinical Excellence (NICE) and the pan-Canadian Oncology Drug Review (pCODR)). Associations between scores and NICE/pCODR recommendations were examined by logistic regression models. Inter-rater reliability was assessed using intra-class correlation coefficients. **Results:** From 109 included RCTs, 108 ASCOv1, 111 ASCOv2 and 83 ESMO scores were determined. Correlation coefficients for ASCOv1 vs. ESMO, ASCOv2 vs. ESMO, and ASCOv1 vs. ASCOv2 were 0.36 (95% CI 0.15-0.54), 0.17 (95% CI -0.06-0.37) and 0.50 (95% CI 0.35-0.63), respectively. Compared with NICE QALYs, correlation coefficients were 0.45 (ASCOv1), 0.53 (ASCOv2) and 0.46 (ESMO); with pCODR QALYs, coefficients were 0.19 (ASCOv1), 0.20 (ASCOv2) and 0.36 (ESMO). None of the frameworks were significantly associated with NICE/pCODR recommendations. Inter-rater reliability was good for all frameworks. **Conclusions:** The weak-to-moderate correlations between the ASCO frameworks and ESMO-MCBS, with QALYs, and with NICE/pCODR funding recommendations suggest different constructs of clinical benefit measured. Construct convergent validity with the ESMO-MCBS in fact did not increase with the updated ASCO framework.

6510 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM

Pharmaceutical industry payments and oncologist drug selection. *First Author: Aaron Philip Mitchell, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Financial relationships between physicians and the pharmaceutical industry are common, and have the potential to influence clinical practice in potentially inappropriate ways. Oncology may be an ideal setting to study the influence of industry payments on physician drug choice given the high levels of competition for market share and high prices commanded by orally administered oncologic drugs. **Methods:** We linked the Open Payments database of industry-physician financial transactions with the Medicare Part D Prescriber file by physician name and practice location. We used McFadden's conditional logit model to determine whether receipt of industry payments was associated with higher odds of using a drug manufactured by the same company. We applied this model to clinical scenarios in which oncologists may choose between multiple, on-patent drugs: metastatic renal cell cancer (mRCC) (sunitinib, sorafenib, and pazopanib) and chronic myeloid leukemia (CML) (imatinib, dasatinib, and nilotinib). The primary, binary independent variable was receipt of payments from a manufacturer of one of these drugs in 2013; the primary dependent variable was choosing that manufacturer's drug in 2014. We divided industry payments into two categories, research payments and non-research "general" payments (including meals, travel, lodging, and speaking/consulting fees), and analyzed each payment type separately. **Results:** Physicians who received general payments from a manufacturer had increased odds of prescribing that manufacturer's drug for both mRCC (OR: 1.78, 95%CI 1.23-2.57, mean payments $566) and CML (OR: 1.29, 95%CI 1.13-1.48, mean payments $166). Research payments were associated with an increased odds of manufacturer drug use for mRCC (OR: 2.13, 95%CI 1.13-4.00, mean payments $33,391) but not CML (OR: 1.10, 95%CI 0.83-1.45, mean payments $185,763). **Conclusions:** Receipt of general payments from pharmaceutical companies is associated with increased prescribing of those companies' drugs. An association between research payments and prescribing was less consistent. This study suggests that conflicts of interest with the pharmaceutical industry may influence oncologists in high-stakes treatment decisions for patients with cancer.

6511 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM

Oncologists' perceptions of affordability in the NCCN evidence block value frameworks. *First Author: William Bruce Wong, Roche/Genentech, San Francisco, CA*

Background: The increasing prevalence of cancer coupled with approvals of new drugs and technologies used in therapy have brought increased scrutiny to the cost and value of treatments in oncology. To address the rising concern about oncology drug costs, NCCN has developed the Evidence Blocks (EB) framework to help assess the value of oncology regimens. The objective of this study was to assess and understand oncologist's perceptions of affordability in the context of the NCCN EB framework. **Methods:** Data were collected from an electronic cross-sectional survey of 200 US-based oncologists recruited from an online panel. Using the NCCN EB framework, oncologists were asked to rate a variety of hypothetical cancer therapies and assign costs (in US dollars) to the five levels of affordability. Additional questions assessing perceived patient out-of-pocket costs and comfort level in assessing affordability were also included in the survey. **Results:** Oncologists' ratings for an existing cancer immunotherapy were generally similar across the EBs (ratings of 4), however oncologists rated affordability higher (3: Moderately Expensive) vs. the actual NCCN panel affordability rating (1: Very Expensive). The affordability rating was similar across a variety of hypothetical cancer therapies and tumor types (rating of 3). Oncologists estimated the costs for this rating of 3 to range from $4600-$6000 per month, which was inconsistent with actual drug costs. Oncologists estimated the mean monthly out-of-pocket costs for patients with insurance to range from $1260 for a new oral medication to $1700 for a new infused medication. Only 26% of oncologists were comfortable or very comfortable with rating costs associated with affordability levels. **Conclusions:** Surveyed oncologists rated cancer therapies as more affordable than NCCN panel ratings. Costs associated with affordability were not consistent with actual treatment costs; however, most oncologists were not comfortable with rating affordability.

6512 Clinical Science Symposium, Sat, 1:15 PM-2:45 PM

How costs get discussed (or not) in routine oncology practice. *First Author: Rahma M. Warsame, Mayo Clinic, Rochester, MN*

Background: Cancer patients are nearly 3x more likely to declare bankruptcy than people without cancer. However, little is known about the dynamics of the healthcare provider/patient (pt) conversations around cost issues, the range of topics explored, and the factors that may influence them. We reviewed audio recordings of a cross-section of medical oncology conversations to determine frequency, patterns and attitudes of pts and providers on cost. **Methods:** We audio recorded conversations between 5/3/2012 & 11/20/2013 for adult patients with any solid tumor malignancy seen in an outpatient medical oncology clinic at one of three sites in the Upper Midwest and Southern California. Basic demographic variables were abstracted from chart review. Recordings were de-identified, reviewed and flagged for any mention of cost. We used descriptive statistics and inductive qualitative content coding methods to further characterize conversation themes. **Results:** Among 525 recordings, 151 (28%) contained any mention of cost. Median age (range) of pts was 58 years (22-93), and 75% Caucasian, 18% Hispanic, 5% Asian, and 1% Black. Average length of cost discussions was $<$ 2 minutes, and pts usually initiated the discussion (106/151). Among the 151 conversations, social service referrals were mentioned only 6 times (4%). Through qualitative analysis we identified several key topics: *insurance coverage*, *disability*, *drug copays*, and *transportation*. The recording dynamics most frequently displayed *acknowledging but not taking action* on the part of clinicians. Only 25% of clinicians behave confidently in how to address a patients cost concerns. **Conclusions:** In a diverse cross-section of oncology visits, cost comes up only 1/4 to 1/3 of the time and focuses on insurance coverage, disability and out of pocket drug costs. However clinicians often leave these issues unaddressed. Discussing financial burdens and identifying way to improve existing conversations will be important to mitigate additional financial distress.

Institution	Avg. Conversation (min)	Avg. Cost conversation (min)	Provider initiated N (%)	Patient initiated N (%)	Both initiated N (%)
Mayo Clinic	28.6	1.8	28 (33)	54 (64)	3 (3)
USC Norris	15.2	1.2	1 (5)	18 (90)	1 (5)
LA County	14.9	1.5	10 (22)	34 (76)	1 (2)

6513 Poster Discussion Session; Displayed in Poster Session (Board #335), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

The impact of positive SWOG treatment trials on population survival. *First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Recently, tremendous prominence has been given to the investigation of the impact of different research processes as part of the Cancer Moonshot. More than half a century ago, the National Cancer Institute (NCI) established a network of publicly-funded cancer cooperative research groups to systematically advance the science of clinical trial research and the evaluation of new treatments for efficacy and safety. Our objective was to examine the extent to which positive NCI-sponsored cancer treatment trials have benefited cancer patients in the U.S. population. **Methods:** We used study data from SWOG, an NCI-sponsored Network cooperative research group. We identified all treatment trials over SWOG's 60-year history (1956-2016) for which the new experimental therapy provided a statistically significant improvement in overall survival. We assumed the new, proven treatments from these trials established new standards for care in the treatment community. Twenty-three treatment trials were identified from a variety of difference cancer types. We estimated population life-years gained from the trials through 2015 by mapping the impact of the new treatments onto the U.S. cancer population, using an area-under-the-survival-curve approach that combined trial-specific hazard function and hazard ratio results with SEER and life-table data. Calculations were age-adjusted. Dollar return on investment was estimated as the ratio of total investment by the National Cancer Institute in the SWOG treatment trial program divided by the estimate of life-years gained. **Results:** In total, 12,361 patients were enrolled to the 23 positive trials from 1965-2012. We estimated that 3.34 million years of life were gained through 2015. Estimates were greater than 2 million life years gained under 95% of model simulations. The dollar return on investment was $125 per life year gained. **Conclusions:** SWOG treatment trials have had a substantial impact on population survival for cancer patients over 60 years. The National Cancer Institute's investment in its cancer cooperative group research program has provided exceptional value and benefit to the American public.

6514 Poster Discussion Session; Displayed in Poster Session (Board #336), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Comparison of reporting phase I trial results in ClinicalTrials.gov and matched publications. *First Author: Daniel Shepshelovich, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: The 2007 Food and Drug Administration (FDA) Amendments Act mandated reporting of results of clinical trials in ClinicalTrials.gov, a large public registry, within 12 months of completion. We compared results reported for phase I trials in ClinicalTrials.gov and matched primary publications. **Methods:** The ClinicalTrials.Gov database was searched for completed adult phase I cancer trials with reported results. Only trials with dose escalation of systemically administered medications were included. PubMed was searched for matching primary publications, defined as identical intervention, number of arms and enrolled subjects, published prior to November 1, 2016. Results reported in the primary publication were compared with the ClinicalTrials.gov database using a 28-point score (2 = complete agreement; 1 = partial agreement; 0 = no mention) for 14-items related to study design (4 items), outcome measures (4 items) and safety profile (6 items). The ClinicalTrials.gov database was used as the reference for results reporting. Linear regression was used to identify factors associated with incomplete reporting. **Results:** After a review of 583 trials in ClinicalTrials.gov, 163 matching primary publications were identified, comprising 95 (58%) phase I and 68 (42%) phase I/II trials. Publications reported outcomes that did not appear in ClinicalTrials.gov in 25% of trials. Outcomes were omitted or downgraded in publications in 39% of trials. The overall median reporting score was 23/28 (interquartile range 21-25). Items that were incompletely reported in publications were: inclusion criteria (29%), primary outcome definition (26%), secondary outcome definitions (53%), adverse events (71%), serious adverse events (80%) and dates of study start and database lock (91%). Phase I ($p < 0.001$) and multicenter trials ($p = 0.002$) were associated with higher reporting scores than phase I/II and single center trials. **Conclusions:** Reported results in primary publications for early phase cancer trials are frequently inconsistent or incomplete compared with ClinicalTrials.gov entries. ClinicaTrials.gov may provide a more comprehensive overview of safety data from new cancer drug trials.

6515 Poster Discussion Session; Displayed in Poster Session (Board #337), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Trends in the geographic distribution of cancer clinical trials in the US: 2008-2015. *First Author: Caroline Savage Bennette, University of Washington, Seattle, WA*

Background: Access to and patient enrollment in cancer clinical trials is likely strongly impacted by where trial enrollment sites are located. Our objective was to evaluate temporal trends in the geographic location of cancer clinical trials launched in the US. **Methods:** We obtained the recruiting location(s) of all public- and privately-funded phase II/ III cancer clinical trials launched in the US between 2008 and 2015 from the ClinicalTrials.gov database. We linked the recruiting location(s) of each trial to the relevant hospital service area (HSA), which are defined by ZIP codes as local health care markets for hospital care (n = 3436). We estimated the number of cancer clinical trial sites in each HSA each year between 2008 and 2015. We also calculated a statistical measure of inequality, the Gini coefficient. The Gini coefficient would be 0 if all hospital service areas launched the same number of cancer clinical trials, and would be 1 if all cancer clinical trials were launched in only a single hospital service area. **Results:** 62% of HSAs (n = 2133) did not launch a single cancer clinical trial between 2008 and 2015. There was a small and non-statistically significant decline in the overall number of cancer clinical trial sites in the United States between 2008 and 2015 (-1.6% per year [95% CI: -4.0, 0.9]). During this same period of time, however, inequality in the geographic distribution of cancer clinical trial sites considerably deepened. For example, in 2008-09, no trials were launched in 68% of HSAs while 19% of trial sites were in only 1% of HSAs. Trials launched in 2014-15 were even more concentrated: no new trials were launched in 74% of HSAs while 25% of trial sites were in the top 1% of HSAs. The Gini coefficient increased significantly from 0.683 (95% CI: 0.666, 0.700) for trials launched in 2008-09 to 0.726 (95% CI: 0.706, 0.746) for those launched in 2014-15. **Conclusions:** Our findings indicate increased inequality in the geographic distribution of cancer clinical trials launched in the United States since 2008. The underlying causes and consequences of such increasing concentration warrant further analysis given the importance in ensuring equitable geographic access to cancer clinical trials in the US.

6516 Poster Discussion Session; Displayed in Poster Session (Board #338), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Quantifying gender ascertainment bias in hereditary cancer testing. *First Author: Anthony Chen, Myriad Genetic Laboratories, Inc., Salt Lake City, UT*

Background: Historically, hereditary cancer genetic testing has been much more prevalent among women, in part due to gender-specific cancer risks associated with Hereditary Breast and Ovarian Cancer Syndrome (HBOC). Despite expanded genetic testing that includes hereditary cancer syndromes that affect both men and women, the gender gap still persists. Here we report on gender ascertainment bias in hereditary cancer testing by evaluating the proportion of test cancellations in men and women who were not affected with cancer at the time of testing. **Methods:** A commercial testing cohort was queried to identify individuals for whom genetic testing with a multi-gene pan-cancer panel was ordered between September 2013 and December 2016. Individuals who were ascertained for testing based on a clinical suspicion of HBOC or Lynch syndrome (LS) and did not have cancer at the time of testing were included. Test cancellations (i.e. a test order that did not yield any reported result) due to lack of insurance coverage were assessed, as this is directly related to clinical testing criteria. **Results:** Genetic testing was ordered for 259,919 individuals who did not have cancer at the time of testing, which included 6007 men (2.3%) and 253,912 women (97.7%). Overall, 21.2% of tests ordered for men were cancelled due to lack of insurance coverage, which is significantly higher than the cancellation rate among women (14.4%, $p < 0.001$). This trend was observed among individuals tested for suspicion of HBOC (18.7% for men vs. 13.2% for women; $p < 0.001$), but not for those tested for LS (26.6% for men vs. 25.1% for women; $p = 0.137$). Among those whose tests were not cancelled, the positive mutation rate was twice as high for men compared to women (9.6% vs 4.6%, respectively; $p < 0.001$). **Conclusions:** In this analysis, the proportion of genetic tests ordered was substantially biased towards women. Cancellation rates for men were significantly higher compared to women, while the mutation positive rate was twice as high. Although men and women who are unaffected with cancer have an equal probability of having a family cancer history that meets HBOC testing criteria, the data presented here suggests that there is a higher clinical standard for men to receive genetic testing.

6517 Poster Discussion Session; Displayed in Poster Session (Board #339), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Factors influencing prostate cancer treatment decisions for African American (AA) and Caucasian (CA) men. *First Author: Brittaney-Belle Elizabeth Gordon, University of North Carolina School of Medicine, Chapel Hill, NC*

Background: Prostate cancer causes a disproportionate burden to AA men, and AA men are less likely than CA men to receive aggressive treatment. This is the first study to examine factors influencing treatment decision-making of AA vs. CA men in a population-based cohort. **Methods:** 1171 men were enrolled soon after diagnosis and before treatment through Rapid Case Ascertainment of the North Carolina state cancer registry. Researchers asked patients regarding their priorities in treatment decision-making and information sources. Differences in AA and CA men were compared using the chi-square test. **Results:** The most important factor for both AA and CA men was curing cancer, and preserving QOL was second most important. However, AA men were more concerned about additional factors including impact on daily activities (74% very important AA vs 58% CA for intermediate/high risk disease), recovery time (81% vs 50%), cost (66% vs 32%) and treatment time (76% vs 39%) ($p < .001$ for each item). The most important source of information impacting treatment decisions for CA men were physician recommendations (61%), personal research (32%) and family/friend opinion (7%); for AA men, the corresponding numbers were 50%, 32% and 19%. **Conclusions:** AA and CA men with prostate cancer are both concerned about curing cancer, but AA men are more likely to consider multiple other social and personal factors as important in their decision-making process. Improved understanding of these differences may provide opportunities to address racial disparities in prostate cancer.

Factors influencing treatment decisions in AA vs CA men with low and intermediate/high risk cancer.

	CA(%)		AA(%)		
	Very Important	Not Very Important	Very Important	Not Very Important	P-value
Low Risk					
Curing Cancer	88	12	92	8	.26
Preserving quality of life	86	14	90	10	.29
Impact on daily activities	62	39	69	31	.14
Recovery time	47	53	73	27	< .001
Family/Friend Burden	73	27	89	11	< .001
Cost	35	65	70	30	< .001
Treatment time	34	66	69	31	< .001
Intermediate/High Risk					
Curing Cancer	94	6	96	4	.45
Preserving quality of life	83	17	88	12	.11
Impact on daily activities	58	42	74	26	< .001
Recovery time	50	50	81	19	< .001
Family/Friend Burden	72	28	78	22	.10
Cost	32	68	66	34	< .001
Treatment Time	39	61	76	24	< .001

6518 Poster Discussion Session; Displayed in Poster Session (Board #340), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Racial composition in trials supporting the U.S. approval of anti-cancer new molecular entities (NMEs): 2011- 2016. *First Author: Lola A. Fashoyin-Aje, U.S. Food and Drug Administration, Silver Spring, MD*

Background: In New Drug- and Biologics License Applications, clinical trials provide the primary safety and efficacy data upon which approval decisions are made. Low numbers of patients from racial groups that experience higher incidence and/or mortality from some cancers compared to the overall US population, may limit the generalizability of trial results. The Census estimates that the US population is 77.1%White, 13.3% Black/ African American (AA), 5.6% Asian, 1.2% American Indian/ Alaska Native (AIAN), and 0.2% Native Hawaiian/ Other Pacific Islander (NHPI). FDA conducted an analysis to compare the racial composition in trials supporting the approval of NMEs for the treatment of solid tumor malignancies. **Methods:** We reviewed the marketing applications of the 33 NMEs approved between 2011- 2016 to identify trials that provided the primary evidence of safety and efficacy. **Results:** A total of 29941 patients were enrolled. The table below illustrates enrollment by race (excluding Non-Hispanic, Hispanic, Other, Mixed Race & Missing) and approval year. **Conclusions:** The proportion of White patients enrolled in the US (88%) is higher than the proportion of Whites in the US population. However, the enrollment of AA and NHPI/AIAN patients is low and below the proportional representation of AA and NHPI/AIAN in the US. While enrollment targets may differ across cancer type and by race, the racial composition of patients enrolled in the trials that support the approval of cancer therapeutics should be reflective of the likely US patient population for whom these agents will be prescribed. The majority of Asian patients enrolled were from RoW while the majority of AA and NHPI/AIAN patients were enrolled from the US. Increasing the representation of racial minority patients in oncology trials will require targeted recruitment and enrollment of these patients in US sites.

	2011		2012		2013		2014		2015		2016		Total	
	RoW	US	RoW	US	RoW	US	RoW	US	RoW	US	RoW	US	RoW	US
n	3730	2347	4732	1607	8205	775	1059	743	3282	1048	874	1539	21882	8059
Asian,%	3	1	9	3	42	8	14	3	21	6	8	3	22	3
AA,%	1	3	1	6	*	*	*	2	*	9	1	6	*	5
Native,%	*	*	*	*	0	0	*	*	*	1	*	*	*	*
White,%	95	93	89	86	51	85	84	93	73	80	78	88	72	88

RoW= Rest of the world; Native= NHPI/AIAN; *Less than 0.5%.

6519 Poster Discussion Session; Displayed in Poster Session (Board #341), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Comparison of comorbidity measures to predict postoperative lung cancer survival in the National Cancer Database (AFT-03). *First Author: Melisa L. Wong, Divisions of Hematology/Oncology and Geriatrics, University of California, San Francisco, San Francisco, CA*

Background: Comprehensive assessment of comorbidity in cancer registries is critical for comparative effectiveness research. The National Cancer Database (NCDB) measures comorbidity with a diagnosis code-based Charlson Comorbidity Index (CCI) abstracted from discharge abstracts or billing face sheets. However, the prognostic performance of this code-based CCI has not been compared with a medical chart-based CCI or individual comorbid conditions in a nationally representative sample of patients with lung cancer. **Methods:** Through a special study of the NCDB, cancer registrars performed chart abstraction for 18 perioperative comorbid conditions for 9,640 randomly selected patients with stage I-III non-small cell lung cancer resected in 2006-07 at 1,150 Commission on Cancer-accredited facilities. We compared the prognostic performance of the NCDB code-based categorical CCI (0, 1, 2+), special study chart-based continuous CCI, and individual comorbid conditions in 3 separate Cox proportional hazards models for 5-year postoperative overall survival. All models adjusted for demographic and clinical characteristics. **Results:** Median age was 67 (IQR 60-74). The most common comorbidities were COPD (40%) and CAD (21%). Five-year postoperative overall survival was 55.5%. Agreement between the code- and chart-based CCIs was 51.9% with the code-based CCI underestimating comorbidity for 36.2% patients. The model including individual comorbid conditions had the best prognostic performance (R^2 0.196, C index 0.654). COPD, CAD, CHF, dementia, diabetes, moderate/severe renal and liver disease, peripheral vascular disease, psychiatric disorder, and substance abuse were independently associated with decreased survival. The chart-based CCI model (R^2 0.189, C index 0.650) predicted postoperative survival better than the code-based CCI model (R^2 0.181, C index 0.645). **Conclusions:** The NCDB code-based CCI underestimates comorbidity in patients with surgically resected lung cancer. The chart-based CCI and data on individual comorbid conditions improved prognostic performance and would be valuable additions to the NCDB to strengthen comparative effectiveness research.

6520 Poster Discussion Session; Displayed in Poster Session (Board #342), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Asymptomatic distant recurrence detection and survival in early stage breast cancer: A nationally representative study. *First Author: Jessica R. Schumacher, Department of Surgery, University of Wisconsin, Madison, WI*

Background: Breast cancer follow-up guidelines recommend imaging for distant metastases only in the presence of signs/symptoms. However, data supporting this recommendation predates the current era of improved imaging and targeted therapies based on molecular subtype. The objective was to assess the relationship between mode of distant recurrence detection and survival. **Methods:** A stage-stratified random sample of Stage II-III breast cancer patients diagnosed in 2006-7 was selected from NCDB records from 1,217 CoC-accredited facilities (10/hospital n = 10,853). Women were categorized by subtype: 1) ER or PR+/HER2-; 2) ER and PR-/Her2- (triple negative); 3) HER2+. Medical records abstracted for 5-years post-surgery supplemented NCDB data and assessed distant recurrence and mode of detection (prompted by signs/symptoms or surveillance imaging), imaging (chest CT, abdomen/pelvis CT/MRI, head CT/MRI, bone scan, PET/CT), death date. The relationship between mode of recurrence detection and days from initial cancer diagnosis to death was assessed using propensity-weighted multivariable Cox proportional hazards regression stratified by subtype. Propensity weights, based on receipt of surveillance systemic imaging, accounted for sociodemographic and tumor/treatment factors. **Results:** 5-year distant recurrence was 22.3% for triple negative, 14.8% HER2+, and 11.2% for ER or PR+/ HER2- patients. Asymptomatic imaging detected recurrence in 22.9% and signs/symptoms in 77.1%. Patients with asymptomatic as compared to sign/symptom detected recurrences had reduced risk of death in 5 years if triple negative (HR = 0.68, 95% CI = 0.50-0.93) or HER2+ (HR = 0.40, 95% CI = 0.24-0.65) with no significant association for ER or PR+/HER2- (HR = 1.2, 95% CI = 0.88-1.51). This translated to a between-group difference in weighted median survival of 5 months for triple negative and 13 months for HER2+ patients. **Conclusions:** This is the first nationally representative study to show a survival advantage with asymptomatic detection of distant metastases for patients, with the benefit limited to triple negative and HER2+ disease. Further research to confirm observational findings is warranted.

6521 Poster Discussion Session; Displayed in Poster Session (Board #343), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Changes in stage at diagnosis of screenable cancers after the Affordable Care Act. *First Author: Xuesong Han, American Cancer Society, Atlanta, GA*

Background: Extensive evidence links inadequate insurance with later stage at cancer diagnosis, particularly for cancers that can be detected by screening. The Affordable Care Act (ACA) implemented in 2014 has substantially increased insurance coverage for Americans 18-64 years old. This study aims to examine any changes in stage at diagnosis after the ACA for the following cancers for which screening is recommended for individuals at risk: female breast cancer, colorectal cancer, cervical cancer, prostate cancer, and lung cancer. **Methods:** We used National Cancer Data Base, a nationally hospital-based cancer registry capturing 70% new cancer cases in the US each year, to identify nonelderly cancer patients with screening-appropriate age who were diagnosed during 2013-2014. The percentage of stage I disease was calculated for each cancer type before (2013 Q1-Q3) and after (2014 Q2-Q4) the ACA. 2013 Q4-2014 Q1 was excluded as a washout/phase-in period. Prevalence ratios (PR) and 95% confidence intervals (CI) were calculated using log-binomial models controlling for age, race/ethnicity and sex if applicable. **Results:** 121,855 female breast cancer patients aged 40-64 years, 39,568 colorectal cancer patients aged 50-64 years, 11,265 cervical cancer patients aged 21-64 years, 59,626 prostate cancer patients aged 50-64 years, and 41,504 lung cancer patients aged 55-64 years were identified. After the implementation of the ACA, the percentage of stage I disease increased statistically significantly for female breast cancer (47.8% vs. 48.9%; PR = 1.02 [95%CI 1.01-1.03]), colorectal cancer (22.8% vs. 23.7%; PR = 1.04 [95%CI 1-1.08]), and lung cancer (16.6% vs. 17.7%; PR = 1.06 [95% CI 1.02-1.11]). A shift to stage I disease was also observed for cervical cancer (47.2% vs. 48.7%; PR = 1.02 [95% CI 0.98-1.06]) although not statistically significant. In contrast, the percentage of stage I decreased for prostate cancer (18.5% vs. 17.2%; PR = 0.93 [95%CI 0.9-0.96]) in 2014. **Conclusions:** The implementation of the ACA is associated with a shift to early stage at diagnosis for all screenable cancers except prostate cancer, which may reflect the recent US Preventive Services Task Force recommendations against routine prostate cancer screening.

6522 Poster Discussion Session; Displayed in Poster Session (Board #344), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Closure of Medicare Part D coverage gap by the Affordable Care Act (ACA) and use of oral anti-myeloma agents. *First Author: Adam J. Olszewski, Alpert Medical School of Brown University, Providence, RI*

Background: Medicare Part D pays for oral anti-myeloma immunomodulatory drugs (IMiDs, lenalidomide and thalidomide), but has a coverage gap resulting in an out-of-pocket (OOP) expense of > $ 3000 for the 1st prescription (Rx). Patients (pts) eligible for Low Income Subsidies (LIS) are exempt from cost sharing, and LIS is associated with IMiD receipt (*Olszewski, ASH 2016*). In 2011, the ACA partly closed the coverage gap with a 50% manufacturer discount on the price of brand-name drugs within the gap. We examined effects of this policy on IMiD use. **Methods:** From the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we selected Part D enrollees who started anti-myeloma chemotherapy in 2008-2012. We identified IMiD use in periods pre-ACA (2008-10) and post-ACA (2011-12), among pts with or without LIS. After confirming parallel trends in IMiD use before the ACA, we examined the effect of ACA discount on IMiD use in a difference-in-differences (DiD) model, using LIS recipients as controls whose OOP costs were not influenced by the ACA. **Results:** Among 3,313 Part D enrollees (of whom 31% received LIS), 41% received IMiDs as part of their anti-myeloma regimen. Compared with the pre-ACA period, in the post-ACA period the median gross IMiD cost of the 1st Rx increased for all pts (Table). OOP costs for the 1st Rx, and for the 1st year of IMiD therapy, decreased for LIS non-recipients. Proportion of pts entering catastrophic coverage with their 1st IMiD Rx decreased from 71% to 49%. However, there was no statistically significant effect of the ACA discount on the proportion of pts treated with IMiDs (DiD estimator, 3% [95% CI, -4 to 10]; *P*=.40), or on the time from diagnosis to 1st Rx (median 1.5 mo. in all groups). **Conclusions:** The ACA-mandated partial closure of coverage gap lowered the OOP costs for Part D enrollees treated with IMiDs. As the median OOP cost remains > $2400 for the 1st Rx, and > $4900 for the 1st year of therapy, the policy may be insufficient to overcome the financial barrier for beneficiaries who do not receive the LIS.

	No LIS		LIS	
	Pre-ACA	Post-ACA	Pre-ACA	Post-ACA
% Receiving IMiD	40%	41%	41%	39%
Median IMiD cost				
1st Rx - Gross	$ 6936	$ 7765	$ 6854	$ 7846
1st Rx - OOP	$ 3869	$ 2433	$ 3	$ 3
1st year - OOP	$ 6002	$ 4925	$ 6	$ 7

6523 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A multicenter analysis of patient reported risk factors for not working during cancer therapy. *First Author: Victoria Susana Blinder, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Treatment for most types of cancer results in work disruptions. The aim of this study is to identify risk factors for not working during cancer therapy using a patient-reported outcome tool. **Methods:** Patients of all cancer types, who were undergoing treatment with curative or palliative intent, were enrolled in a survey-based study at Memorial Sloan Kettering Cancer Center and the North Carolina Cancer Hospital from 1/2014 to 7/2015. All patients working full- or part- time at the time of cancer diagnosis were included in this analysis. Patient reported outcomes were collected using a survey tool at any time during active cancer treatment. The primary outcome of this analysis was self-reported work status at the time of survey completion. **Results:** Of 119 patients who were working before their cancer diagnosis, 68% were working at the time of survey completion. The mean age was 52.9 (range 20-80). Younger age was associated with working: 82% of patients age < 40 were working during treatment vs. 31% of patients age > 65 (p=0.01). The number of days patients reported being completely unable to work in the past month was significantly associated with work status; only 26% of patients who missed > 10 days continued to work compared to 69% who missed ≤ 10 days (p<0.01). Patients who report having a flexible work schedule were 23% more likely to continue to work during treatment (69% vs. 46%, p=0.01). In a multivariable model controlling for having an employer contingent health plan, and household income > 200% of the federal poverty level (fpl), only age, having a flexible work schedule, and inability to work > 10 days were independently associated with work status during treatment (Table). **Conclusions:** Having a flexible work schedule allowed for more work interruptions without job loss. Patients who are likely to miss more than 10 days of work and who have inflexible work schedules are at high risk of unemployment and should be targeted for employment retention initiatives.

Variables associated with working	Odds Ratio	95% CI
Age (continuous)	**0.94**	**0.90 – 0.99***
Flexible work schedule	**3.11**	**1.12 – 8.67***
Inability to work > 10 days	0.15	0.05 – 0.50*
Employer contingent insurance	2.57	0.83 – 7.90
Income > 200% FPL	0.66	0.14 – 3.16

*p-value <0.03

6524 Poster Discussion Session; Displayed in Poster Session (Board #346), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Relationship between out-of-pocket spending and drug value for oral oncolytics reimbursed by commercial insurers: 2007-2014. *First Author: Lisa Rotenstein, Harvard Medical School, Boston, MA*

Background: With total and out-of-pocket (OOP) spending for oral oncolytics rising, there is increased interest in choosing oncology treatments based on their clinical value relative to cost. We sought to determine if OOP spending varied for higher versus lower-value oral oncology drugs reimbursed by commercial insurers. **Methods:** This was a retrospective analysis of commercial insurer prescription drug claims filed between 2007-2014 for 13 oral oncolytics approved before 2009. We calculated mean monthly OOP payments for each patient. We then categorized oral oncolytics by their overall and progression-free survival benefits for each FDA-approved indication, using evidence from published studies. We assessed the relationship of survival benefit with mean monthly OOP payment, adjusting for demographic and plan characteristics. **Results:** Our population included 44,109 patients ages 18-65 (mean age = 52.5 years, SD = 9.4 years) with a cancer diagnosis who filled 731,261 prescriptions. The most commonly represented oncolytics were imatinib (37.4% of fills) and lenalidomide (17.7% of fills). Approximately 57.6% of fills were for drug-indication pairs with an overall survival benefit of 5+ months. In adjusted analyses, there was no significant difference in mean monthly OOP payment between drugs without evidence of benefit and those with 0-5 months progression-free survival benefit or 5+ months of overall survival benefit ($p > 0.05$). Meanwhile, drugs with 5-10 months progression-free survival benefit or 0-5 months overall survival benefit had higher OOP payments than those without benefit ($p < 0.01$). **Conclusions:** OOP payments for oral oncolytics were not clearly related to indication-specific value. This suggests that despite increased attention to value- and indication-based drug pricing, cost-sharing for oral oncolytics does not currently reflect these goals.

6525 Poster Session (Board #347), Mon, 1:15 PM-4:45 PM

Disrupting end-of-life cancer care delivery: Results from the engagment of patients with advanced cancer trial. *First Author: Manali I. Patel, Stanford Hospital, Menlo Park, CA*

Background: Sustainable approaches to improve quality and safety of care of patients with advanced cancer while concurrently reducing costs is a growing national need. As part of the Veterans Administration Engagement of Patients with Advanced Cancer (EPAC) trial, we trained a lay health worker (LHW) to engage patients with stage 3 and 4 cancer in early advance care planning (ACP). The goal of this follow-up study was to examine the effect of the LHW intervention on patient-reported care experiences, healthcare utilization, and costs in the last 30 days of life for patients who died within 15 months of enrollment. **Methods:** We evaluated patient-reported experiences with decision-making, healthcare utilization, and total healthcare costs 30 days prior to death. A T-test was used to compare patient experiences with decision-making. To compare ED use and hospitalizations, we utilized an exact Poisson regression. A generalized linear model with gamma link-log function was used to compare total costs. The latter methods adjusted for length of follow-up. **Results:** In the 30 days prior to death, 60 patients died in each arm within 15 months of enrollment (difference not statistically significant). Patients in the intervention had significantly improved rates of ACP documentation (98% versus 18% $p < 0.001$), improved experiences with decision-making as measured by an index ranging from 0-5 with higher values representing more favorable experience (4.73 (SD 0.61) vs 4.15 (SD 1.02)) $p < 0.001$), higher utilization of hospice (77% vs 52%, $p < 0.005$), lower rates of any emergency department use (5% versus 45% $p < 0.001$) and any hospitalization (5% versus 43% $p < 0.001$), and significantly lower total costs of care ($1,048 versus $23,482 $p < 0.001$) compared to the patients randomized to the usual care arm. **Conclusions:** Integrating a LHW into oncology care to engage patients in early advance care planning resulted in significantly improved patient experience, decreased utilization and decreased total costs in the last month of life. LHWs may represent a sustainable resource to facilitate optimal patient-centered cancer care at the end-of-life. Clinical trial information: NCT02966509.

6526 Poster Session (Board #348), Mon, 1:15 PM-4:45 PM

Cancer drug assessment: What is driving high clinical added value in France? *First Author: Judith Fernandez, French National Authority for Health, La Plaine Saint-Denis, France*

Background: Concerns about the increase of cancer drug prices emphasized the need to base pricing decisions on clinical added value (CAV). In France, the CAV assessment is done by the National Authority for Health (HAS) on a 5-point scale based on clinical data. The magnitude of the CAV is partly used by the economic committee for healthcare products to determine drugs prices: a major to moderate CAV leads to the highest prices. Recognizing the importance of presenting clear statements, we analyzed which criteria are taking into account for CAV appraisal. **Methods:** A retrospective and descriptive study analysis of all new hematology/oncology cancer indications assessed by HAS between 2010 and 2015 has been conducted. For each appraisal, information regarding the level of evidence and clinical effect has been collected. **Results:** 78 new cancer indications (58 drugs) have been assessed: 20 had a major to moderate CAV (25%), 32 a minor CAV (41%) and 26 no CAV (33%). The percentage of major to moderate CAV was higher when a comparative pivotal trial was conducted (25%, 16/62 vs. 20%, 4/16). Among the 62 comparative trials, 58 had a superiority design (94%) supporting a major to moderate CAV in 27% (16/58) of the cases. Overall survival (OS) was measured in 91% of the pivotal trials (n = 71) and in 24% (n = 19) as a primary outcome. A higher proportion of major to moderate CAV were observed in trials using OS as a primary endpoint (31%, 6/19) than progression free survival (PFS) (23%, 9/39) or response rate (25%, 5/20). When a major to moderate CAV was obtained, a median absolute gain of 4 and 8 months for OS and PFS respectively were observed. All non-inferiority or non-conclusive designs led to no or minor CAV whatever the quantity of clinical effect. **Conclusions:** CAV is assessed in a two-step process where clinical effect is taken into account when level of evidence is appropriate. Consequently, there is not a unique profile of outcomes supporting a major to moderate CAV but a combination of several key elements such as study design, primary endpoint, and statistical significance. HAS appraisals remain multi-factorial, and medical need add a nuance to HAS expectations in terms of level of evidence.

6527 Poster Session (Board #349), Mon, 1:15 PM-4:45 PM

Changes in insurance coverage associated with health care reform for cancer survivors aged 19-64 years. *First Author: Amy J. Davidoff, Yale School of Public Health, New Haven, CT*

Background: Beginning in 2014, Medicaid eligibility was expanded in over half of states, enrollment was simplified, and insurance marketplaces were created in all states with premium subsidies for selected individuals, as a result of implementation of the Affordable Care Act (ACA). We examine changes in insurance coverage for cancer survivors overall, and for targeted subgroups affected by specific ACA elements. **Methods:** We pooled data for cancer survivors aged 19-64 years from the 2012-2015 National Health Interview Survey. Using information on family structure, income, and employment, and linked state-specific Medicaid eligibility policies, we assigned survivors to 3 targeted groups: 1) Medicaid eligible pre-ACA; 2) Medicaid expansion eligible; 3) eligible for premium tax credits for Marketplace plans; and 3 groups not targeted for benefit: a) eligibility gap (income < 100% federal poverty level (FPL) in states not expanding Medicaid); b) with alternative "affordable" coverage; and c) high income (> 400% FPL). Linear probability regressions examined pre(2012-13)/post (2014-15) coverage changes by eligibility category, adjusting for demographic characteristics. **Results:** Among 4,115 (wtd N = 6.90M) cancer survivors, insurance pre-ACA was 69% private, 15.2% public, and 12.2% uninsured. Post-ACA, overall public coverage increased by 3.2 percentage points (pct pt) ($p = .036$), whereas the percent uninsured decreased by 4.5 pct pt ($p < .001$). Relative to the high income category, the adjusted percent uninsured decreased by 8.4 pct pt (95% CI:1.2-15.5) among pre-ACA Medicaid eligible, by 16.7 pct pt (95% CI:8.9-24.4) among the newly Medicaid eligible, and by 11.3 pct pt (95% CI:1.0-23.4; $p = .069$) among premium subsidy eligible. No coverage gains were observed for the other 2 categories. Approximately 531,000 cancer survivors remained uninsured after ACA implementation, with over half eligible for either Medicaid (12%) or subsidized Marketplace plans (44%). **Conclusions:** In the first 2 years post-ACA, cancer survivors experienced substantial increases in insurance coverage, with changes limited to targeted subgroups. Over half of remaining uninsured were eligible for coverage.

6528 Poster Session (Board #350), Mon, 1:15 PM-4:45 PM

Validation of natural language processing (NLP) for automated ascertainment of EGFR and ALK tests in SEER cases of non-small cell lung cancer (NSCLC). *First Author: Bernardo H. L. Goulart, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The Surveillance, Epidemiology, and End Results (SEER) registries lack information on the Epidermal Growth Factor Receptor (EGFR) mutation and Anaplastic Lymphoma Kinase (ALK) gene rearrangement test results. With the goal of enabling population-based outcomes research in molecularly selected NSCLC subgroups, we conducted a validation study of NLP for ascertainment of EGFR and ALK testing from electronic pathology reports (e-paths) of patients included in the Seattle-Puget Sound (SPS) and Kentucky Cancer (KCR) SEER registries. **Methods:** We obtained 4,278 and 1,041 e-paths pertaining to 1,634 and 565 patients with stage IV non-squamous NSCLC diagnosed from 1/1/2011 to 12/31/2013 and included in the SPS and KCR registries, respectively. Two oncologists independently reviewed all reports to generate a gold-standard dataset. We used 855 of the SPS reports to train hybrid rule-based and machine learning algorithms for detection of test status (reported vs. not reported), and test result if reported (positive vs negative) for EGFR mutational analysis and ALK testing by FISH, IHC, or gene sequencing. In the remaining 3,423 SPS reports, we conducted a 5-fold cross-validation analysis to estimate the internal NLP sensitivity, specificity, positive predictive value, and negative predictive value for test status and results, respectively. We used a hierarchical rules system to assess the NLP accuracy at the patient level. For external validation, we repeated all analyses in the KCR dataset. **Results:** In the SPS internal validation report sample, the validity metrics ranged from 97% to 99% for EGFR and ALK test status, and from 95% to 100% for EGFR and ALK test results, respectively. In the KCR external validation report sample, the metrics ranged from 74% to 96% for EGFR and ALK test status, and 2% to 100% for test results, respectively. At the patient level, the NLP accuracy for EGFR and ALK was 95% and 96% (SPS cohort), and 70% and 72% (KCR cohort) respectively. **Conclusions:** NLP is a valid method for determining EGFR and ALK test status and results for patients included in SEER registries with access to e-path, but the algorithms likely need to be registry-specific.

6529 Poster Session (Board #351), Mon, 1:15 PM-4:45 PM

Financial conflicts of interest at three prominent oncology clinical pathway vendors. *First Author: Robert Michael Daly, Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The American Society of Clinical Oncology (ASCO) reports that in 2015 62% of oncology practices are adhering to a clinical pathway and 31% are adhering to more than one pathway. ASCO and the American Medical Association have raised concerns about the conflicts of interest of those that design these pathways. **Methods:** Using the public Centers for Medicare and Medicaid Services Open Payments database, we abstracted the 2015 financial conflicts of interest for the 2016 voting members of the Value Pathways (a combined effort of US Oncology and NCCN), the medical oncology committee chairs for Via Oncology, and the medical advisory board for eviti. We focused on national pathway vendors and on non-research general payments, such as gifts, consulting, and speaker fees. **Results:** Nearly all involved in pathway development received non-research general payments in 2015, including 92% of US oncology, 84% of NCCN, 84% of Via Oncology, and 69% eviti. The average general payments ranged from $3.5K for US Oncology Value Pathways voting members to $15.3K for NCCN Value Pathways voting members. Eight percent of US Oncology voting members, 19% of the eviti medical advisory board, 28% of Via Oncology chairs, and 42% of NCCN voting members received $10,000 or more in general payments in 2015. **Conclusions:** Given the prominent role clinical pathways have on oncologists' prescribing behavior and the often subjective nature of determining on-pathway treatment, pathway vendors should take care to make accessible their conflict of interest policies and elucidate how they manage relationships of concern.Steps would include potentially limiting the number of committee members receiving payments and limiting the amount of general payments to each physician.

6530 Poster Session (Board #352), Mon, 1:15 PM-4:45 PM

What does the general population think about chemotherapy shortages? *First Author: Zachary Ak Frosch, Brigham and Women's Hospital, Boston, MA*

Background: Chemotherapy shortages have been increasingly recognized, and most oncologists report their patients have been at least intermittently affected. Despite their potential impact, little is known about the perspectives of the general population regarding shortages. **Methods:** In October 2016, we conducted a survey using the GfK KnowledgePanel, an online probability-based sample representative of adults in the United States. We assessed awareness of shortages, and provided vignettes in which a substitute chemotherapy drug had either a major or minor difference in side effects or effectiveness. We asked respondents whether they would want to be informed of a substitution, and, if the original drug were available elsewhere, would transfer care to receive it. We also asked if cancer centers were to publish drugs in shortage at their center, if such data would affect decisions about where to seek care. Analyses applied post-stratification sampling weights to draw national inferences. **Results:** Of 737 potential participants, 420 (57%) responded; 16% had heard of chemotherapy shortages. Respondents with a personal history of cancer were more likely to have heard of shortages (31% vs 14%, $p = 0.03$), as were those with greater education ($p = 0.01$) and those who reported more sources of health information ($p = 0.01$). Most desired to be informed about a chemotherapy substitution in the setting of both major (87%) and minor (83%) differences in side effects, as well as both major (87%) and minor (82%) differences in effectiveness. In contrast, only 61% reported they would transfer care if a substitute drug had major differences in side effects, and even fewer (40%) for minor differences. Similarly, 72% and 46% reported they would transfer care if a substitute had major or minor differences in effectiveness respectively. Finally, 57% reported that publically-reported shortage data would be a "big factor" in deciding where to be treated. **Conclusions:** Our data suggest that the general population is largely unaware of chemotherapy shortages. Moreover, in the setting of even minor changes in effectiveness or side effects, respondents wanted to be made aware of substitutions. With major differences, many would seek care elsewhere.

6531 Poster Session (Board #353), Mon, 1:15 PM-4:45 PM

Mammography use in breast cancer survivors: An administrative claims study. *First Author: Kathryn Jean Ruddy, Mayo Clinic, Rochester, MN*

Background: Annual mammography is recommended to screen residual breast tissue for new cancers and recurrent disease after treatment for early stage breast cancer. This study aimed to assess mammography rates over time in breast cancer survivors. **Methods:** We used administrative claims data from a large U.S. commercial insurance database, OptumLabs, to retrospectively identify privately- and Medicare Advantage-insured women with operable breast cancer who had residual breast tissue after definitive breast surgery between 2006 and 2015. We required coverage for at least 13 months following surgery. For each subsequent 13-month time period, we only included women without a loss of coverage, bilateral mastectomy, metastatic breast cancer diagnosis, or non-breast cancer diagnosis. We calculated the proportion of patients who had a mammogram during each 13-month period following breast surgery. We used multivariable logistic regression to test for factors associated with mammography in the first 13 months. **Results:** The cohort included 26,011 women followed for a median of 2.9 years (IQR 1.9-4.6) after surgery; 63.1% were less than 65 years of age, and 74.4% were white. In their first year of follow-up, 86% underwent mammography, but by year 7, this decreased to 73%. Fewer than 1% underwent MRI instead of mammography. In multivariable analysis, mammograms were less likely during the first year after surgery among women aged < 50 years (odds ratio [OR], 0.7; 95% confidence interval [CI], 0.6 to 0.8), African Americans (OR, 0.7; 95% CI, 0.7 to 0.8), patients who underwent mastectomy (OR, 0.7; 95% CI, 0.6 to 0.7), and patients residing in the Western part of the country (OR, 0.9; 95% CI, 0.7 to 0.9). Those with 1-2 comorbidities were more likely (OR, 1.1; 95% CI 1.1-1.2) than those with none to have a mammogram during that period. Mammography use did not differ significantly by year of diagnosis (2006-2015). **Conclusions:** Even in an insured cohort, a substantial proportion of breast cancer survivors do not undergo annual surveillance mammography. Mammography use falls as the time from the early stage breast cancer diagnosis increases. Understanding factors associated with lack of mammographic screening may help improve survivorship care.

6532 Poster Session (Board #354), Mon, 1:15 PM-4:45 PM

Impact of insurance status on treatment for stage 0-IV breast cancer. *First Author: Rachel Adams Greenup, Department of Surgery, Duke University Medical Center, Durham, NC*

Background: Health insurance can influence utilization of cancer care. We sought to determine whether insurance status impacts treatment patterns and survival in women with stage 0-IV breast cancer. **Methods:** Women ages 18-69 years old, diagnosed with unilateral stage 0-IV breast cancer between 2004 and 2014 were selected from the National Cancer Data Base. Insurance status was categorized as Private, Medicare (65+ yo), Medicare (18-64 yo), Medicaid, or Uninsured. After adjustment for known covariates, generalized and binary logistic regression were used to estimate the association of insurance type with receipt of treatment. A multivariate Cox proportional hazards model was used to estimate the association of insurance status with overall survival. **Results:** A total of 610,450 women met inclusion criteria. Median age was 56 (48-63). Insurance status included: 72.1% Privately insured, 13.9% Medicare 65+, 4.8% Medicare 18-64, 7.1% Medicaid, and 2.1% Uninsured. Women with private insurance were more likely to present with stage 1 breast cancer, and less likely to present with stage 4 disease when compared to Medicaid or Uninsured patients (stage 1: 63.4%, 49.4%, 48.2%, $p < 0.01$; stage IV: 0.8%, 1.8%, 2.1%, $p < 0.01$). Risk of death was higher in uninsured or Medicaid patients when compared to those with private insurance (HR 1.52, 95% CI 1.41-1.64; HR 1.6, 95% CI 1.52-1.68). Receipt of chemotherapy and radiation did not differ between Medicaid, Uninsured, or Privately insured patients, but women without private insurance were more likely to receive neoadjuvant chemotherapy (OR 1.14, 95% CI 1.09-1.19; OR 1.16, 95% CI 1.07-1.25, respectively, $p < 0.01$). Uninsured women were more likely to undergo mastectomy without reconstruction (OR 1.57, 95% CI 1.49-1.65), and less likely to undergo unilateral or bilateral mastectomy with reconstruction than lumpectomy and radiation (OR 0.57, 95% CI 0.53-0.61; OR 0.35, 95% CI 0.32-0.39). **Conclusions:** Stage at diagnosis and risk of death were higher in Medicaid and uninsured breast cancer patients when compared to those with private insurance. Insurance status did not predict differences in receipt of surgery, chemotherapy, or radiation but did affect oncologic outcomes.

6533 Poster Session (Board #355), Mon, 1:15 PM-4:45 PM

Assessment of actionability of cancer genomic testing panels based on a structured clinical trial knowledge base. *First Author: Mia Alyce Levy, Vanderbilt University, Nashville, TN*

Background: Today's oncologist is responsible for choosing appropriate cancer genomics tests to inform patient treatment from multiple available platforms, weighing cost, availability, sensitivity and specificity, and clinical actionability. Knowledge-driven clinical decision support tools can assist clinicians in choosing the panel that is most informative in a given clinical space. **Methods:** Using a queryable knowledgebase of >1800 active clinical trials containing structured eligibility criteria curations for diagnosis and genomic alterations, we compared two CLIA-regulated genomic panels for clinical actionability over the landscape of solid, breast, and lung cancer clinical trials. **Results:** The larger panel (73 genes) was more actionable than the smaller panel (62 genes) in the breast cancer (10x more trials returned) and solid tumor (2.7x more trials returned) clinical trial space, while the smaller panel returned 1.2x more trials in the lung cancer space (see table). **Conclusions:** This analysis demonstrates that patient diagnosis has a significant effect on the potential clinical actionability of a given genomic panel. Further, this analysis demonstrates the clinical utility of knowledge-driven clinical decision support tools for test selection, especially given the often-limited tumor sample available, cost of genomic panel testing, and continuously shifting trial landscape.

Number of trials with eligibility criteria containing genes tested on two-CLIA regulated panels.

	Breast Cancer Trials	Lung Cancer Trials	Solid Cancer Trials
Panel 1 (73 genes)	22	15	71
Panel 2 (62 genes)	2	18	19

6534 Poster Session (Board #356), Mon, 1:15 PM-4:45 PM

Disparities in access to breast cancer treatment: An observational study based on insurance status. *First Author: Karthik Kailasam, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI*

Background: Breast cancer is the second leading cause of cancer death in Caucasians and African-Americans, and the most common cause of cancer death in Hispanic women. **Methods:** A retrospective analysis was done with data obtained from 1473 hospitals by National cancer database (NCDB) for the years 2004-2014. Patients with breast cancer were analyzed for differences in treatment offered based on their insurance status. Patients in the insurance group were enrolled under either Private, Medicare, Medicaid or other government insurance. Treatments offered were surgery, chemotherapy, radiation therapy or a combination of the above. Patients with unspecified insurance status and those who were on active surveillance were excluded from the analysis. **Results:** A total of 2,245,259 patients with breast cancer from all age groups were identified from the registry. 47,294 patients did not have insurance; among which 3275 (7.4%) were not offered any treatment. Among 2,093,809 patients with insurance, 58,726 (2.8%) patients were not offered any treatment. Hence, patients without insurance were twice (OR 2.65; CI 2.55-2.75 $p < 0.0001$) more likely to not receive any first course treatment. Sub-group analysis for different stages of breast cancer showed; carcinoma in-situ (OR 2.44; CI 2.20-2.71 $p < 0.0001$), stage1 (OR 2.68; CI 2.43-2.96 $p < 0.0001$), stage2 (OR 2.86; CI 2.61-3.12 $p < 0.0001$), and stage 3 (OR 2.56; CI 2.25-2.92 $p < 0.0001$) have similar odds for not being offered any treatment. However, the odds of receiving treatment were better for stage 4 breast cancer (OR 1.44; CI 1.32-1.55 $p < 0.0001$). Uninsured Caucasians (OR 2.70; CI 2.56-2.85 $p < 0.0001$) were less likely to receive any treatment compared to uninsured African-Americans (OR 2.16; CI 2.00-2.33 $p < 0.0001$) and uninsured Hispanics (OR 1.66; CI 1.52-1.82 $p < 0.0001$) **Conclusions:** With the recent suggested changes in health care policy, we can expect the number of uninsured patients to rise and therefore more patients might not have access to breast cancer treatment.

6535 Poster Session (Board #357), Mon, 1:15 PM-4:45 PM

Does access to cancer drugs relate to survival benefit? A European study in countries with different economic status. *First Author: Nils Erik Wilking, Skane University Hospital, Stockholm, Sweden*

Background: As new cancer drugs come at a high cost, it is of interest to examine if drugs with high impact on survival has a relative higher uptake compared to drugs with limited impact on survival in countries with limited resources (low Gross National Product; GDP/capita) versus countries with better resources (medium or high GDP/capita). **Methods:** Based on published clinical trial data, including ESMO- and ASCO value scales, we selected three drugs with high impact on survival and their main indications; imatinib/Chronic Myeloid Leukemia (CML), rituximab (some use outside oncology)/lymphoma and trastuzumab/breast cancer compared to everolimus/ renal cancer, sorafenib/renal cancer and bevacizumab/colorectal cancer as drugs with limited impact on survival. Countries in Europe were divided into three economic groups: upper-tier GDP/ capita 36,000 – 73,400 €; (Austria, Belgium, Denmark, Finland, Ireland, The Netherlands, Norway, Sweden, Switzerland); mid-tier GDP 22,800 – 35,400 €; (France, Germany, Italy, Spain, UK) low-tier GDP 5,800 – 18,100 € (Bulgaria, Croatia, Czech Republic, Greece, Hungary, Poland, Portugal, Romania, Slovakia, Slovenia). Sales data from IMS Health and epidemiological data from IARC Cancer Mondial, (WHO) were used. Access to drugs was measured as use in g/case (defined as cancer mortality in 2012) and includes total usage from introduction until end of 2014. Access in the upper-tier country group was set as 100% usage. **Results:** As seen in the table, access in mid-tier countries was 64-76% and low-tier countries 34-55% respectively for drugs with higher survival impact and access in mid-tier countries was 73-105% and low-tier countries 34-59% respectively, for drugs with lower survival impact. More detailed data on access in individual countries within each GDP/capita group will also be presented. **Conclusions:** Proven survival benefit did not affect spending on costly cancer drugs in countries with lower GDP.

Drug	High-tier GDP access g/case	Mid-tier GDP % of high-tier	Low-tier GDP % of high-tier
Imatinib	2093.9	76	55
Rituximab	386.6	64	52
Trastuzumab	57.1	67	34
Everolimus	6,4	73	36
Sorafenib	699.1	105	59
Bevacizumab	27.6	83	34

6536 Poster Session (Board #358), Mon, 1:15 PM-4:45 PM

Enrollment of high-risk patients with diffuse large B-cell lymphoma in clinical trials. *First Author: Kah Poh Loh, University of Rochester Medical Center, Rochester, NY*

Background: Contemporary precision medicine trials in DLBCL often require real-time central pathology review for enrollment. Central review may lead to treatment delays and prevent high risk patients (pts) with aggressive presentations from enrolling onto clinical trials. We explored reasons pts with DLBCL were not enrolled on trials and the implication of non-enrollment on trial design and interpretation. **Methods:** We retrospectively analyzed all pts with histologic diagnosis of DLBCL or HGBL from 4/14 to 6/16 at the University of Rochester. Therapeutic trials open during this time included 3 sponsored and 2 NCTN studies. The Kaplan-Meier method was used to estimate the distribution of progression-free survival (PFS; time from start of treatment until progression/death or until the last date the patient was known to be progression free) and overall survival (OS). **Results:** 140 pts were identified; 22% enrolled on a trial. Reasons for non-enrollment included: 1) Protocol ineligibility (n=58); (2) Physician choice (n=24) and; 3) Patient choice (n=20). Reasons were unclear in 8 pts. Of the 24 pts who were not enrolled due to physician choice, 21 required urgent treatment secondary to symptoms or rapid progression. Compared to pts treated on trial, pts with rapid progression had higher risk clinical features (table). There was a trend towards a lower 1-year PFS rate in pts who required urgent treatment compared to those on trial (72.1% vs. 56.1%; p=0.08). There was no statistical difference in OS. **Conclusions:** At our institution, for patients with DLBCL meeting trial eligibility criteria, 42% required urgent chemotherapy and failed to enroll. Exclusion of these high risk patients in precision medicine trials has important implications in the interpretation and generalizability of clinical trials in DLBCL. In this curable malignancy, excluding high risk patients from trials limits the event rate, and associated power to demonstrate impact of novel therapies.

	Total N=47	On trial N=30	Off trial N=17
Median Age (yrs)	66	66	66
ECOG ≥2 (%)	21	13	35
Stage (%)*			
Limited	32	40	18
Advanced	68	60	82
Elevated LDH (%)*	57	47	77
IPI (%)*			
0-1	21	27	12
2	15	17	12
3	34	43	18
4-5	30	13	59
GCB (%)	51	47	59
Non-GCB (%)	49	53	41
***MYC* Rearrangement (%)**	13	7	24

*P < 0.10

6537 Poster Session (Board #359), Mon, 1:15 PM-4:45 PM

Comparison between Canadian and British oncology drug review recommendations and their impact on patient access. *First Author: Matthew K. Smith, University of Calgary Cumming School of Medicine, Calgary, AB, Canada*

Background: Access and funding for oncology medications in Canada and the United Kingdom are influenced by recommendations released by the pan-Canadian Oncology Drug Review (pCODR) and the National Institute for Health and Care Excellence (NICE), respectively. This study investigated variations between these organizations' recommendations and the clinical implications these differences had on access to medications. **Methods:** The pCODR Drug Review and NICE Technology Appraisal Guidance databases were reviewed to identify all oncological drug recommendations made by both agencies between 2008 and 2016. Recommendations were matched and then evaluated according to an algorithm to identify clinically relevant differences that restricted access in one jurisdiction relative to the other. Length of time from drug submission to final recommendation by NICE and pCODR were compared using Wilcoxon rank sum tests, as was the length of time between regional funding approval. **Results:** Between 2008 and 2016, 31 medication indications were evaluated by both pCODR and NICE. For 12 indications, funding was only supported by one agency. Eight indications were approved by both agencies, but with clinically relevant differences in wording, with each agency making a more restrictive recommendation four times. Average time from submission to recommendation was faster for pCODR than NICE (213.8 days vs. 407.9 days; $p < 0.001$) but the average time to funding decision (see table) was similar (410.1 days in Canada vs. 407.9 days in the United Kingdom; $p = 0.71$). **Conclusions:** Although clinically relevant differences in recommendations do exist between NICE and pCODR, neither agency was consistently more restrictive. pCODR recommendations were made more quickly than NICE, but this did not translate into faster funding approval in Canada. Jurisdictional barriers exist for cancer patients which could be mitigated through harmonization and acceleration of drug review processes.

Length of time from the submission of a medication indication to a funding decision.

Agency	Mean Length (days)
NICE (n=31)	407.9
pCODR to Provincial Funding Decision	
AB(n=22)	417.6
BC (n=17)	410.1
SK (n=21)	401.8
MN (n=20)	448.0
ON (n=20)	373.5

6538 Poster Session (Board #360), Mon, 1:15 PM-4:45 PM

A machine learning approach to predicting short-term mortality risk for patients starting chemotherapy. *First Author: Ravi Bharat Parikh, Brigham and Women's Hospital, Boston, MA*

Background: Patients who die soon after starting chemotherapy incur symptoms and financial costs without survival benefit. Prognostic uncertainty may contribute to increasing chemotherapy use near the end of life, but few prognostic aids exist to guide physicians and patients in the decision to initiate chemotherapy. **Methods:** We obtained all electronic health record (EHR) data from 2004-14 from a large national cancer center, linked to Social Security data to determine date of death. Using EHR data before treatment initiation, we created a machine learning (ML) model to predict 180-day mortality from the start of chemotherapy. We derived the model using data from 2004-11 and report predictive performance on data from 2012-14. **Results:** 26,946 patients initiated 51,774 discrete chemotherapy regimens over the study period; 49% received multiple lines of chemotherapy. The most common cancers were breast (23.6%), colorectal (17.6%), and lung (16.6%). 18.4% of patients died within 180 days after chemotherapy initiation. Model predictions were used to rank patients in the validation cohort by predicted risk. Patients in the highest decile of predicted risk had a 180-day mortality of 74.8%, vs. 0.2% in the lowest decile (area under the receiver-operating characteristic curve [AUC] 0.87). Predictions were accurate for patients with metastatic disease (AUC 0.85) and for individual primary cancers and chemotherapy regimens—including experimental regimens not present in the derivation sample. Model predictions were valid for 30- and 90-day mortality (AUC 0.94 and 0.89, respectively). ML predictions outperformed regimen-based mortality estimates from randomized trials (RT) (AUC 0.77 [ML] vs. 0.56 [RT]), and National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) estimates (AUC 0.81 [ML] vs. 0.40 [SEER]). **Conclusions:** Using EHR data from a single cancer center, we derived a machine learning algorithm that accurately predicted short-term mortality after chemotherapy initiation. Further research is necessary to determine applications of this algorithm in clinical settings and whether this tool can improve shared decision making leading up to chemotherapy initiation.

6539 Poster Session (Board #361), Mon, 1:15 PM-4:45 PM

Accelerating clinical trial enrollment with comprehensive genomic profiling (CGP) and just-in-time clinical trial sites: An index case of a paradigm shift. *First Author: Gaurav Singal, Foudation Medicine, Inc., Cambridge, MA*

Background: In many instances, trials may offer the best or only therapeutic option for patients with rare findings. However, conducting clinical trials of novel therapeutics targeting rare molecular variants is challenging. Patient populations are small, distributed, and predominantly in community settings where trial access remains limited by awareness and site availability. These challenges increase costs of drug development and approval, delaying widespread patient access. **Methods:** Foundation Medicine deployed a trial education and access program, "Precision Enrollment," with Ignyta (a trial sponsor) and Pharmatech (a site management organization, or SMO, enabling "Just-In-Time" clinical trials) (Wiener, JCO 2007). Infrastructure and algorithms developed at Foundation Medicine ("SmartTrials Engine") matched sequenced patients (avg n = 800/wk) with activating NTRK, ROS1, or ALK fusions to the phase II study of Entrectinib (NCT02568267). Oncologists at Foundation Medicine, through peer-to-peer outreach, facilitated trial access by providing trial and nearest site information to treating providers of matched patients. **Results:** 107 treatment-eligible patients with NTRK, ROS1, or ALK fusions were matched by the SmartTrials Engine; 36 (33%) expressed interest in trial participation. One such patient with NSCLC and a CD74-ROS1 fusion was unable to participate at an open trial site due to inability to travel. The patient's site was part of the "Just-In-Time" network, with IRB and contract pre-approval, and was activated in only 3 days. Total time from patient identification to initiation of therapy was 7 days. **Conclusions:** We demonstrate a novel methodology for patient matching to trials targeting rare genomic findings, including in community settings. If extended, such innovative partnerships combined with computational matching infrastructure, could improve drug development and therapeutic access.

6541 Poster Session (Board #363), Mon, 1:15 PM-4:45 PM

Thirty-day readmissions in metastatic cancer patients: Room for improvement? *First Author: Rachel Solomon, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: To date, cancer has been excused from most readmission reduction efforts. Yet reported readmission rates for cancer patients discharged from medical services are as high as 27%. Some readmissions for patients with metastatic disease may be avoidable. We assessed the prevalence of potentially preventable readmissions and associated factors in adult patients with metastatic cancer. **Methods:** We measured 30 day readmissions for dehydration, cancer-related pain, and failure to thrive in patients with primary diagnosis metastatic cancer on index admission to a New York State hospital between December 1, 2012 and December 31, 2014. We used competing risk models to assess the effects of demographics, comorbidities, hospital type, payor, and discharge disposition. **Results:** During the study period, 11,275 patients had 19,307 index hospitalizations with primary diagnosis, metastatic cancer. The 30 day readmission rate was 24.5% of which 8.9% (424) were potentially preventable. Black (HR 1.26, 1.17-1.35) and Hispanic patients (HR 1.19, 1.09-1.31) had higher rates of readmission than whites. Being older (HR per 10 years of age 0.94, 0.90-0.97), female (HR 0.95, 0.91-0.99), having private insurance (HR 0.87, 0.87-0.81) and discharge to hospice (HR 0.62, 0.42-0.91) decreased risk of readmission. Discharge home with services (HR 1.21, 1.14-1.27) or to a skilled nursing facility (SNF) (HR 1.11, 1.01-1.23) conferred higher risk than going home unaided. Index hospitalization at public hospitals increased risk (HR 1.1, 1.02-1.18); teaching hospitals were protective (HR 0.84, 0.774-0.92). Patients with potentially preventable readmissions were younger (HR per 10 years of age 0.85, 0.78-0.93). Compared to those who went home unaided, patients discharged with services were more likely (HR 1.31, 1.05-1.64) and those discharged to SNF were less likely to have avoidable returns (HR 0.55, 0.37-0.81). Payor, gender, race, comorbidities, and index hospital type did not contribute. **Conclusions:** While the overall rate of potentially preventable admissions among metastatic cancer patients is low, higher readmission rates among those discharged home with help suggests that services supplied are not sufficient to address their health needs.

6542 Poster Session (Board #364), Mon, 1:15 PM-4:45 PM

National coverage analyses for NCI clinical trials: A pilot project to reduce participation barriers. *First Author: Andrea Denicoff, National Cancer Institute, Rockville, MD*

Background: Since the implementation of the ACA, many insurers have followed Medicare's lead in covering routine care costs associated with clinical trials (CTs). However, questions remain on how to distinguish routine care from non-billable research costs, and this has important financial implications for both sites and patients. As a result, many sites individually conduct coverage analyses (CAs) prior to opening CTs to determine billable routine costs. This is a significant duplication of effort for NCI network CTs that are open at hundreds of sites. A 2015 ASCO-NCI initiative identified the centralized creation of CAs for national CTs as a potential solution to reduce site burden, increase CT transparency and billing compliance, and ultimately reduce barriers to CT participation. We provide initial findings from the resulting NCI pilot program. **Methods:** NCI set up a Coverage Analysis Working Group (CAWG) made up of representatives from NCI's Cancer Trials Support Unit (CTSU), network groups, NCI, and billing compliance consultants. CAWG created a CA template and development process for NCI network trials. CAWG will survey site users in April 2017 to evaluate the first year of the pilot project. **Results:** CAs for 7 CTs were first posted to the CTSU website on 4/20/16. As of January 2017, CAs have been posted for 22 CTs: 17 NCTN and 5 NCORP. This represents 14.6% of the 150 large, later-phase network trials available on the CTSU. These CAs had been posted for a mean of 219 days (median 238) as of 1/31/17. In this time, CAs were downloaded an average of 319 times (median 301), for a total of 7,007 downloads. An additional 26 CAs have been posted for MATCH (n = 20) and LUNG-MAP (n = 6) sub-studies and downloaded 7,035 times. Survey results evaluating this CA pilot will be presented in June 2017. **Conclusions:** Providing centralized CAs to NCI's national network trials is feasible and well received with sites reporting that this pilot is reducing the time and effort of opening CTs and improving CT funding transparency. Collaboration is needed with CMS and third party payers to enhance clarity around CT coverage policy and billing compliance, along with continued feedback to make further improvements to reduce trial barriers.

6543 Poster Session (Board #365), Mon, 1:15 PM-4:45 PM

Communication about immunotherapy: Barriers and information to discuss. *First Author: Kristen Gillespy, Winship Cancer Institute, Atlanta, GA*

Background: Since immunotherapy is a promising new therapeutic approach to cancer treatment, improving physician/patient communication about this approach is important. No communication guidelines exist. To begin to fill this gap, we identified provider and patient preferences for information, and identified barriers to communication about immunotherapy. **Methods:** We qualitatively interviewed 15 oncology professionals who offer immunotherapy treatment about the information they deemed important to communicate to patients and the communication barriers. After a discussion about immunotherapy options with a provider, we interviewed 18 oncology patients about the information that was most useful to them and their impressions of immunotherapy. We captured impressions on two 1-5 scales with 5 being 'very positive impression' and 'very likely to be cured' and by picking words from a list of positive and negative terms like 'effective' and 'risky.' All open-ended questions were qualitatively coded. We reached saturation of themes with 18 patients. **Results:** Patients identified 4 useful topics to discuss: treatment options, benefits, treatment logistics, and side effects. Providers identified 3 topics important topics to convey: side effects, realistic view of benefit and treatment logistics. The most frequently provider-identified barrier to communication was patients' baseline misconceptions about immunotherapy's effectiveness. Supporting this, patients' impressions were very positive (average of 4 on impressions scale and 3.9 on potential to be cured scale.) The most frequently chosen word patients chose to describe immunotherapy treatment was 'hopeful' (10/18 55%). **Conclusions:** There is largely agreement on the important topics to discuss about immunotherapy, though half of the patients thought a discussion of treatment options would be useful and only one physicians mentioned options. Of note, communication is hampered by patients' preconceptions about immunotherapy's effectiveness. Communication guidelines should identify techniques to effectively overcome this barrier.

6544 Poster Session (Board #366), Mon, 1:15 PM-4:45 PM

A patient navigation program to enhance access to care for undeserved patients with a suspicion or diagnosis of cancer in Mexico City. *First Author: Alexandra Bukowski, Global Cancer Institute, Boston, MA*

Background: High cancer mortality rates in developing nations are partially driven by advanced stages at diagnosis and limited access to care. In Mexico, the interval from problem identification to start of treatment can be up to 7 months, mostly due to healthcare system delays. We implemented a patient navigation (PN) program aimed at reducing time to referral to cancer centers for patients (pts) with a suspicion or a diagnosis of cancer seen at a public general hospital in Mexico City. **Methods:** Pts age $>$ 18 seen at *Hospital General Ajusco Medio* in Mexico City who required referral to a cancer center were enrolled. Baseline demographic, economic and psychosocial data were collected. A Patient Navigator assisted pts with scheduling; paperwork; obtaining results in a timely manner; transportation; and with other cultural barriers. The goal of the PN program was for at least 70% of enrolled patients to obtain a specialized appointment at a cancer center within the first 3 months from enrollment. **Results:** 53 pts (median age 54, range 19-80; 51% female) were included between 01/16 and 12/16. 19% (n = 10) had breast/GYN, 19% (n = 10) GU, 19% (n = 10) endocrine, 19% GI (n = 10) and 14% (n = 13) other tumors. All the pts were uninsured, 59% (n = 30) had less than middle school education, 80% (n = 41) were unemployed and 96% (n = 49) had a monthly household income of $<$ $360 USD. 54% (n = 28) reported deprivation in at least one basic living need (education, running water, toilet, electricity or flooring). The most commonly identified barriers to healthcare access were financial (73%, N = 37), lack of transportation (47%, N = 24), fear (37%, N = 19) and poor communication with healthcare workers (35%, N = 18). Mean time to referral was 11 days (range 0–46, SD 11.2) and mean time to cancer specialist appointment 26 days (range 1–94, SD 21.18). 92% of pts successfully obtained appointments at a cancer center in $<$ 3 months. **Conclusions:** Compared with previously reported data, this PN program shortened time to referral to a cancer center for pts with a suspicion or diagnosis of cancer in Mexico City. PN represents a potential solution to overcome barriers to healthcare access for underserved pts with cancer in developing countries.

6545 Poster Session (Board #367), Mon, 1:15 PM-4:45 PM

Exploring the time delay between regulatory approval and health techonology assessments (HTAs) of oncology therapies in France, Germany, England, Scotland, Canada, and Australia. *First Author: Ashley Jaksa, Context Matters, New York, NY*

Background: Drugs in the USA become available from the moment of FDA approval. Access to oncology therapies outside of the USA may be delayed by regulatory and additional payer HTA processes. This study aimed to examine the time from regulatory approval to an HTA reimbursement decision in countries with mandatory HTA. **Methods:** Oncology HTAs (N=569) for medicines approved by the EMA, Health Canada, and the Therapeutic Goods Administration (Australia) were matched on indication with HTAs from France, Germany, Canada, England, Scotland, and Australia. Resubmissions were excluded. The date of the first reimbursement decision was subtracted from the date of the regulatory approval to determine the time taken to complete HTA and to issue reimbursement decision. Trends by country were examined. **Results:** Time between regulatory approval and HTA reimbursement required a mean of 321 days (Median=214 days; Std.Dev. 330 days). Access in England took the longest, on average, (547 days) to issue a decision compared to the other countries. This time was two to three times longer than any other country. Australia had the shortest time to issue a reimbursement decision, which was approximately 6 months. **Conclusions:** Approximately one additional year is required after regulatory approval for oncology medicines to complete HTA and receive a reimbursement decision, potentially delaying patient access to oncology medicines outside the USA. The large variability in time to a reimbursement decision by country is likely due to varying processes. Additional research is needed to clarify the impact of these delays on access to care and patient outcomes.

Country	HTA agency	HTAs (n)	Time to HTA conclusion (# days)	Min (# days)	Max (# days)
Australia	PBAC	66	182	-296	1422
Canada	pCODR	21	220	23	795
Scotland	SMC	141	313	10	1247
France	HAS	135	269	21	1814
Germany	G-BA	87	237	99	727
England	NICE	119	547	0	2772
Overall	All	569	321	-296	2772

6546 Poster Session (Board #368), Mon, 1:15 PM-4:45 PM

Telehospice: Implementation lessons from rural hospice care with mobile tablets. *First Author: Gary C. Doolittle, University of Kansas Medical Center, Westwood, KS*

Background: In underserved rural communities, hospice personnel often travel great distances to reach patients, resulting in challenges to maintain access, quality, cost-effectiveness and safety. To address these disparities, the University of Kansas Medical Center piloted the country's first TeleHospice (TH) service in 1998. Barriers such as technology limitations, costs and attitudes towards technology limited adoption (Cook et al., 2001). An updated academic-community project utilizes secure mobile videoconferencing to support TH services in Kansas' frontier communities. **Methods:** Leveraging lessons learned from the early work, a secure cloud-based videoconferencing solution was chosen for ease of use. To maximize limited resources, the selection of hospice partners was guided by Gustafson et al.'s (2003) Organizational Change Manager, which also informed implementation gaps. The academic team partnered with Hospice Services, Inc., a leader in rural hospice care, providing services to 16 Kansas counties. **Results:** From February 2016 through January 2017, 116 TH encounters occurred, encompassing 707 attendees over 7,462 minutes. The most common TH uses to date have been: administrative (e.g., connecting hospice staff across 16 counties); professional-to-professional (e.g., connecting hospice nurses at homes to additional TH professionals); and family support (e.g., connecting adult children with loved ones). Initial use of videoconferencing for administrative purposes developed a comfort level in using it for clinical and family support purposes. For staff meetings alone, the hospice has saved approximately $2,500/month in travel, with TH staff noting increased morale driven by increased team communication. **Conclusions:** Compared with early work, technology advances and a community-centered approach have increased TH adoption. With decreasing budgets as well as rural hospice closures, innovative, cost-effective and community-driven approaches such as TH are needed to decrease disparities. As dissemination occurs in national hospice organizations, continued research is needed to understand best fit within frontier hospices, to inform future urban applications and to address reimbursement.

6547 Poster Session (Board #369), Mon, 1:15 PM-4:45 PM

Implementation of a telechemotherapy center in the Peruvian jungle to improve patients' quality of life. *First Author: Tatiana Vidaurre, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru*

Background: Instituto Nacional de Enfermedades Neoplásicas (INEN) is located in Lima (capital of Peru). There are no oncologists in regions like Peruvian jungle. Approximately 6% of medical attentions at INEN are people from this cities; so they must spend money and time to receive their treatment far from their cities. The purpose was to implement a module of outpatient chemotherapy in a non-specialized hospital, located in Peruvian jungle, for chemotherapy administration monitored by oncologists from INEN through the use of information and communication technologies (ICT). **Methods:** Two working teams were organized by formal agreement between INEN and local authorities to properly implement the infrastructure and to train local staff from December 2014 to November 2015. Questionnaire EORTC QLQ-C30 (v3) was used to assess QoL at the beginning and 3 months later. **Results:** A chemotherapy room with 18 armchairs, an area with a laminar flow hood to mix drugs at pharmacy, and videoconferencing equipment were implemented in Lamas, San Martin (1100 Km from Lima). Two general practitioners, 3 nurses and a pharmacist from Lamas, were trained during 3 months at INEN. Since November 2015, 31 patients were admitted. They received 181 cycles of chemotherapy in 248 rounds of administration, monitored by teleconference. Additionally 227 videoconference meetings to evaluate patients and to coordinate with local team were performed. Global health status improved from 76.67% to 83.33%. We observed benefit in functional scales, likewise symptoms related to disease did not vary, nevertheless financial difficulties decreased from 33.3% to 6.67%. In terms of money and time, this meant an average saving of $150.00 and 4 hours of travel time. **Conclusions:** Using ICT, we successfully implemented a tele-chemotherapy module in the heart of Peruvian jungle without harming patients quality of life. They will not need to travel to Lima for receiving their treatment.

6548 Poster Session (Board #370), Mon, 1:15 PM-4:45 PM

Themes and costs underlying avoidable terminal oncology ICU hospitalizations. *First Author: Robert Michael Daly, Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: ICU admissions in the last 30 days of life are an indicator of poor care. Our prior research found nearly half of terminal oncology ICU hospitalizations are potentially avoidable. **Methods:** Data were derived from 72 patients consecutively cared for in an academic medical center's oncology practice who died in an ICU between July 1, 2012 and June 30, 2013. Oncologists, intensivists, and hospitalists used a standardized assessment tool to review each patient's electronic health record from 3 months prior to hospitalization until death; they made a clinical determination of avoidability. Two investigators, blinded to the specialty, used a grounded theory approach to extract clinical themes associated with the reviewer's determination of avoidability. Total, direct, and indirect costs were abstracted for each avoidable hospitalization. **Results:** Thirty-four (47%) of the examined hospitalizations were deemed avoidable. The primary themes associated with avoidability, and the percentage by specialty, were as follows: 1) failure to initiate appropriate advance care planning in the outpatient setting (68% oncologists, 55% intensivists, 65% hospitalists), 2) failure to integrate understanding of limited prognosis (23% oncologists, 24% intensivists, 26% hospitalists), and 3) failure of clinical management (6% oncologists, 21% intensivists, 6% hospitalists). A failure to educate and integrate surrogates into timely medical decision-making was a prominent secondary theme for oncologists (22%), intensivists (18%), and hospitalists (29%). The total cost per patient averaged $44,532 with direct and indirect costs averaging $25,215 and $19,317, respectively. High cost areas were ICU level care (35%) and pharmaceuticals (16%). **Conclusions:** The themes identified suggest potential preventative interventions, including higher rates of outpatient advance care planning, oncology inpatient communication to promote patient's prognostic understanding, prevention of failures in clinical management, and better education and integration of surrogates. Given 8% of oncology patients expire in the ICU and 47% were identified as avoidable, the potential national annual cost of these avoidable hospitalizations is $997MM.

6549 Poster Session (Board #371), Mon, 1:15 PM-4:45 PM

Forecasting financial impact of alternative payment models to cancer drug manufacturers. *First Author: Jennifer M. Hinkel, McGivney Global Advisors, Wayne, PA*

Background: Payers are moving from fee-for-service (FFS) reimbursement models towards value-based Alternative Payment Models (APMs). In Medicare, this trend has emerged via MACRA legislation and the Oncology Care Model (OCM). Reimbursement changes carry financial implications for payers, providers, and drug manufacturers. **Methods:** Financial impact of APMs was modeled as a function of Volume Factors and Price Factors in sales of a cancer drug product. Volume Factors included utilization patterns and market share. Price Factors included launch price, price increases, and both mandated and negotiated discounts. The model described three APM categories: Buy & Bill Plus (similar to OCM), Episode-Based Payment, and Third-Party Buy & Bill. The model included assumed timelines of APM implementation and the share of commercial insurer and Medicare markets implementing. Assumptions were generated in a multi-stakeholder workshop applying a modified Delphi method and Nominal Group Technique to arrive at consensus. The model included input ability for existing product forecast data including expected patient numbers, market share, payer mix, channel mix, price, 340B discount parameters, and additional concessions. Combinations of inputs and assumptions were run through the model as scenarios to generate results. **Results:** Across all scenarios, Episode-Based Payment resulted in revenues averaging 34% below baseline forecast at the ten-year mark. Third-Party Buy and Bill resulted in revenues averaging 100% of baseline at the ten-year mark. Buy and Bill Plus resulted in revenues averaging 66% below baseline at the ten-year mark. Market share as a function of clinical differentiation appeared to be a significant factor influencing revenue impact, with highly differentiated products outperforming others in all APMs. **Conclusions:** While much attention is paid to the impact of reimbursement reform on oncology provider economics, with subsequent impacts to patient access, less attention has been focused on impact to drug manufacturers. APM implementation could significantly impact manufacturer revenues, which in turn may impact both access to such therapies and research investment towards new anti-cancer therapies.

6550 Poster Session (Board #372), Mon, 1:15 PM-4:45 PM

Are physicians social networks linked to breast cancer screening recommendations for older adults? *First Author: Craig Evan Pollack, Johns Hopkins University, Washington, DC*

Background: Physicians' prior experiences caring for patients with breast cancer along with experiences in their social networks including family members and friends may be a key and understudied driver of recommendations for cancer screening. **Methods:** The Breast Cancer Social Networks study (CanSNET) is a national, mailed survey of 2,000 primary care providers (PCPs) randomly selected from the American Medical Association Masterfile. PCPs were asked to provide detailed characteristics on up to 2 women they know who have been diagnosed with breast cancer and "whose cancer, broadly speaking, had the greatest impact" on them, including friends, family members and patients. Each woman was categorized as being diagnosed (a) through screening with a good prognosis, (b) not through screening with a good prognosis, (c) through screening with a poor prognosis or (d) not through screening with a poor prognosis. We used a logistic regression model to assess the association between the network member and recommendations for routine screening mammograms to average-risk women ages 75+, adjusting for provider and practice characteristics. **Results:** Overall 871 physicians responded to the survey yielding an adjusted response rate of 52.3% (out of 1665 eligible). We found that 67% of physicians recommended screening for women 75+. The sample reported on 762 patients, 378 family members and 476 other network members who had been diagnosed with breast cancer. Ten percent of patients and 25.1% of family members reported on died of their disease. In adjusted models, we found that physicians who reported on family members who did not receive a mammogram and had a poor prognosis were significantly more likely to recommend screening compared to those who did not (Odds Ratio 1.22, 95% Confidence Interval 1.03, 1.43). **Conclusions:** Physicians' experiences with their social networks was linked to their breast cancer screening recommendations, underscoring the potential for information that is learned from social networks to differ from clinical guidelines and highlighting the need to address a broad array of influences in trying to reduce potential overscreening in cancer.

6551 Poster Session (Board #373), Mon, 1:15 PM-4:45 PM

The association between employment changes and healthcare use in the year after cancer diagnosis. *First Author: John F. Dickerson, Kaiser Permanente Center for Health Research, Portland, OR*

Background: Employed adults diagnosed with cancer face difficult decisions about continuing/returning to work and intensity of work following diagnosis. We examined the association between employment changes and healthcare use among cancer survivors. **Methods:** Data on adults enrolled at two health plans (Kaiser Permanente (KP) Colorado and KP Washington), diagnosed with breast, colorectal, lung, melanoma, and prostate cancers between 2003-2008, who responded to a 2013 survey with items on employment patterns following diagnosis were used. Survey data were linked to electronic health record (EHR) data on healthcare use, demographics, and cancer characteristics. Employment status and changes following diagnosis were measured. Multivariable logistic and negative binomial regression models were used to assess associations between employment changes and healthcare use in the year after diagnosis, adjusting for demographic and cancer characteristics. **Results:** Among 465 cancer survivors with complete survey and EHR data, 225 (48.4%) reported being employed since diagnosis. Among employed survivors, 126 (56.0%) reported making an employment change. Those who made a change were more likely to be female, diagnosed with AJCC stage 3 or 4 cancer, have received chemotherapy or hormone therapy, and had a caregiver (all $p < 0.01$). The most common employment changes were taking extended paid time off (53.2%), unpaid time off (39.7%), and switching to a flexible schedule (29.4%). Employment changes were made at initial diagnosis (18.3%), during treatment (70.6%), and ≤12 months post-treatment (26.2%); 28.6% made more than one change. Survivors who made an employment change had significantly more oncology visits (IRR = 1.85 [95% CI: 1.14-3.00]) and higher odds of hospitalization (OR = 5.18 [95% CI: 2.50-10.8]), but not primary care visits (IRR = 1.19 [95% CI: 0.94-1.50]) in the year after diagnosis, compared to those who did not make a change. **Conclusions:** Employment changes among cancer survivors are common and may be associated with treatment intensity and other healthcare use in the year after diagnosis. Prospective studies are needed to assess the impact of employment and healthcare use patterns on health outcomes.

6552 Poster Session (Board #374), Mon, 1:15 PM-4:45 PM

Temporal trends in the intensity and duration of oncologic care among colorectal cancer (CRC) patients (pts). *First Author: Leo Chen, University of British Columbia (UBC), Surrey, BC, Canada*

Background: Substantial advances in therapy of CRC pts occurred between 2000 and 2012 contributing to a significant increase in overall survival. The objective of this study is to quantify the change in treatment (tx) intensity as measured by clinic and tx visits at a network of medical and radiation oncology clinics. **Methods:** Electronic scheduling records of stage I-IV CRC patients referred between 2000-2012 to the six oncology centers comprising the British Columbia Cancer Agency were reviewed and stratified by tx phases: I and II (adjuvant first 6 months, continued), III and IV (palliative first 6 months, continued), and V (last 6 months of life). Clinic Visit Intensity (CVI), Chemo Tx Intensity (CTI), number of chemo agents and number of cycles (CC), Radiotherapy (Rx) courses (RC) and fractions (RF) were measured, and trends by referral year were modelled using zero inflated negative binomial regression. Mean duration of visit for chemo tx (CHD) and clinic visits (CVD) were modelled using linear regression. Sex, age at diagnosis, stage, income, and community size were included in models if terms were significant. **Results:** 15,157 pts were included across 10 cohorts. CTI and CC increased significantly in tx phases II-V with later year of referral, while phase I results were stable or decreased, likely due to the substitution of oral for intravenous regimens. Rx increased only in advanced phases. Mean duration of scheduled time showed significant increases. **Conclusions:** CRC pts referred in 2012 vs 2000 receive significantly greater intensity and duration of care in tx phases II-V. Results have significant implications for resource allocation and the patient experience.

Relative metric if referred in 2012 vs. 2000.

Site		Colon					Rectal				
Phase		I	II	III	IV	V	I	II	III	IV	V
Relative Rate	CVI	107%	854%*	127%*	151%*	110%	182%*	908%*	132%*	230%*	141%*
	CTI	52%*	601%*	243%*	375%*	178%*	49%*	911%*	192%*	427%*	208%*
	CC	45%*	1229%*	191%*	375%*	166%*	45%*	270%*	195%*	378%*	208%*
	RC	NA	NA	NA	84%	NA	76%*	NA	162%*	159%	82%
	RF	NA	NA	97%	139%*	133%	99%	NA	46%*	248%*	165%*
Relative Mean Duration (Minutes)	CVD	+13.5*	+7.9*	+10.0*	+0.4	+5.8*	+8.1*	+7.7*	+11.8*	+8.8*	+7.7*
	CHD	+46.7*	+69.3*	+53.5*	+68.3*	+57.5*	+12.1*	+64.9*	+36.6*	+68.9*	+56.3*

* $p<0.05$

6553 Poster Session (Board #375), Mon, 1:15 PM-4:45 PM

Self-reported financial stress among patients evaluated at a community cancer program. *First Author: Christopher S. Lathan, Dana-Farber Cancer Institute, Boston, MA*

Background: Cancer related financial stress has been linked to a multitude of factors including socio-economic status, but its impact on the quality of life (QOL) for underserved populations is less well characterized. We evaluated patient reported financial stress, QOL, and quality of health (QOH) at an outreach cancer program located in a federally qualified health center. **Methods:** Study participants were interviewed at initial clinic visit for financial stress, QOH and QOL between January 2012 and December 2016. Demographic information, insurance coverage, clinical parameters, and comorbidities were abstracted from participants' medical records. Responses to the financial stress index question "how difficult is it for you or your family to meet monthly payment of your/your family bills?" and overall QOL and QOH of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 were analyzed. Proportional odds logistic regression models were constructed for 5-point quality of life measures and three levels of financial toxicity. **Results:** Of the 288 participants analyzed, 52% and 12% reported somewhat and extreme financial stress. In an adjusted analysis, patients who reported financial stress were more likely to be younger in age (OR = 4.03, $p < 0.001$) unemployed (OR = 3.24, $p = 0.002$), have less than bachelor's degree (OR = 0.035, $p = 0.018$), insured by Medicaid (OR = 3.22, $p < 0.011$), and were more likely to rate their QOL (OR = 3.76, $p = 0.031$) as poor, compared to those without financial stress. Race, gender, presence of cancer diagnosis and comorbidities were not associated with financial distress. Independent predictors of poor QOL were disability (OR = 3.12, $p = 0.005$), depression (OR = 2.12, $p = 0.007$) and extreme financial difficulty (OR = 2.57, $p = 0.011$). There was a nearly perfect positive correlation between overall QOL and QOH ($r = 0.984$, $p < 0.001$). **Conclusions:** There is a high prevalence of financial burden among underserved minority patients seeking cancer related care, and this is closely associated with poor quality of life. Interventions targeting cancer disparities need to assess financial stress in order to address this issue.

6554 Poster Session (Board #376), Mon, 1:15 PM-4:45 PM

Factors associated with 21-gene assay receipt among women with lymph node positive breast cancer. *First Author: Megan Roberts, National Cancer Institute, Bethesda, MD*

Background: The 21-gene Breast Recurrence Score (RS) assay predicts breast cancer (BC) recurrence and adjuvant chemotherapy benefit in select patients with lymph node-positive (LN+), hormone receptor-positive (HR+), HER2 negative BC. This study examines factors associated with assay uptake among women with LN+ BC in SEER databases. **Methods:** In this population-based study, incident BC cases in SEER registries (2010-2013) were linked to RS results from assays performed by Genomic Health. Our study sample included women with non-metastatic, LN+ ($\geq$1 positive LN), HER2-, HR+, BC. We use logistic regression to identify demographic, SES, and tumor characteristics associated with having the 21-gene assay ordered. **Results:** A total of 4428 (14.0%) of 31520 women with LN+, HR+, HER2-, BC had the assay ordered. Uni- and multi-variate analyses identified key factors that were significantly associated with the proportion of women tested. In the multivariable analysis, age (aOR: 2.23, $p<0.001$, 65-74 v <45 years) and BC diagnosis year (aOR:1.75, $P<0.001$ 2013 vs 2010) were positively associated with assay receipt; whereas number of positive LN (aOR: 0.14, $p<0.001$, 4+ positive LN vs 1 positive LN), tumor grade and size, low SES, being black, and being widowed were negatively associated with assay uptake ($p<0.001$). Having Medicaid was associated with lower odds of test receipt ($p=0.01$). Finally, we identified geographic variation in assay ordering. See univariate results (Table). **Conclusions:** Important demographic and SES variables were associated with test receipt in LN+ disease, and differed from those previously reported in node negative disease. Moving forward, increased awareness of these disparities, particularly among low SES, Medicaid, Black and widowed patients, along with targeted interventions may help to improve quality of care and equity in test receipt.

Most Commonly Tested Groups		Least Commonly Tested Groups	
Age <45	18.6	Age 65-74	8.4
1 Positive LN	25.0	4+ Positive LN	3.5
2013 Diagnosis	17.0	2010 Diagnosis	11.1
Tumor Grade I	23.1	Tumor Grade III/IV	8.1
Tumor ≤1 cm	23.6	Tumor Size >5 cm	4.8
White	14.7	Black	11.3
SES 5th Quintile	17.2	SES 1st Q	10.8
Married	15.0	Widowed	11.1
Insured	15.1	Any Medicaid	9.4
Hawaii	18.4	Utah	8.6

6555 Poster Session (Board #377), Mon, 1:15 PM-4:45 PM

Financial assistance for fertility preservation at cancer diagnosis: An analysis of the LIVESTRONG Fertility program. *First Author: Lenore Omesi, New York-Presbyterian, Columbia University Medical Center, New York, NY*

Background: Fertility preservation (FP) is a critical component of comprehensive adolescent and young adult (AYA) cancer care that is discussed and/or offered to only a fraction of eligible patients. Barriers include lack of insurance coverage making FP prohibitively expensive for many patients. The Sharing Hope program, now known as LIVESTRONG Fertility, was created by Fertile Hope in 2004 and acquired by LIVESTRONG in 2009. LIVESTRONG Fertility provides financial assistance to AYA cancer patients through discounted FP rates and access to free medications through a pharmaceutical company. Our aims were to review demographic characteristics of patients served, identify geographic utilization patterns, and quantify the program's financial impact. **Methods:** De-identified records maintained by Fertile Hope/LIVESTRONG from 2004 to 2011 were retrospectively reviewed. Patient population, treating institutions and cost savings/patient were summarized using descriptive statistics. **Results:** 1171 men and 1319 women were approved for financial assistance between 2004 and 2011. Median age was 24 years (range 12-67) for men and 30 years (range 13-49) for women. The most common diagnoses included testicular cancer (34%) and Hodgkin Lymphoma (HL) (18%) among males and breast cancer (48%), HL (13%) and genitourinary cancers (13%) among females. Applications were received from individuals residing in 49 of the United States, as well as Washington DC and Puerto Rico. The applicants received care from a total of 1,245 cancer centers. For men, $438,711 was saved, averaging $375/patient. For women, $3,904,303 was saved in practitioner cost and $4,665,775 in medication costs averaging $6,497/patient. **Conclusions:** Financial assistance for FP at the time of a cancer diagnosis for AYAs is a persistent and growing need. Female cancer patients face significantly greater costs to preserve fertility. Further studies are needed to determine the true financial burden to patients and the degree to which lack of financial resources and insurance coverage prevent FP in this population.

Utilization rates by year.

	2004	2005	2006	2007	2008	2009	2010	2011
male	8	37	76	173	168	235	173	301
female	4	25	67	124	180	238	284	397

6556 Poster Session (Board #378), Mon, 1:15 PM-4:45 PM

Global Cancer Institute multidisciplinary tumor boards as a tool to improve patterns of clinical practice for breast and gynecologic cancer in resource-limited settings. *First Author: Jessica St. Louis, Global Cancer Institute, Boston, MA*

Background: Multidisciplinary tumor boards (MTBs) are commonly practiced in high-income countries (HICs) to ensure adherence to guidelines through a team approach to patient care. The Global Cancer Institute (GCI) established online MTBs in 2012 to facilitate live telemedicine discussions of breast and gynecologic case scenarios between specialists in low- and middle-income countries (LMICs) and expert specialists in HICs. GCI MTBs aim to improve clinical knowledge and patterns of practice for specialists in LMICs through an interactive online forum. **Methods:** In each monthly MTB, three patient case scenarios are presented by specialists in LMICs for live discussion with an expert panel of specialists based in HICs. Guideline or clinical trial-based discussions are held for each case scenario. Best practices for clinical care in limited resource settings are also discussed. Links to clinical practice guidelines, clinical trials, and resources are provided to all MTB attendees. For educational purposes, each MTB is live streamed and uploaded to a private YouTube channel for viewing by community oncologists and trainees worldwide. **Results:** The GCI MTBs program has recruited over 500 LMIC participants from 48 hospitals in 24 countries across Latin America, Eastern Europe, Africa, and Asia. 17 expert breast cancer specialists and 13 expert gynecologic cancer specialists provide multidisciplinary guidance. To date, 130 breast cancer case scenarios and 80 gynecologic cancer case scenarios have been presented. For breast MTBs, 73% of case scenarios were invasive ductal carcinomas. Common subtypes presented were ER/PR+ (63%), HER2+ (30%), and triple negative disease (28%). 56 cases involved advanced disease management (43%). For gynecologic MTBs, common gynecologic cancer case scenarios were cervical (74%) and ovarian (15%). 37 cases involved advanced disease management (46%). **Conclusions:** GCI MTBs are a useful educational tool for specialists in LMICs to improve patterns of clinical practice and engage in multidisciplinary discussions. GCI continues to expand its MTBs to cancer facilities in LMICs.

6557 Poster Session (Board #379), Mon, 1:15 PM-4:45 PM

Increase in time to initiating cancer therapy and association with worsened survival in curative settings: A U.S. analysis of common solid tumors. *First Author: Alok A. Khorana, Cleveland Clinic, Cleveland, OH*

Background: Increase in time to treatment initiation (TTI) for new cancer diagnoses causes patient distress and may adversely affect outcomes. We investigated trends in TTI for common solid tumors treated with curative intent, determinants of delayed TTI and impact on overall survival. **Methods:** We utilized population-based, prospective data from the National Cancer Database for newly diagnosed US patients with early-stage breast, prostate, lung, colorectal, renal and pancreas cancers from 2004-13. TTI was defined as days between diagnosis of cancer and first treatment (surgery, systemic or radiation therapy). Negative binomial regression and Cox proportional hazard models were used for analysis. **Results:** The study population of 3,672,561 patients included breast (N = 1,368,024), prostate (N = 944,246), colorectal (N = 662,094), non-small cell lung (NSCLC) (N = 363,863), renal(N = 262,915) and pancreas (N = 71,419) cancers. Median TTI increased from 21 days in 2004 to 29 days in 2013 ($P < 0.0001$). Aside from year, determinants of delays included care at academic centers and change in treating facility. Increased TTI was associated with worsened overall survival (OS) for stages I and II breast, lung, renal, and pancreas cancers, and stage II colorectal cancers, with hazard ratios per week of delay ranging from1.005 (1.002-1.008) to 1.030 (1.025-1.035), adjusting for comorbidities and other variables. Prolonged TTI ($>$ 6 wks) was associated with substantially worsened OS e.g., 5-yr OS for stage I NSCLC was 56% ($\pm$0.2) for TTI $\leq$ 6wks v 43% ($\pm$0.2) for TTI $>$ 6 wks and for stage I pancreas was 38% ($\pm$0.6) v 29% ($\pm$1) respectively ($P < 0.0001$ for both). **Conclusions:** TTI has lengthened significantly over recent years, associated with multiple factors. Increase in TTI is associated with substantial increase in mortality ranging from 0.5-3.2% per week of delay in curative settings such as early-stage breast, lung and pancreas cancers. Simplifying access and navigation of complex health systems is essential to diminish this apparently iatrogenic impact on outcomes.

6558 Poster Session (Board #380), Mon, 1:15 PM-4:45 PM

Minority patient reported attitudes regarding tissue donation and participation in cancer research. *First Author: Davendra Sohal, Cleveland Clinic, Cleveland, OH*

Background: Minority populations are underrepresented in biospecimen banks created for cancer research, which has implications for future therapeutic approaches. Patients' reluctance to donate biospecimens is perceived to be a potential barrier but is poorly studied. We present interim analyses of a survey to assess attitudes in a patient cohort comprised of racial/ethnic minorities. **Methods:** Patients filled out a validated 23-item survey [*J Cancer Educ, 2014. 29: p. 580-7*] for this prospective cohort study approved by the Cleveland Clinic IRB. Surveys were provided in the outpatient oncology clinic of a Cleveland Clinic community hospital. Eligibility requirements included tissue diagnosis of any solid tumor malignancy in non-curative setting; age $\geq$ 18 years, ECOG PS 0-2, self-reported race/ethnicity as any other than non-Hispanic White, undergoing cancer therapy in the next 30 days. Data are presented for the first 90 patients surveyed in 2015-2016. **Results:** Median age was 69 years (range, 35-92). Only 24 (27%, 1 missing) had been asked to donate samples in the past; of those, 20 (83%) had donated. The majority (n = 60, 67%) were willing to donate samples. A higher proportion (75%) responded as being likely to donate samples if they learned more about the research and reasons for sample donation. A smaller proportion was likely to donate samples if they received money (30%) or health services (40%) in return. Many (55-73%) disagreed with negative statements such as, "I will be treated as a guinea pig," and only (3-4%) disagreed with trust statements such as, "I trust sample banks/medical researchers/procedures." However, 42% endorsed being "concerned that something like the Tuskegee study could happen again." **Conclusions:** The majority of racial and ethnic minority patients in this study were willing to donate biospecimens for research, with an even greater likelihood of participation if appropriate rationales were provided. While systemic mistrust persists, the vast majority trusted medical researchers and procedures. Our findings suggest that underrepresentation of minorities in cancer biospecimen repositories, not likely attributable to patient reluctance, must be addressed to achieve health equity.

6559 Poster Session (Board #381), Mon, 1:15 PM-4:45 PM

Racial disparities in treatment and outcomes of colorectal cancer in young adults. *First Author: Olatunji Boladale Alese, Winship Cancer Institute, Atlanta, GA*

Background: The incidence of colorectal cancer (CRC) in young adults is increasing. Minority populations with CRC are known to have worse outcome. The objective of this study is to evaluate the impact of race on the outcome of young adults with CRC. **Methods:** Data were obtained from all US hospitals that contributed to the National Cancer Database (NCDB) between 2004 and 2013. Univariate and multivariate testing was done to identify factors associated with patient outcome. Kaplan-Meier analysis and Cox proportional hazards models were used for association between patient characteristics and survival. **Results:** A total of 83,449 patients between 18 and 50 years of age were identified. The mean age was 43.6 years (SD$\pm$6), with a male preponderance (53.9%). About 72% were non-Hispanic Whites (NHW) while African Americans (AA) made up 15.1%. Distribution across stages I-IV was 15.6%, 22.4%, 33.9% and 27% consecutively, similar among the races. 41.8% of NHW and 28.4% of AA had rectal cancers ($p<0.001$). Despite equally receiving standard of care (SOC) as per NCCN guidelines, AA had significantly lower 5year survival rates (58.8%) compared to Hispanics (64.8%) and NHW (66.9%; HR 1.42; 1.38-1.46; $p<0.001$). Patients with colon cancer had worse outcome compared to rectal cancer (HR 1.21; 1.18-1.24; $P<0.001$). In terms of survival, NHW (HR 0.85; 0.81-0.88; $p<0.001$) and Hispanics (HR 0.75; 0.70-0.79; $p<0.001$) were more likely to benefit from chemotherapy compared to AA. As expected, SOC utilization was associated with improved survival across all racial groups, especially in AA with HR of 0.64 (0.60 – 0.69; $p<0.001$). **Conclusions:** Despite comparable rates of standard of care utilization, AA young adults with CRC had worse outcomes compared to other races. Colon cancer was significantly more common in AA than rectal cancers, which may have contributed to their worse outcomes.

Survival by race among patients who received standard of care (77.8% of all patients).

Race Group	No. of Subject	12 Mo Survival (95% CI)	60 Mo Survival (95% CI)
AI/API/Other	3234	93.1% (92.2%, 93.9%)	67.6% (65.7%, 69.5%)
AA	9749	91.1% (90.5%, 91.7%)	58.8% (57.7%, 59.9%)
Hispanic	5233	93.3% (92.6%, 94.0%)	64.8% (63.2%, 66.3%)
NHW	46668	93.7% (93.4%, 93.9%)	66.9% (66.4%, 67.4%)

6560 Poster Session (Board #382), Mon, 1:15 PM-4:45 PM

An intervention study to reduce black-white treatment disparities in early stage non-small cell lung cancer. *First Author: Paul R. Walker, East Carolina University Brody School of Medicine, Greenville, NC*

Background: Racial disparities in the treatment of non-small lung cancer (NSCLC) continue to exist leading to poorer outcomes in African-Americans (AA) compared to Caucasians (C). Our previous multi-institutional prospective cohort study of 386 patients identified a surgical rate in early stage NSCLC of 66% C but only 55% AA ($p = 0.05$; OR 0.75; 95% CI 0.57-0.99). *(Cykert et al JAMA 2010)* A 3 year retrospective chart review of all patients with early stage NSCLC at the 3 academic institutions involved in this current intervention study identified 714 patients with early stage NSCLC. Baseline surgical rates 69% for C and 66% for AA. Combined stereotactic body radiation therapy (SBRT) with surgery C 80% and AA 76%. Controlling for comorbidities, COPD, age and other demographic data, the OR for surgery AA compared to C 0.64 (95% CI 0.43-0.96) and for combined surgery or SBRT AA compared to C 0.61 (95% CI 0.43-0.96). **Methods:** Patients with a stage I or II NSCLC were identified and randomized to each institution's standard of care approach or to an 'intervention' component utilizing a trained navigator to enhance patient communication and treatment understanding. **Results:** 244 patients were prospectively recruited into this intervention study. Mean age 65.7 years; 54% women; 89 (34%) AA. The intervention group showed an overall surgical rate of 74% (74.8% C, 71.4% AA; $p = 0.6$). Combined treatment of either surgery or SBRT increased an ablative treatment to 91.9% for C and 94.1% AA patients ($p = 0.5$). Logistic regression was performed comparing the intervention group to the baseline group. Results showed that overall treatment improved for both C and AA, the surgical and overall treatment disparity between C and AA was no longer present, while age, COPD, and clinical stage remained significant predictors of treatment. **Conclusions:** A multifaceted intervention designed to enhance patient communication and treatment understanding removed the surgical and overall early lung cancer treatment disparity between AA and C. Clinical trial information: NCT01687738.

6561 Poster Session (Board #383), Mon, 1:15 PM-4:45 PM

The Affordable Care Act Dependent Coverage Expansion (ACA-DCE): Disparities in impact in young adult oncology patients. *First Author: Elysia Marie Alvarez, Stanford University Medical Center, Palo Alto, CA*

Background: Private health insurance is associated with improved outcomes in cancer patients. We know little, however, about the impact of the ACA-DCE, which extended private insurance to young adults (up to age 26) beginning in 2010, on the insurance status of young adults with cancer. This study sought to determine the effect of the ACA-DCE on having private insurance coverage among hospitalized young adult oncology patients. **Methods:** We performed a retrospective, population-based analysis of hospitalized young adult oncology patients (22-30 years-old) in California during 2006-2014 (n = 11,062) using the Office of Statewide Health Planning and Development database. Multivariable regression analyses examined the social and clinical predictors of having private insurance. Results are presented as adjusted odds ratios (OR) and 95% confidence intervals (CIs). A difference-in-difference analysis examined the influence of the ACA-DCE on insurance coverage by race/ethnicity and zip code federal poverty level. **Results:** Multivariable regression demonstrated patients of black and Hispanic race/ethnicity were less likely to have private insurance both before and after the ACA-DCE, compared to non-Hispanic white patients. Younger age (22-25 years) was associated with having private insurance after the ACA-DCE implementation (OR 1.18, CI 1.05-1.33; reference, 27-30 years). In the difference-in-difference analysis, private insurance increased among non-Hispanic whites aged 22-25 living in medium- (2006-2009: 64.6% versus (vs) 2011-2014: 69.1%; p = 0.003) and high-income zip codes (80.4% vs 82%; p = 0.043) and among Asian patients aged 22-25 living in high-income zip codes (73.2 vs 85.7%; p = 0.022). Private insurance decreased for all Hispanic patients aged 22-25 between the two time periods. **Conclusions:** The ACA-DCE provision was an important first step in increasing coverage, but it was not universal and generated disparity in coverage as gains occurred for non-Hispanic white and Asian patients living in higher income zip codes. This policy change was shown to increase coverage for a traditionally underinsured population and attention should now focus on those remaining uninsured.

6562 Poster Session (Board #384), Mon, 1:15 PM-4:45 PM

Disparities in prognosis communication among parents of children with cancer: The impact of race and ethnicity. *First Author: Maya Ilowite, Dana-Farber Cancer Institute, Boston, MA*

Background: Most parents of children with cancer say they want detailed prognostic information about their child's cancer. However, prior work has been conducted in populations of limited diversity. We sought to evaluate the impact of parental race/ethnicity on prognosis communication experiences amongst parents of children with cancer. **Methods:** We surveyed 357 parents of children with cancer, and the children's physicians at Dana-Farber Cancer Institute/Boston Children's Hospital and Children's Hospital of Philadelphia. Our outcome measures were parental preferences for prognostic information, physician beliefs about parental preferences, prognosis communication processes and communication outcomes. Except where noted, associations were assessed by logistic regression with generalized estimating equations to correct for physician clustering. **Results:** 87% of parents wanted as much detail as possible about their child's prognosis, with no significant differences by race/ethnicity (P = .50). Physician beliefs about parental preferences for prognosis communication varied based on parent race/ethnicity. 60% of physicians for White parents reported they believed parents wanted as much detail as possible about their child's prognosis, versus 36%, 38%, and 64% of physicians, respectively, for Black, Hispanic, and Asian/Other parents (P = .04). Parent race/ethnicity was not associated with actual prognostic disclosure as reported by parents (P = .79) or by physicians (P = .61). Accurate understanding of prognosis was higher amongst White (51%) versus non-White parents (range 22%-29%), although this difference was not statistically significant (P = .13, unadjusted). **Conclusions:** The majority of parents, regardless of racial and ethnic background, want detailed prognostic information about their child's cancer. However, physicians rarely recognize the information needs of Black and Hispanic parents. Despite this discrepancy, prognosis communication outcomes were largely equivalent. Our findings suggest that in order to meet parents' information needs, physicians should ask about the information preferences of parents of children with cancer prior to prognosis discussions.

6563 Poster Session (Board #385), Mon, 1:15 PM-4:45 PM

Disparities in next generation sequencing in a population-based community cohort of patients with advanced non-small cell lung cancer. *First Author: Carolyn Jean Presley, Yale Cancer Center, New Haven, CT*

Background: The use of next generation sequencing (NGS) in patients with advanced non-small cell lung cancer (NSCLC) is increasing. This study explored disparities in the use of NGS testing. **Methods:** This retrospective observational study utilized Flatiron Health's longitudinal, demographically and geographically diverse database containing electronic health record data from 191 oncology practices across the U.S. We identified patients diagnosed with advanced (stages IIIB/IV or recurrent) non-squamous NSCLC who received first line treatment and either NGS testing or standard biomarker testing (e.g., EGFR, ALK) alone. NGS included any multi-gene panel testing $>$ 30 genes. Logistic regression modeled the association between patient characteristics and receipt of NGS testing, accounting for clustering of patients by oncology practice. **Results:** Among 5,688 adults with advanced NSCLC, 4,813 (84.6%) patients received standard biomarker testing alone and 875 (15.4%) patients received NGS testing. The median age of the sample was 67y (IQR: 41-85), the majority was white (63.6%) vs. black (7.5%) vs. unknown (13.4%), and had a history of smoking (79.9%). Among the youngest patients ($<$ 45y), 31.5% received NGS compared to 11.3% among the oldest (76-85y; P $<$ .001). Approximately 16% of white patients received testing, compared to 11.4% of black patients (P $<$ .001). Patients with Medicaid received testing less often than commercially insured patients (11.7% vs 17.0%; P = .10). Patients had significantly lower odds of receiving NGS testing if they were older ($\geq$75 vs. $<$ 45 years of age; adjusted OR: 0.21, 95% CI: 0.13-0.34), black vs. white race (aOR: 0.63, 95% CI: 0.44-0.90) or were Medicaid vs. commercially insured (aOR: 0.54, 95% CI: 0.30-0.97). **Conclusions:** Significant age, race, and insurance-related disparities exist in the receipt of NGS testing among patients with advanced lung cancer in real world clinical practice.

6564 Poster Session (Board #386), Mon, 1:15 PM-4:45 PM

Asian representation in clinical trials of new drugs for the treatment of cancer. *First Author: Lola A. Fashoyin-Aje, U.S. Food and Drug Administration, Silver Spring, MD*

Background: In the US, statistics for Asians are often aggregated with other racial groups. This poses challenges in estimating the cancer burden and in defining cancer clinical trial enrollment targets in this demographic subgroup. 'Asian' refers to persons with origins in the Far East, Southeast Asia, or the Indian sub-continent. Asians comprise 6% of the US population and the largest Asian subgroups in the US are of Chinese (22%), Filipino (19%), Asian Indian (19%), Vietnamese (10%), Korean (9%), and Japanese (7%) descent. The representation of Asian patients in global clinical trials may not be reflective of the Asian subgroups in the US. FDA conducted an analysis to describe patients categorized as 'Asian' in clinical trials supporting the approval of new drugs. **Methods:** We reviewed the marketing applications of 33 new molecular entities approved for the treatment of solid tumor malignancies between 2011- 2016 to identify trials that provided the primary evidence of safety and efficacy. **Results:** A total of 29,941 patients were enrolled; 17 % were Asian. Most Asian patients were enrolled in Korea (20%), Taiwan (20%), mainland China (20%), Japan (16%), and US (5%). Few patients were enrolled in India (3%); the Philippines (1%); Vietnam (0). In the US, Asian patients comprised 3% of the total number of patients enrolled. **Conclusions:** Asian patients represented a heterogeneous mix. A large proportion was enrolled in Taiwan (20%) and Korea (20%), whereas the largest proportion of US Asians have origins in mainland China (22%), the Philippines (19%), India (19%), and Vietnam (10%). Nevertheless, although Asians share a common ancestry, it is not clear whether data from global clinical trials are generalizable to Asian patients in the US. Therefore, strategies to improve the enrollment of US Asian patients in clinical trials are needed. Among patients enrolled in the US, 3% were Asians, a proportion that is below US Asian population estimates (6%). While most site-specific cancer incidence and death rates are lower in US Asians compared to Whites, the rates of some cancers (e. g., stomach and liver) are higher in this group. Therefore, studies are needed to determine adequate enrollment targets in this demographic subgroup.

6565 Poster Session (Board #387), Mon, 1:15 PM-4:45 PM

Difference in cardiovascular disease incidence by sociodemographic factors in adolescent and young adult (AYA) cancer survivors. *First Author: Theresa Keegan, Center for Oncology Hematology Outcomes Research and Training (COHORT), UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: AYA cancer survivors are at increased risk of developing cardiovascular disease (CVD) compared to AYAs without a history of cancer. In AYA cancer survivors, few population-based studies have focused on CVD risk and none have considered whether the occurrence of CVD differs by sociodemographic factors. **Methods:** Analyses focused on 64,918 patients aged 15-39 y at diagnosis for one of 14 first primary cancers during 1996-2010 and surviving > 2 years after diagnosis, with follow-up through 2013. Data were obtained from the California Cancer Registry and State hospital discharge data. CVD included coronary artery disease, heart failure, and stroke. We estimated the cumulative incidence of developing CVD, accounting for death as a competing risk, stratified by race/ethnicity, neighborhood socioeconomic status (SES) at diagnosis, health insurance status at diagnosis/initial treatment and cancer type. We examined the impact of CVD on mortality using multivariable Cox proportional hazards regression with CVD as a time-dependent covariate. **Results:** Overall, 2374 (3.7%) patients developed CVD, and 7690 (11.9%) died over the follow-up period. Survivors of acute myeloid leukemia (12.6%), acute lymphoid leukemia (11.1%), central nervous system cancer (9.0%) and non-Hodgkin lymphoma (6.0%) had the highest incidence of CVD at 10-years. Incidence was significantly higher among Blacks (6.7%) at 10-years than non-Hispanic Whites (3.0%), Hispanics (3.7%) and Asian/Pacific Islanders (3.7%) ($p < 0.001$). AYA survivors with public or no insurance (vs private) had a higher 10-year incidence of CVD (5.8% vs 2.9%; $p < 0.001$), as did survivors residing in low (vs high) SES neighborhoods (4.1% vs 2.7%; $p < 0.001$). These sociodemographic differences in CVD incidence were apparent across most cancer sites. The risk of death was increased by five-fold or higher among AYAs who developed CVD. **Conclusions:** AYA cancer survivors who were uninsured or publicly insured, of Black race/ethnicity, or who resided in lower SES neighborhoods are at increased risk for developing CVD and experiencing higher mortality. The proactive management of CVD risk factors in these subgroups may improve patient outcomes.

6566 Poster Session (Board #388), Mon, 1:15 PM-4:45 PM

Audit study of cancer research mentorship opportunities by NCI-funded PIs: Analysis of a pathway barrier for diversity. *First Author: Jeffrey D. Robinson, Portland State University, Portland, OR*

Background: The pipeline of diverse cancer researchers is critical. Audit studies suggest that racial discrimination disadvantages black (vs. white) people with respect to educational/professional advancement (Milkman, 2012). We hypothesized that prospective Black (B) male doctoral students would experience greater disparity in responses when seeking access to NCI-funded PIs compared to prospective Caucasian (W) males. Primary aim: To explore response and acceptance rates for B (vs. W) men seeking cancer-research mentorship. We also explore similar differences when considering evaluators' race and sex. **Methods:** Between 9-9:30 am (local time) during a Monday in Oct 2015, identical emails were sent to 1028 randomly selected PIs affiliated with 65 NCI-designated cancer centers. PIs were randomly assigned to receive emails from either 'Brad Anderson' (W; n = 513) or 'Lamar Washington' (B; n = 515). Primary outcomes: (1) any response within one week (yes/no); and (2) type of response if received (agree to meet/not agree to meet). Logistic regression was used to examine unadjusted and adjusted effects of condition (W/B) on the primary outcomes. In adjusted models, PI sex and time zone were included as covariates (PIs identified as African American = 1.2%). **Results:** Approximately 50.0% and 48.3% of the sample responded to 'Brad' and 'Lamar,' respectively. Condition was not a significant predictor of 'any response' in either unadjusted (p = .62, odds ratio 95% CI = 0.83-1.35) or adjusted (p = .62, odds ratio 95% CI = 0.83-1.36) models. In the adjusted model, neither PI sex nor time zone were significant predictors of 'any response.' For those who responded, 43.7% and 40.9% 'agreed' to meet with Brad and Lamar, respectively. Condition was not a significant predictor of 'response type' in either unadjusted (p = .53, odds ratio 95% CI = 0.78-1.61) or adjusted (p = .51, odds ratio 95% CI = 0.78-1.64) models. In the adjusted model, only PI sex was a significant predictor of 'response type' (p = .03, odds ratio 95% CI = 1.04-2.29), with males (45.8%) being more likely to 'agree to meet' than female PIs (35.6%). **Conclusions:** We did not find strong evidence of bias by NCI-funded PIs against B (vs. W) prospective Ph.D. students.

6567 Poster Session (Board #389), Mon, 1:15 PM-4:45 PM

Associations between cancer patients' advance care and financial planning and surviving spouses' financial well-being. *First Author: Alexi A. Wright, Dana-Farber Cancer Institute, Boston, MA*

Background: The "financial toxicity" associated with cancer treatment, including high out-of-pocket expenses and lost earnings, may have lasting financial effects for surviving spouses. Although advance care planning (ACP) is used as a cancer quality metric, the value of financial planning is unknown. **Methods:** We examined associations between cancer patients' written ACP and financial planning (will) and surviving spouses' financial well-being using prospective, nationally representative data from the 2004-2014 waves of the Health and Retirement Study. We assessed change in household, non-housing (financial) wealth, including debt, among 962 surviving spouses of cancer decedents. Because wealth varies widely in the US, we fit multivariable quantile regression models at the 25^{th}, 50^{th}, and 75^{th} percentiles to examine associations between cancer decedents' ACP, financial planning, and wealth, adjusting for sociodemographic characteristics. **Results:** Among cancer decedents, 33% completed both ACP and a will, 27% only a will, 10% only ACP, and 30% neither. The median wealth of surviving spouses was \$22,309 (25^{th} percentile = \$0, 75^{th} percentile = \$134,238). Among spouses of cancer decedents in the 25^{th} percentile of wealth before death, completion of ACP and a will was associated with \$5,348 (95% CI = \$1,172-\$9,523) more financial wealth after death compared with no planning. Use of ACP and a will was also associated with \$46,851 (95% CI = \$2,810-\$90,891) more financial wealth at the 75^{th} percentile. There were no differences in the wealth of surviving spouses after death between patients who completed only a will, only ACP, or no planning (Ps > .09). **Conclusions:** Completion of ACP and financial planning was associated with greater wealth among both affluent and non-affluent surviving spouses compared with no planning. Efforts to sensitively incorporate financial planning into cancer patients' care have the potential to improve surviving family members' financial well-being.

6568 Poster Session (Board #390), Mon, 1:15 PM-4:45 PM

Miami NICE trial: Nutritional support for patients incurring chemotherapy side effects. *First Author: Damien Mikael Hansra, Oncology and Radiation Associates/Mercy Research Institute, Miami, FL*

Background: Few studies have been performed addressing nutritional interventions & mitigation strategies to address side effects such as weight gain, anorexia, dysgeusia, in patients (pts) undergoing chemotherapy. We aim to study the effect of nutritional counseling on body mass index (BMI) and other side effects in pts undergoing systemic chemotherapy. **Methods:** Prospective randomized study of 50 pts into two groups (A & B). Group A was randomized to standard of care: oncologist visits once per month x 3 months, routine physician counseling & dietary recommendations. Group B: standard of care + nutritionist intervention which included 3 visits x 30 mins each. Nutritionists performed an initial assessment of pts at the first session (template provided in poster) then tailored dietary counseling monthly x3 months which includes dietary strategies to mitigate side effects, pt & caregiver education, recipes, & handouts (provided in poster). Inclusions: medically insured male & female adults with active malignancies (hematologic &boncologic) on chemotherapy (neoajuvant, adjuvant, palliative). Exclusions: pts with head & neck, stomach, esophagus, pancreatic tumors & pts with pre-existing cachexia. Data collected: pt gender, age, race, ethnicity, cancer subtype, TNM staging, chemotherapy regimen. Primary objective: compare change in BMI at visit 1, 2, &3. Secondary endpoints: anorexia, nausea, vomiting, depression, etc. reported in poster. Mean change in BMI, secondary endpoints compared using students T-test with ANOVA using SAS software version 8.0 & minitab version 17. **Results:** Group A initial BMI = 28.85 vs group B initial BMI = 27.34 (p = 0.05). Change in BMI group A vs B at visit 1 (0.4 vs 0.09, p = 0.002), visit 2 (4.6 vs -0.52, p = 0.001), visit 3 (6.5 vs 0.46, p = 0.003). Demographics & secondary endpoints reported in poster. **Conclusions:** We found dietary counseling in addition to standard of care was associated with significant mitigation of weight gain in patients on systemic chemotherapy. Dietary counseling is a relatively simple, inexpensive, individualized, & reproducible method to mitigate chemotherapy related weight gain.

6569 Poster Session (Board #391), Mon, 1:15 PM-4:45 PM

Prospective assessment of psychosocial outcomes of contralateral prophylactic mastectomy. *First Author: Abenaa M. Brewster, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Increasing numbers of women are choosing contralateral prophylactic mastectomy (CPM) despite the lack of knowledge about its effect on long-term psychosocial adjustment. The objective of the study was to examine patient-centered psychosocial outcomes of women with breast cancer who have CPM versus those who do not in order to enhance shared surgical decision making. **Methods:** We enrolled 308 women with newly diagnosed, non-hereditary breast cancer prior to surgery (CPM or no CPM) at MD Anderson Cancer Center and Kelsey-Seybold Clinic between 2012 and 2015. Women completed validated questionnaires assessing psychosocial factors including quality of life (QOL), body image concerns, cancer distress, trust in physician and decision satisfaction pre-surgery and at 1, 6 and 12-months post-surgery. Repeated measures models were fitted to assess the association between psychosocial outcomes measured at each time point and CPM status adjusting for time effect. **Results:** Among 252 women (mean age 56) who completed pre and post-surgery questionnaires, 60% were non-Hispanic white, 16% non-Hispanic black, 16% Hispanic, 8% mixed race and 17% had CPM. Women who had CPM had higher scores for cancer distress and body image concerns and lower scores for QOL than women who did not have CPM at pre-surgery ($p = 0.04$, $p < 0.01$, $p = 0.20$, respectively), and at 1 month ($p = 0.42$, $p < 0.001$, $p < 0.01$, respectively), 6 months ($p = 0.03$, $p < 0.001$, $p = 0.05$, respectively) and 12 months ($p = 0.01$, $p < 0.001$, $p = 0.01$, respectively) post-surgery. After adjusting for time effect, women who had CPM had higher post-surgery scores for cancer distress ($p = 0.03$), body image concerns ($p < 0.0001$), QOL ($p < 0.01$) and lower trust in physician ($p = 0.03$) than women who did not have CPM. There was no statistically significant difference by CPM status for cancer knowledge or decision satisfaction. **Conclusions:** This is the first study to demonstrate that psychosocial factors such as cancer distress, QOL and body image concerns are not improved by having CPM. The results highlight the importance of evaluating psychosocial factors pre- and post- surgery and the need to incorporate psychosocial assessment and counseling in the CPM decision making process.

6570 Poster Session (Board #392), Mon, 1:15 PM-4:45 PM

PROMs and PREMs in Dutch integrated head and neck cancer care. *First Author: Rosella Hermens, Scientific Institute for Quality of Healthcare, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands*

Background: Providing patient-centred care is an essential component of high quality integrated care. A method to get insight in patients perspectives about the quality of health care they received, is measuring Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs). We aimed to determine the outcomes of, and differences between PROs and PREs over time and between treatment groups for patients with head and neck cancer (HNC). **Methods:** Patientswere recruited from nine hospitals participating in the DHNA. Validated questionnaires were distributed at baseline, 3, 6 and 12 months follow-up. Included PROMs were EuroQol 5 Dimension 3 Level (EQ-5D-3L), EORTC QLQ-C30 and -H&N35. Included PREMs, Consumer Quality index for Oncologic care (CQO) and Radiotherapeutic care (CQR), have similar domains with different questions. With descriptive analysis, ANOVA and mixed model analysis, differences over time and between treatment groups were analyzed. **Results:** Questionnaires were filled in by 426 patients. Pain decreased significantly at 6 and 12 months follow-up (14 and 21 points on a scale of 0-100) and dry mouth increased significantly at 3, 6 and 12 months follow-up compared to baseline (35, 27 and 20 points). Sticky Salvia, problems with social eating and sense problems increased at 3 and 6 months follow-up, but were similar to the baseline score at 12 months follow-up. Pain and sticky saliva differed between radiotherapy and chemoradiotherapy or surgery and radiotherapy respectively ($p \leq 0.05$). Regarding the CQO domain scores, all treatment groups differed significantly from each other ($p \leq 0.05$), especially for the domain Personal input. There was no difference regarding the CQR domain scores. Recognizing the emotional side of HNC and guidance after the treatment scored low in patients. **Conclusions:** This study gives clues to improve healthcare according the experiences of the patient and we can predict more carefully the outcomes of the patients with different treatment types. PROMs according to the ICHOM criteria and PREMs are promising for measuring and improving quality and personalization of HNC care. However, recognizing the emotional side of HNC and intensifying guidance after the treatment period needs improvement.

6571 Poster Session (Board #393), Mon, 1:15 PM-4:45 PM

Assessing performance status and clinical outcomes with wearable activity monitors. *First Author: Gillian K. Gresham, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Performance status (PS) is assessed to inform treatment decisions and predict outcomes in cancer. PS is often evaluated using ECOG or KPS scales, limited by their subjective and static nature. Wearable activity monitors provide oncologists with the opportunity to obtain continuous objective data on patients' daily activity including steps, stairs climbed, and sleep. We evaluated the association between wearable activity monitor data, PS, and clinical outcomes. **Methods:** Patients with advanced cancer were enrolled in a prospective, observational study conducted at Cedars-Sinai Medical Center. Patients wore a Fitbit Charge HR for 3 consecutive clinic visits. ECOG/KPS were rated by treating physicians and serious adverse events (AE, clinically relevant grade 3+ by CTCAE v4), hospitalizations, and 6-month survival were collected. Correlations between PS and activity metrics were calculated. Multivariable regression models were fit to predict AEs and hospitalizations with activity data. The association between activity metrics and time to death was evaluated using survival analysis. **Results:** 35 patients (median age 62 years, 53% male) were evaluated. Most had gastrointestinal cancers (82%). Patients had ECOG PS of 0 (20%), 1 (40%), 2 (23%), and 3(17%). There were 10 (29%) pts with serious AEs, 14 (40%) hospitalizations, and 11 (31%) deaths. Average daily steps were significantly correlated with ECOG PS and KPS (r=0.73 and 0.70, respectively). Relationships between activity metrics, AEs, hospitalizations, and overall survival (OS) are displayed in the table below. **Conclusions:** We found a significant association between wearable activity monitor data and the risk of AEs, hospitalization and death. There is a strong correlation between step counts and KPS/ECOG PS. The potential of wearable activity data to predict outcomes and supplement PS assessment should be explored in future studies. Clinical trial information: NCT02659358.

	Adverse Events Odds ratios (p-value)	Hospitalizations Odds ratios (p-value)	Overall Survival Hazard Ratios (p-value)
Steps (per 1000 step increase)	0.36 (0.03)	0.23 (0.02)	0.48 (0.01)
Stairs (per 10 stair increase)	0.59 (0.11)	0.44 (0.06)	0.27 (0.04)
Sleep duration (per 1 hour increase)	1.78 (0.1)	1.94 (0.09)	1.79 (0.01)

6572 Poster Session (Board #394), Mon, 1:15 PM-4:45 PM

What are patients' biggest concerns? A patient reported outcome case-management system. *First Author: Rahma M. Warsame, Mayo Clinic, Rochester, MN*

Background: Cancer patients (pts) receive complex care that may cause physical, emotional, & financial sequelae. Current practice limits clinician time to address patient concerns. The Patient Reported Outcome Quality Of Life (PROQOL) system was developed as a self-reported electronic questionnaire to assess symptoms, QOL and provide data about bothersome issues. Our aim was to determine if the PROQOL system improves QOL without negatively impacting routine clinic workflow. **Methods:** Eligible pts had multiple myeloma, amyloidosis, head & neck or gynecologic cancer seen in Hematology/Oncology clinics at Mayo Clinic, and were stratified by stem cell transplant and active treatment status. Pts were randomized 2:1 to PROQOL system or usual care. PROQOL system was offered prior to every visit. Pts select from various categories about their single biggest concern, and receive a printed list of actionable resources based on selected concern. Clinicians also receive the PROQOL results to review with pts. Providers and pts randomized to PROQOL completed a "was it worth it survey" (WIWI). An 8 item Linear Analogue Self-Assessment was used to assess QOL. The study was powered to detect a 0.5 standard deviation difference in QOL between groups. Herein we report the planned results of first 6 months. **Results:** Among the first 118 pts accrued, 55% were female, median age was 63 (32-86), & 93% were on therapy. Median time from diagnosis to PROQOL was 26 months. The PROQOL system took 3.6 minutes to complete. Baseline median QOL (range) was 7 (3-10) for both groups. The most common PROQOL issue selected was "cancer & diagnosis" (36.5%) followed by "physical health" (35.3%). Specific concerns were related to treatment plan, prognosis, fatigue, sleep, and neuropathy. WIWI showed: 71% of pts thought it was worthwhile, 83% would participate again, 80% would recommend it, & 65% used resources provided. 80% of providers reported the PROQOL did not interfere with care & 75% believed the pt wellbeing may improve. **Conclusions:** Notably treatment plan & prognosis remain pts' greatest concern despite being over 2 year from diagnosis. The PROQOL system demonstrates integrated PRO reporting in clinic is quick & worthwhile to pts & providers.

6573 Poster Session (Board #395), Mon, 1:15 PM-4:45 PM

Self-reported health and access to care among cancer caregivers: Analysis of the 2015 behavioral risk factor surveillance system (BRFSS). *First Author: Emily Castellanos, Vanderbilt University Medical Center, Nashville, TN*

Background: Caregivers play a vital role in the support and treatment of cancer patients. Caregiver well-being can impact patient-perceived quality of care. The study objectives were to compare self-reported health and access to care between cancer caregivers and non-caregivers, and to determine the relationship of caregiving burden to self-reported health and access to care. **Methods:** We used data from the Caregiver and Core Modules of the 2015 BRFSS, an annual federal survey of health-related behavior, health conditions, and preventive service use. Caregiver burden was assessed by time (hours per week and duration of caregiving) and task (personal care and household management tasks). Measures of self-reported health and access to care between cancer caregivers and non-caregivers were compared using *t*-test or Chi-Square testing. Associations of caregiver burden with self-reported health and access to care were assessed with linear and logistic regressions. **Results:** 1,910 cancer caregivers and 84,412 non-caregivers were included. Compared to non-caregivers, cancer caregivers were more likely to report inability to see a physician due to cost (15% vs 9%; $p < 0.001$), depression (25.0% vs 17.9%; $p < 0.001$), and poor mental health (mean days per month 5.7 vs 3.1; $p < 0.001$). Compared to caregivers with low task burden, those with moderate or high task burden reported both more poor mental health days (moderate ß = 1.8, 95% CI 0.5 – 3.1, p = 0.008; high ß = 2.0, 95% CI 0.6 – 3.3, p = 0.004) and increased likelihood of cost barriers (moderate OR 1.6, 95% CI 1.03 – 2.5, p = .035; high OR 1.8, 95% CI 1.2 – 2.9, p = .008). Increased time burden was associated with more poor mental health days (moderate ß = 1.5, 95% CI 0.2 – 2.7, p = .02; high ß = 4.4, 95% CI 3.3 – 5.6, $p < .001$) but not cost barriers. No differences in insurance, personal health provider, medical check-ups, or self-reported poor physical health were identified. **Conclusions:** Cancer caregivers are more likely than non-caregivers to report poor mental health, depression, and difficulty seeing a physician due to cost. Caregivers with high caregiving burden are at increased risk of experiencing poor mental health and cost barriers to medical care.

6574 Poster Session (Board #396), Mon, 1:15 PM-4:45 PM

Association between progression-free survival and health-related quality of life in oncology: A systematic review and regression analysis. *First Author: Bruno Kovic, Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada*

Background: The goal of cancer care is to improve not only survival duration but also health-related quality of life (HRQoL). Progression-free survival (PFS) has become an important surrogate outcome in assessing efficacy of new cancer drugs, but the relationship between improved PFS and HRQoL is not clear, particularly in the absence of an overall survival (OS) benefit. The objective of this study was to examine the relationship between PFS and HRQoL through a systematic review and analysis of published evidence. **Methods:** We searched MEDLINE, Embase, and Cochrane databases for randomized controlled human trials addressing oncology treatments published since 2000. We utilized the difference in median PFS time duration between treatment groups, with eligible trials being those reporting no significant OS benefit. We calculated and compared HRQoL between treatment groups using the difference in standardized mean incremental area under the curve adjusted to per month values. Weighted simple regressions were used to examine the PFS-HRQoL association, separately for physical, emotional, and global HRQoL domains. **Results:** 35,960 citations were identified, with 42 final articles reporting 30 clinical trials being eligible for inclusion. The 30 trials involved 10,731 patients across 12 types of cancer using 6 different instruments. 67% of all trials had improved PFS, and 56%, 54%, and 62% of trials had improved physical, global, and emotional HRQoL, respectively. The PFS with physical domain (n = 18) regression coefficient (slope) β = -0.205 (95% CI; -0.649 to 0.239), with emotional domain (n = 13) β = 0.775 (95% CI; -0.048 to 1.598), and with global domain (n = 24) β = 0.094 (95% CI; -0.271 to 0.459). **Conclusions:** Our systematic review and analyses revealed weak and non-significant association between PFS and HRQoL. In the absence of OS benefit, when longer PFS doesn't correspond to better HRQoL, using PFS as the proxy for efficacy for oncology drugs is problematic.

6575 Poster Session (Board #397), Mon, 1:15 PM-4:45 PM

Understanding the non-curative potential of palliative chemotherapy: Do patients hear what they want to hear? *First Author: Andrea Catherine Enzinger, Dana-Farber Cancer Institute, Boston, MA*

Background: Misconceptions about the curative potential of PC are common, and may arise from gaps in informed consent. Another contributing factor could be patients' desire, or lack of desire, for information about prognosis and PC outcomes. **Methods:** We surveyed 137 patients with advanced colorectal (N = 102) or pancreatic cancer (N = 35) within 2 weeks of consultation about 1st or 2ndline PC, as part of randomized trial of a PC education intervention at 6 US sites. Patients rated how much information they wanted about PC risks/benefits, including impact on prognosis. Responses ranged from no information to as much as possible on a 5-point Likert scale. They reported decision-making preferences; whether a doctor discussed curability, and how likely they thought PC was to cure their cancer. Chi square and Wilcoxon tests examined whether information and decision-making preferences, or curability discussions were associated with expectations of cure. Multivariable logistic regressions evaluated whether associations were modified by age, race, gender, marital status, or cancer type. **Results:** Only 44.5% of patients accurately reported that their cancer was not at all likely to be cured by PC. Most patients wanted a lot, or as much information as possible about PC risks/benefits, including likelihood of cure (81.7%), cancer control (84.7%), and impact on length of life (80.3%). Most patients preferred shared (70.8%) versus active or passive decision-making. Neither decision-making nor prognostic information preferences were associated with expectations of cure. Patients (13.9%) who did not recall curability discussions were less likely to have accurate expectations (21% v 48%; OR, 0.29; 95% CI, 0.07-.97). Patient characteristics did not significantly confound this association. **Conclusions:** Most patients value shared decision-making and want maximal information about PC risks/benefits, including impact on prognosis. Despite wanting prognostic information and reporting curability discussions, many patients report inaccurate expectations about cure from PC. Future studies should examine whether these assertions reflect misunderstandings, differences in belief, or expressions of hope.

6576 Poster Session (Board #398), Mon, 1:15 PM-4:45 PM

Differences in mortality among patients with acute leukemia admitted on weekends as compared to weekdays. *First Author: Kaushal Parikh, New York Medical College, Valhalla, NY*

Background: The association between weekend admissions and patient outcomes has been widely reported for several acute illnesses. However, this is the first study using a nationwide database to focus on outcomes of weekend admissions for acute leukemia. **Methods:** We used the 2002-2012 Nationwide Inpatient Sample Databases to identify patients admitted with a diagnosis of acute leukemia. Admissions were identified as weekend or weekday admissions and rates of mortality, in-hospital complications, existing comorbidities, and demographic differences were assessed. Adjusted logistic regression models were used to analyze mortality and complication outcomes. **Results:** Out of a total of 71,392 patients included in the analysis, 12,234 (17.1%) patients were admitted over the weekend. While there has been a general decline in admissions and mortality in acute leukemia from 2002-2012, mortality was 18.8% for weekend admissions and 16.3% for weekday admissions ($p < 0.001$). Weekend admissions independently predicted higher mortality (adjusted odds ratio 1.128, 95% confidence interval, 1.06 to 1.20; $p < 0.001$). These patients were also less likely to receive an early bone marrow biopsy than their weekday counterparts (45% vs 26.5%; $p < 0.001$). Bone marrow biopsy was independently associated with a reduced in-hospital mortality (aOR 0.395, 95% CI 0.373 to 0.417; $p < 0.001$). Admissions to teaching hospital were also associated with a lower mortality (aOR 0.890, 95% CI 0.845 to 0.936; $p < 0.001$). Weekend admissions were also more likely to have in-hospital complications than weekday admissions (52.4% vs 50.5%; $p < 0.001$). **Conclusions:** There was a significantly increased mortality among acute leukemia patients admitted on a weekend. Our study suggests that patients admitted over the weekend may be clinically sicker or receive inferior care than weekday admissions. We also conclude that patients admitted to teaching hospitals have a better outcome and emphasize the importance of availability of resources and early presentation to tertiary care centers.

6577 Poster Session (Board #399), Mon, 1:15 PM-4:45 PM

Feasibility of wearable physical activity monitors in cancer patients (PAMCaP). *First Author: Muhammad Shaalan Beg, Division of Hematology/Oncology, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Wearable physical activity monitors (PAMs) provide a degree of functional assessment not possible with prior clinical instruments. Subjective assessments of functional status are prone to inaccuracy and current objective assessment techniques are limited to the research setting. The relevance of physical activity monitors (PAMs) to measure functional status in cancer patients is unclear. The feasibility of using these devices in cancer patients is not known. **Methods:** This is a prospective pilot trial of a commercially available PAM in cancer patients. Patients with Eastern Cooperative Group performance status (ECOG PS) 0-2 receiving systemic therapy at an NCI Designated Comprehensive Cancer Center were enrolled. (NCT02583815). The primary objective was to determine feasibility of PAM use, defined as device use of more than 50% of the study observation period. Secondary objectives were to correlate PAM-reported measures: median, minimum and maximum steps/day, minutes of activity/day, (light/ fairly active/ very active); with 1) clinician assessed ECOG PS and 2) quality of life tool scores (FACT-G, QIDS, PQSI and BFI). Patient experience with wearable PAMs was assessed at the end of study. **Results:** We enrolled 32 patients: median age = 56 years (range 23-72), female = 67%, and white = 78%. Most patients had gastrointestinal (52%) and breast (19%) primaries. Clinician assessed PS was ECOG 0 in 56%, 1 in 37% and 2 in 7%. Majority of patients (81%) met the primary end point. Mean PAM measured steps for ECOG 0 was 5911 steps/d, ECOG 1 was 1890 steps/d and ECOG 2 was 845 steps/d (p = 0.002). Minimum steps/day correlated with BFI (r = -0.56, p $<$ .01), FACT-G (r = 0.45, p 0.01) and QIDS (no vs mild vs moderate depression, p 0.01). Patients reported a positive experience with the devices (74%). **Conclusions:** Wearable PAMs are a feasible tool to measure physical activity in cancer patients receiving systemic therapy. PAM derived measures correlate with clinician assessments of performance status. Future work should develop methods to systematically incorporate PAMs in oncology clinical trials and practice. Clinical trial information: NCT02583815.

6578 Poster Session (Board #400), Mon, 1:15 PM-4:45 PM

Correlation of changes in disposition of geriatric (≥ 65 years) cancer patients receiving hematopoietic stem cell transplantation with an increase in healthcare costs. *First Author: Achuta Kumar Guddati, SUNY Downstate Medical Center, Brooklyn, NY*

Background: The increasing proportion of geriatric cancer patients in the general population has contributed to rising health care costs. The disposition of hematopoietic stem cell transplant (HSCT) recipients in the geriatric population is an important factor determining the cost of their health care. A database with nationwide representation for outcomes of HSCT over a 12 year period was analyzed. **Methods:** Data regarding patients who underwent HSCT was extracted from the Nationwide Inpatient Sample (NIS) from 2000 to 2011 using ICD-9-CM codes. HSCT hospitalizations were classified into allogeneic transplantation, autologous transplantation, subsequent hospitalization (s/p transplant) with graft versus host disease (GVHD) and subsequent hospitalization (s/p transplant) with other complications. NIS variables were used to identify in-hospital complications and discharge disposition. **Results:** The proportion of elderly patients (≥ 65 years) who received any type of transplant or were admitted with GVHD or other related complications who were discharged with additional support and to specialized facilities has increased over the past decade. The exception to this trend has been noted for allogeneic transplants and may be due to a more conservative approach towards their disposition (ie, higher level of care and longer length of stay). The trends from 2000 to 2011 are summarized in the table below. **Conclusions:** A higher percentage of geriatric cancer patients who receive HSCT are being discharged to nursing homes. These rates have significantly changed over the past decade ($p > 0.05$) and represents an additional contribution to the rising health care costs. This proportion of patients are expected to rise as increasingly older patients are being allowed to receive HSCT and represents a higher future demand for health care services.

	≥ 65 years			
	Autologous transplantation	Allogeneic transplantation	s/p Transplant with GVHD	s/p Transplant with other complications
Home	87 to 80%	77 to 69%	77 to 55%	71 to 66%
Home Healthcare	10 to 16%	16 to 27%	16 to 26%	17 to 20%
Nursing Home	3 to 4%	7 to 3%	6 to 19%	11 to 14%
Others	< 1%	< 1%	< 1%	0-1%

6579 Poster Session (Board #401), Mon, 1:15 PM-4:45 PM

Symptom burden and hospital length of stay among patients with curable cancer. *First Author: Sara D'Arpino, Massachusetts General Hospital, Boston, MA*

Background: Prolonged hospital admissions are often inconsistent with patients' preferences and incur significant costs. While patients' symptoms may result in hospitalizations, the relationship between patients' symptom burden and their hospital length-of-stay (LOS) has not been fully explored in patients with curable cancers. **Methods:** We prospectively enrolled patients with curable cancer and unplanned hospital admissions between 8/2015 and 12/2016. Within the first 5 days of admission, we assessed patients' physical (Edmonton Symptom Assessment System [ESAS]; scored 0-10 with higher scores indicating greater symptom burden) and psychological symptoms (Patient Health Questionnaire 4 [PHQ-4]; scored categorically and continuous with higher scores indicating greater distress). We created summated ESAS total and physical symptom variables. To assess the relationship between patients' symptom burden and their hospital LOS, we used separate linear regression models adjusted for age, sex, marital status, education level, time since cancer diagnosis, and cancer type. **Results:** We enrolled 452 of 497 (91%) approached patients (mean age = 61.9 years; 188 [42%] female). Over half had hematologic cancers (n = 249, 55%). Mean hospital LOS was 8.3 days. Over one-tenth of patients screened positive for PHQ-4 depression (n = 74, 16%) and anxiety (n = 60, 13%) symptoms. Mean ESAS symptom scores were highest for fatigue (6.6), drowsiness (5.4), pain (4.9), and lack of appetite (4.8). In multivariable regression analysis, patients' physical and psychological symptoms were associated with longer hospital LOS (table). **Conclusions:** Patients with curable cancer and unplanned hospital admissions experience a substantial symptom burden, which predicts for prolonged hospitalizations. Importantly, patients' symptoms are modifiable risk factors that, if properly addressed, can improve care delivery and may have the potential to help decrease prolonged hospitalizations.

Symptom burden associated with hospital LOS	B	95% Confidence Interval	Standard Error	P-value
ESAS Physical	0.10	0.04 to 0.17	0.03	**0.003**
ESAS Total	0.10	0.05 to 0.15	0.03	**< 0.001**
PHQ-4 Depression	0.68	0.15 to 1.20	0.27	**0.011**
PHQ-4 Anxiety	0.55	< 0.01 to 1.09	0.28	**0.0498**

6580 Poster Session (Board #402), Mon, 1:15 PM-4:45 PM

Inpatient hematology and oncology rehabilitation. *First Author: Leann Blankenship, Beaumont Health, Department of Hematology and Oncology, Oakland University William Beaumont School of Medicine, Royal Oak, MI*

Background: Functional decline in cancer patients impacts quality of life and overall survival. Increasing attention has been focused on cancer rehabilitation in survivors, largely in the outpatient setting. Beaumont Health System has shifted its focus to include the acute setting by developing an inpatient cancer rehabilitation unit (IPCR) to improve the comprehensive care of patients. **Methods:** We retrospectively reviewed the patients admitted to IPCR from January 1 - December 31, 2016 for the following: demographics, length of stay (LOS), function independence measure (FIM) gain and efficiency, discharge location, and primary tumor type. **Results:** IPCR had 117 inpatient admissions; 98 (83.7%) were solid malignancies while 19 (16.3%) were benign hematological disorders and hematological malignancies. Of the 98 patients with solid malignancies, 22 (22.4%) patients had breast cancer, 22 (22.4%) had gastrointestinal cancers, 5 (5.1%) had gynecological cancers, 23 (23.5%) had lung cancer, 8 (8.2%) had CNS malignancies, 11 (11.2%) had other cancers, and 7 (7.2%) had prostate cancer with 81.6% of patients having metastatic disease. Among the hematological malignancies, lymphoma was diagnosed in 11 (57.9%) patients while 3 (15.9%) each had multiple myeloma and leukemia. The mean age of the patients was 68 years and 59% were female. The average LOS was 8.6 days. The mean admission total FIM was 66.7 $\pm$12.8 and discharge total FIM was 87.3 $\pm$16.1. The total improvement in FIM was 20.6 $\pm$13.8 with FIM efficiency of 2.9. There were 21 (18%) patients transferred back to acute care units for decompensation, 7 (6%) went to subacute rehabilitation, 1 (0.85%) went to hospice while 87 (74.3%) were discharge to their homes upon completion of IPCR. **Conclusions:** Our focused rehabilitation was able to decrease the LOS, well above the 90th percentile Center for Medicare and Medicaid Services (CMS) benchmark and other prior studies, as well as enable patients to safely return home with improved FIM. Creating an IPCR unit proved to be beneficial, allowing for more comprehensive and individualized care, even in the setting of advanced malignancies.

6581 Poster Session (Board #403), Mon, 1:15 PM-4:45 PM

Prophylactic anticoagulation to benefit younger patients under 65 years of age with metastatic lung cancer: An analysis of the 2013 Healthcare Cost and Utilization Project (HCUP) data. *First Author: Arindam Bagchi, University Of Toledo, Toledo, OH*

Background: Cancer patients have increased risk of venous thromboses. Venous thromboembolism (VTE) is reported to be a leading cause of death in cancer patients. It has been hypothesized that prophylactic anticoagulation for VTE might improve prognosis and quality of life. Based on our analysis of the 2013 HCUP data, we propose that prophylactic anticoagulation should be considered for patients younger than 65 years with metastatic lung cancer. **Methods:** Patients were selected using ICD-9 diagnoses codes for metastatic lung cancer and VTE. Diagnoses were stratified by site including upper extremity, lower extremity, pulmonary, abdominal and nonpulmonary thoracic VTE. Patients were stratified by age, sex, race and ethnicity. Differences in incidence of VTE among groups were calculated by the Chi-Square method using the SAS software. **Results:** There were a total of 16,577 VTE events amongst 182,863 cases of metastatic lung cancer. Subgroup analyses showed that patients younger than 65 years of age had 356.82 more PE events per 100,000 individuals compared to those at or older than 65 years ($p < 0.0001$). The same age group also showed 374.83 more UE, 286.94 more nonpulmonary thoracic and 263.97 more abdominal (Abd) VTE events per 100,000 individuals (p-values, $p < 0.0001$). There was no statistically significant difference in the incidence of LE VTE's between the subgroups. **Conclusions:** Prophylactic anticoagulation should be considered in patients < 65 years of age with metastatic lung cancer. Increased incidence of VTE in these patients may contribute towards greater morbidity and mortality associated with metastatic lung cancer in this subgroup.

	Age < 65 y	Age > 65 y	
No. of patients	77415	105448	p value
PE	2928 3782.21 events per 100,000	3612 3425.38 events per 100,000	< 0.0001
UE VTE	912 1178.06 events per 100,000	847 803.23 events per 100,000	< 0.0001
LE VTE	2791 3605.24 events per 100,000	3913 3710.83 events per 100,000	0.2352
NonPulm Thoracic VTE	460 594.20 events per 100,000	324 307.26 events per 100,000	< 0.0001
Abd VTE	324 418.52 events per 100,000	163 154.57 events per 100,000	< 0.0001

6582 Poster Session (Board #404), Mon, 1:15 PM-4:45 PM

Patterns in provider types and cost of surveillance testing in early-stage breast cancer patients: A regional study. *First Author: Gary H. Lyman, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Although ASCO Choosing Wisely guidelines recommend against routine surveillance testing or imaging for asymptomatic individuals with early-stage breast cancer (ESBC) treated with curative intent, they are frequently performed. Physician specialty and costs associated with surveillance testing and imaging were examined in ESBC patients. **Methods:** Cancer registry patient records in Western Washington from 2007 to 2015 were linked with claims from two regional commercial insurers. Selected patients had been diagnosed with stage I/II breast cancer and treated with mastectomy or lumpectomy + radiation. Surveillance was considered from the first 4 month gap in treatment (surgery, chemo, radiation) through 13 months or restart of treatment. Evaluation and Management (E&M) and procedure codes for tumor marker (CEA, CA 15-3, CA 27.29) and advanced imaging (PET, CT, bone scan) were identified. Specialty codes were used to determine provider type. Physician visits were matched to tests using E&M codes in the +/- 7 days around each test. Cost included total reimbursed amount from insurers during the surveillance period. **Results:** During surveillance, 2,193 patients averaged 13.3 physician visits [median: 11, IQR: 8-17]. Oncologists (91%) and PCPs (83%) were the most common specialties with an average of 3.7 visits each. Overall, 37% of patients received tumor marker tests (avg = 2.8 tests/patient) and 17% received advanced imaging (avg = 1.5 images/patient). The mean total cost during the surveillance period was $18,403 (SD $26,640). Costs were higher for those patients who received tumor marker testing or advanced imaging. **Conclusions:** Patients frequently see oncologists and PCPs during early surveillance. Targeting oncologists to improve appropriate tumor marker testing could have the largest impact on aligning practice with Choosing Wisely recommendations and potentially reducing the financial burden on patients.

	Tumor Marker (n=2,302)	Advanced Imaging (n=531)
Med Onc	74 %	38%
Rad Onc	1%	4%
General Surgeon	3%	6%
PCP	14%	24%
Reconstructive Surgeon	2%	3%
Other	53%	50%
No office visit	7%	16%
Mean cost (std dev)	$24,380 ($29,392)	$29,998 ($34,922)

6583 Poster Session (Board #405), Mon, 1:15 PM-4:45 PM

Universal testing for hormonal status in breast cancer: Are we choosing wisely? *First Author: Taylor Maxwell Goller, University of Vermont Medical Center, Burlington, VT*

Background: Characterizing estrogen receptor (ER) and progesterone receptor (PR) status has long been standard practice with newly diagnosed breast cancers. ER and PR expression suggests a more favorable prognosis and predicts tumor responsiveness to hormonal therapy. However, this testing comes with considerable cost. At our institution, the Medicare reimbursement rate for a single ER/PR assay is $310. With over 300,000 newly diagnosed breast cancers in the US each year, the total cost of ER/PR testing is close to 100 million dollars. Furthermore, the 2010 American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines suggest that up to 20% of ER/PR testing worldwide may be inaccurate with potential for false negative results. A falsely negative result could lead clinicians to not offer treatment with hormonal therapies. The purpose of this study was to investigate whether nuclear grade could be used to predict ER status, thus saving cost and reducing the potential for false negative test results and the inappropriate withholding of beneficial treatment. **Methods:** A retrospective analysis of prospectively collected data from the University of Vermont Breast Cancer Database identified all newly diagnosed breast cancers of any histologic type with available data on nuclear grade and ER status (2/2008-10/2016). The relationship between nuclear grade and ER status was analyzed (Table). **Results:** Nuclear grades 1 and 2 were associated with a significantly higher proportion of ER positive results than high nuclear grades (chi-square test $p < .001$). **Conclusions:** Nuclear grade 1 and 2 breast cancers are nearly universally ER positive (99% and 97%, respectively). Thus, ER testing may be redundant in these tumors. Elimination of ER testing in nuclear grade 1 and 2 tumors could save tens of millions of dollars each year in the US alone. It could also reduce the potential for false negative test results and the inappropriate withholding of beneficial treatment.

Relationship between nuclear grade and ER expression status.

Nuclear Grade	ER Positive	%	ER Negative	%
3 (n: 1133) 37%	729	64%	404	36%
2 (n: 1642) 54%	1588	97%	54	3%
1 (n: 296) 9%	294	99%	2	1%
All (n: 3071)	2611	85%	460	15%

6584 Poster Session (Board #406), Mon, 1:15 PM-4:45 PM

CEASE: A novel patient directed electronic smoking cessation platform for cancer patients. *First Author: Jennifer M. Jones, Ontario Cancer Institute, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Continued smoking in cancer patients receiving treatment results in decreased efficacy, reduced survival, amd increased risk of recurrence. Despite ASCO and AACR policy statements, routine tobacco use screening and provision of smoking cessation treatment has not been widely implemented in the cancer setting. A paper-based tobacco use screening and clinician-dependent referral program for new ambulatory cancer patients was initiated at Princess Margaret Cancer Centre in 2013 resulting in moderate screen rates but low referral rates. In response, we developed and implemented a tailored patient directed electronic smoking cessation platform (CEASE) which included three elements:1) tobacco use assessment tool; 2) patient education on benefits of cessation; 3) a patient directed automatic referral system to smoking cessation programs. **Methods:** Interrupted time series design to examine the impact of CEASE on process of care (screening rates, referrals offered and accepted) and patient reported (quit attempts, smoking status, uptake of cessation programs) outcomes. Included 20 monthly intervals: 6 pre implementation (Apr-Sept 2015) (PRE), 8 gradual implementation across all tumour sites (Oct 2015-May 2016), and 6 postb implementation (Jun 2016-Nov 2016) (POST). A time series segmented linear regression was conducted to evaluate changes in process of care outcomes (excluding the implementation period). Pre-post self-report patient outcome data was also compared. **Results:** We assessed data from n = 3785 (PRE) and n = 4726 (POST) new patients. Screening rates increased from 44% using the paper-based approach to 65% with CEASE ($p = 0.0019$). Referrals offered to smokers who were willing to quit increased from 24% to 100% ($p < 0.0001$). Accepted referrals decreased from 45% to 26%; though the overall referral rate increased from 11% to 26% ($p = 0.0001$). The proportion of those using tobacco or attempting to quit did not differ at 3-months. However, engagement with the referral source increased from 4% to 62.5% ($p < 0.001$). **Conclusions:** CEASE was successfully implemented across all clinics and resulted in improvements in overall screening and referral rates and engagement with referral services.

6585 Poster Session (Board #407), Mon, 1:15 PM-4:45 PM

Transparency around disapproval reasons of early-phase trial proposals submitted to the National Cancer Institute (NCI). *First Author: Holly A. Massett, National Cancer Institute, Rockville, MD*

Background: NCI's ETCTN accepts Letters of Intent (LOI) for a new clinical trial either from a response to a solicitation for studies, or via unsolicited LOIs, where investigators independently propose novel studies. While the LOI approval rate for the first two years of the ETCTN was 100% for solicited LOI's, it was only 36% for unsolicited LOIs. Therefore, we analyzed all ETCTN LOI disapproval letters (DL) for unsolicited LOIs to identify the major reasons for disapproval. **Methods:** A content analysis was conducted on DLs issued between March 2014 and March 2016 (N = 50). Two coders independently scored disapproval reasons per letter using a code sheet with 22 categories identified from a sample of DLs (Intercoder Reliability = 97%). **Results:** All DLs were issued for unsolicited LOIs (44% = Ph 1; 26% = Ph 1/2; 30% = Ph 2); 271 reasons were identified across the 50 DLs (mean = 5.4/DL). High-level categories included concerns with study design, scientific rationale, feasibility, modality and administrative reasons. The top disapproval reasons were: Insufficient preclinical animal model data (54% of DLs); weak rationale/background (52%); inadequate information for biomarker correlative studies (46%); dose/scheduling plan absent or weak (36%); clinical data not adequately advanced (34%); and, patient population not described/inconsistent with treatment (34%). Top reasons for Phase 1 and 1/2 LOIs resembled the total but Phase 2 LOIs deviated slightly, with 'weak objective/endpoint' and 'biomarker correlative studies' as top DL reasons. Other common reasons were problems with combination study agents, company/drug collaboration, and competing trials. **Conclusions:** The reasons for LOI disapproval can be categorized and quantified. To increase transparency in the NCI ETCTN LOI review process, disapproval reasons for each DL are now collected on a standardized coding sheet, and will be reported quarterly to ETCTN PIs. NCI will also meet with all Grant PIs in Spring, 2017 to jointly discuss concerns and explore quality improvement solutions regarding the LOI submission process. The outcome of this meeting will be reported at ASCO as part of our findings.

6586 Poster Session (Board #408), Mon, 1:15 PM-4:45 PM

Does coaching goals of care discussion skills make a difference? *First Author: Nina A. Bickell, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Advanced cancer patients often have a poor understanding of their cancer prognosis. Goals of Care (GoC) discussions provide information about the cancer, its treatment & prognosis and elicit patient values. Little is known about the best ways to enhance patient understanding, clarify values and move GoC discussions earlier in the disease process. We report the effect of coaching oncologists on GoC discussions. **Methods:** We recruited oncologists & their advanced cancer patients with $<$ 2 year prognosis to a RCT testing a coaching model communication skills training. Patients were surveyed after their post-imaging visit. We define GoC discussions as patient report that their doctor talked about their cancer prognosis and clarified things most important to them given their disease. Outcome variables assess the impact of GoC on patients' knowledge on what to expect and clarity of values. **Results:** We enrolled 22/25 (88%) oncologists and 70% of eligible patients of whom 96 (55%) completed a survey. On average, doctors were 44 yrs old (32-66) and in practice 14.5 yrs (5-40). Patients' mean age was 62 yrs (20-95), 40% females, 58% white, 24% Latino & 22 % black. Overall, 2/3 of patients reported their treatment's goal was to cure their cancer; 14% reported cure to be unlikely. Patients felt more knowledgeable (79% vs 21%; p = 0.02) when their doctors discussed treatments, side effects & quality of life. When patients were asked about things important to them, they report being a bit clearer about their values (65% vs 35%; p = 0.16). Compared to controls, intervention patients felt more knowledgeable (78% v 63%; p = 0.17) but did not feel clearer about their values (60% v 54%; p = 0.59). Multivariate modeling found that poor health literacy (OR = 0.2; 95%CI: 0.07-0.82), having a GoC discussion (OR = 10.2; 1.7-63.1) and being in the intervention group (OR = 8.8; 1.4-55.2) significantly affected knowledge (model c = 0.88; p $<$ 0.01). However, discussing what's important to patients did not help patients feel clearer about their values (OR = 2.7; 0.6-12.2; model c = 0.82; p $<$ 0.05). **Conclusions:** Using a coaching model to teach oncologists communication skills may improve patients' understanding of what to expect with their cancer but does not impact their clarity of values. Clinical trial information: NCT02374255.

6587 Poster Session (Board #409), Mon, 1:15 PM-4:45 PM

Possible mechanisms of serotonin and aprepitant actions in chemotherapy induced nausea and vomiting (CINV): Insights into the mechanisms of serotonin and aprepitant actions in CINV—According to recent multi-institutional double-blind randomized clinical research on the AC regimen. *First Author: Michiko Tsuneizumi, Shizuoka General Hospital, Shizuoka, Japan*

Background: One of our interests has been whether palonosetron(P) would be superior to granisetron(G) when administering triplet antiemetic therapy for the prevention of CINV, since a prior trial demonstrated P to be superior to G for controlling CINV induced by highly emetogenic chemotherapy (HEC) in doublet therapy. In this study(TTT; trial for antiemetic therapy), we assessed the efficacies of P and G for use as triplet antiemetic therapy for AC, by monitoring CINV, focusing complete response (CR; no vomiting and no rescue medicine) in the delayed phase. The primary endpoint of TTT was a CR during the delayed phase with 5-HT3ra plus dexamethasone and aprepitant administration for AC. The purpose of gaining insights into the possible mechanism of action of aprepitant and P was to obtain ideas for the next strategy against CINV. **Methods:** Between 2012 and 2015, 491 breast cancer receiving AC were recruited from 11 institutions, and randomly assigned to either single-dose P(0.75mg) or G(40μg/kg) prior to AC on day 1, both with dexamethasone (9.9 mg) and aprepitant (125mg) on day 1 followed by additional doses (80mg) on days 2 and 3. Age, institution and habitual alcohol intake were used as stratification factors. The primary endpoint was a CR. **Results:** All 491 patients were included in efficacy analyses: 246 patients in the group P and 245 in the group G. The difference in CR during the delayed phase, i.e. 24 hrs after the administration of AC, did not reach statistical significance, however, there was a remarkable difference between 48 and 72 hrs in the day-to-day analysis(p $<$ 0.02). **Conclusions:** P showed better efficacy in controlling CINV between 48 to 72 hours after AC, than G as triplet antiemetic therapy for AC. We can reasonably speculate that the influence of serotonin has two peaks (0-24 hrs and 48-72 hrs). For controlling CINV in the delayed phase, not only an NK1 receptor antagonist but also administering a 5-HT3ra with long life should be considered until 72 hrs after HEC. Clinical trial information: UMIN 000007882.

6588 Poster Session (Board #410), Mon, 1:15 PM-4:45 PM

Phone call for chemotherapy validation in outpatient unit as a way to optimize health care without compromising patients' satisfaction and quality of life. *First Author: Patricia Marino, Institut Paoli-Calmettes, Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Economiques and Sociales de la Santé and Traitement de l'Information Médicale, Marseille, France*

Background: Patients' satisfaction is known to be closely linked to the time spent with the physician. However, longer waiting times may be a source of dissatisfaction as well as organizational dysfunctions of the outpatient unit. Is a validation of chemotherapy by phone call instead of a medical consultation with a senior physician before chemotherapy (CT) is feasible without compromising patients' satisfaction and quality of life? **Methods:** Pts with OMS $<$ 1, able to respond to phone call, $<$ 76 years, receiving day 8 and or d15 of CT were included. We enrolled 343 pts in a before/after study between 2013 and 2016. In the "before" step (control arm), 168 pts had a systematic physician consultation the same day before CT administration. In the intervention arm 175 pts received a phone call by a junior physician the day preceding CT administration. A specific questionnaire for CT -related toxicity of the previous cycle was recorded and CT was validated or not by physician. The day after, pts received prepared CT without appointment with the oncologist and delay in administration for already prepared CT. At the end of CT protocol, socio demographics, patients' satisfaction (In-PatSat32) and health status (EQ-5D) questionnaires were completed by patients. **Results:** Questionnaires were completed by 83% and 74% in before and after step respectively, 241 questionnaires were analyzed. Satisfaction with care showed similar In-PatSat32 scores between arms, for satisfaction with: physician, nurse, organization and services. No differences of perceived health status and toxicity were observed between both groups, but patients' time spent in hospital was lower in the intervention group versus the control group, (p = 0.007). **Conclusions:** An alternative care pathway implementing phone calls before CT administration if feasible without compromising pts' satisfaction, quality of life and toxicity. We believe that saving time of pts, physicians and pharmacists is a way to optimize the model of care in outpatient unit, particularly in the immunotherapy area with more pts received intra venous treatment, probably for a long time.

6589 Poster Session (Board #411), Mon, 1:15 PM-4:45 PM

Concordance assessment of a cognitive computing system in Thailand. *First Author: Suthida Suwanvecho, Horizon Cancer Center, Bumrungrad International Hospital, Bangkok, Thailand*

Background: IBM Watson for Oncology (WFO) was trained by Memorial Sloan Kettering and is a cognitive computing system that uses natural language processing to ingest patient data in structured and unstructured formats. The system provides physicians with treatment options that are derived from established guidelines, the medical literature, and training from patient cases. In this study, we assessed the degree of concordance between treatment recommendations proposed by WFO and oncologists at Bumrungrad International Hospital (BIH). BIH is a 580-bed multispecialty hospital in Bangkok, Thailand. **Methods:** Data from breast, colorectal, gastric, and lung cancer patients treated at BIH were entered into WFO in 2015 and 2016. Retrospective cases were entered after a treatment plan had been determined, and prospective cases were entered during patients' treatment planning sessions. WFO recommendations were provided in 3 categories: "Recommended", "For Consideration", and "Not Recommended." Concordance was analyzed by comparing the decisions made by the oncologists to those proposed by WFO. Concordance was achieved when the oncologist's treatment suggestion was in the "Recommended" or "For Consideration" categories given by WFO. **Results:** A total of 211 cases were assessed, 92 were retrospective and 119 were prospective. The overall concordance rate was 83%; 89% for colorectal, 91% for lung, 76% for breast, and 78% for gastric cancer. Similar concordance rates were observed when retrospective and prospective cases were analyzed separately. Discordance was attributable in part to local oncologists' preferences for non-U.S. guidelines for certain cancers, especially gastric cancer. **Conclusions:** There was a high degree of concordance between WFO treatment options and the decisions made by local oncologists. Similar results were recently reported in a breast cancer concordance study conducted using WFO in India (San Antonio Breast Cancer Symposium 2016, Somashekhar et al). WFO's capabilities as a cognitive decision support tool can be further improved by incorporating regional guidelines. Future work will analyze reasons for discordance such as cost, insurance requirements, and patient and physician preference.

6590 Poster Session (Board #412), Mon, 1:15 PM-4:45 PM

Prevalence and estimated trend in chemotherapy use near death from population-based studies on cancer patients: A systematic review and meta-analysis. *First Author: Pei-Chun Chou, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan*

Background: Chemotherapy (CMT) use near death, based on US national guidelines, is an indicator of aggressive treatment and poor quality of end-of-life (EOL) care. US law also decreased Medicare payments for outpatient CMT since 2005-2006. To evaluate the impact of US payment reform and guidelines on CMT use at EOL, we estimated and compared the overall prevalence of CMT use at EOL in the US and other countries as well as before and after 2007 in the US. **Methods:** Six databases were systematically searched to January 2017 for population-based studies of CMT use at EOL for patients in all cancer groups. Two reviewers independently extracted data.Overall CMT use prevalence was pooled by a random-effects model. Differences in prevalence of CMT use were compared by meta-regression between subgroups (US vs non-US countries; before and after 2007 in the US). **Results:** We identified 9 and 7 articles from the US and non-US countries, respectively. CMT was provided to 28.9% [95% confidence interval (CI) 26.2%-31.8%], 23.2% [95% CI 21.7%- 24.8%], 10.0% [95% CI 8.5%-11.8%], and 4.5% [95% CI 3.9%- 5.2%] of cancer patients in their last 6, 3, and 1 months as well as 14 days of life, respectively. CMT use in the last 6 months was more common in the US than in non-US countries (32.4% vs. 26.2%, p = 0.015) but similar to that of other countries in the last month (9.3% vs.11.2%, p = 0.179) and last 14 days (4.6% vs.5.6%, p = 0.683) of life. Prevalence of CMT use in the last 14 days of life in the US did not differ significantly before and after 2007 (5.1% vs. 5.2%, p = 0.967). **Conclusions:** Many cancer patients worldwide receive CMT at EOL, and the prevalence of CMT use in US patients' last 14 days of life was virtually unchanged over time. Effective interventions should be developed and provided to offset the trend of continuing CMT use at EOL.

6591 Poster Session (Board #413), Mon, 1:15 PM-4:45 PM

Estimating the optimal rate of adjuvant chemotherapy utilization in stage III colon cancer. *First Author: Safiya Karim, Cancer Care and Epidemiology, Queen's University, Kingston, ON, Canada*

Background: Identifying optimal chemotherapy utilization rates can drive improvements in quality of care. We report a benchmarking approach to estimate the optimal rate of adjuvant chemotherapy (ACT) for stage III colon cancer. **Methods:** The Ontario Cancer Registry was linked to electronic chemotherapy records to identify ACT utilization among a random 25% sample of patients with stage III colon cancer diagnosed during 2002-2008 in Ontario, Canada. We explored whether hospital factors (teaching status, regional cancer centre, medical oncologist on-site) were associated with ACT rates. The benchmark population included hospitals with the highest ACT rates that accounted for 10% of the patient population. Hospital ACT rates were adjusted for case mix in a multi-level model accounting for random variation at the hospital level. A Monte Carlo simulation was used to estimate the proportion of observed ACT rate variation that could be due to chance alone. **Results:** The study population included 2,801patients with stage III colon cancer; ACT was delivered to 66% (1861/2801) of patients. There was no difference in hospital ACT rate by teaching status (64% academic vs 67% non-academic, p = 0.107), comprehensive cancer centre status (65% cancer centre vs 67% non-cancer centre, p = 0.362), or having medical oncology on site (67% on site vs 66% not on site, p = 0.840). After excluding hospitals that had case volumes less than 10 (N = 150), unadjusted ACT rates varied across hospitals (range 44% to 91%, p = 0.017). The unadjusted benchmark ACT rate was 81% (95%CI 76%-86%); utilization rate in non-benchmark hospitals was 65% (95%CI 63%-66%). When using adjusted ACT rates in a multi-level model significant variation remained across hospitals ($p < 0.001$). The adjusted benchmark ACT rate was 74% (95%CI 63%-83%); non-benchmark hospital ACT rate was 65% (95%CI 53%-75%). The simulation analysis suggested that the non-random component of ACT rate variation across hospitals was 1.5%. **Conclusions:** There is significant variation in ACT rates across hospitals in routine practice. The estimated benchmark ACT rate is 74%. However, simulation analyses suggest that most of the variation in ACT utilization across hospitals may be due to chance alone.

6592 Poster Session (Board #414), Mon, 1:15 PM-4:45 PM

Code status transitions from full code to do-not-resuscitate (DNR) among hospitalized patients with advanced cancer. *First Author: Kelsey S. Lau-Min, Massachusetts General Hospital, Boston, MA*

Background: Code status discussions ensure the delivery of preference-concordant care. However, the processes by which hospitalized patients with advanced cancer change their code status from full code to DNR are unknown. **Methods:** We conducted a mixed-methods study on a prospective cohort of patients with advanced cancer who were hospitalized from 9/14-10/15. Two physicians used a consensus-driven medical record review to characterize processes leading to code status transitions from full code to DNR. We explored factors associated with these processes using $\chi 2$ and Kruskal-Wallis tests. **Results:** We reviewed 1,047 hospitalizations among 728 patients. Admitting physicians did not address code status in 52.1% of these hospitalizations, leading code status orders to be presumed full. 273 patients (37.5%) transitioned from full code to DNR; 132 (48.4%) of them had erroneous presumed full code status orders on admission. We identified three additional processes leading to transitions from full code to DNR: acute clinical deterioration (15.4%), discontinuation of cancer-directed therapy (17.2%), and hypothetical discussions regarding the futility of CPR (15.4%). Among these processes, code status transitions due to acute clinical deterioration were associated with less patient involvement, shorter time to death, and higher likelihood of inpatient death. Changes due to hypothetical discussions were more likely to involve palliative care. **Conclusions:** Half of code status transitions among hospitalized patients with advanced cancer were due to erroneous full code orders, underscoring a greater need to discuss patient CPR preferences. Transitions due to acute clinical deterioration were associated with less patient engagement and higher likelihood of inpatient death.

	Acute clinical deterioration (N = 42)	Therapy discontinuation (N = 47)	Hypothetical discussions (N = 42)	*p*
Patient involvement %	66.7	85.1	95.2	**0.002**
Initiator of discussion %				
Inpatient team	61.9	51.1	39.0	**< 0.001**
Outpatient oncologist	33.3	35.6	14.6	
Palliative care	4.8	13.3	39.0	
Patient	0.0	0.0	7.3	
Time from code status change to death (median days, IQR)	8 (11)	22 (32)	42 (103)	**< 0.001**
Inpatient death %	47.4	14.3	28.6	**0.005**

6593 Poster Session (Board #415), Mon, 1:15 PM-4:45 PM

Physician volume and discontinuation of rituximab during lymphoma treatment. *First Author: Scott F. Huntington, Yale University, New Haven, CT*

Background: Despite the high complexity of cancer therapies, studies evaluating provider-level volume and outcomes of systemic treatments are lacking. As rituximab was the first approved monoclonal immunotherapy, and has the potential for severe infusion reactions, we hypothesize that low provider volume is associated with early rituximab discontinuation. **Methods:** We conducted a retrospective cohort study using Surveillance, Epidemiology, and End Results -Medicare data.Individuals 66+ years old with B cell non-Hodgkin lymphoma (NHL) diagnosed during 2004-2011 and 1+ rituximab claims were included. A provider was assigned to each patient-rituximab initiation using Medicare claims. We used a 12-month lookback from each initiation to categorize provider volume (0, 1-2, or 3+ rituximab initiations) in the prior year. Our primary outcome was early discontinuation, defined as receipt of 1-2 rituximab cycles within 180 days of initiation. We used a modified Poisson regression to account for provider level correlation and estimated the relative risk of early discontinuation in patients with 6+ months of follow up after rituximab initiation. A Cox proportional hazards model was used to measure the impact of discontinuation on overall survival. **Results:** A total of15,110 patients (median age: 75 years) initiated rituximab with 2,684 providers. The majority (70.4%) initiated rituximab in conjunction with chemotherapy and 1,146 (7.6%) experienced early rituximab discontinuation. Provider experience with rituximab during the previous 12 months was associated with early discontinuation in a dose-dependent manner (adjusted relative risk [aRR]: 1.57, [95% confidence interval [CI]:1.35-1.83], $p < .001$ for 0 vs 3+ initiations; aRR: 1.19 [95% CI:1.03-1.37], $p = .02$ for 1-2 vs. 3+ initiations). In addition, rituximab discontinuation was associated with a higher risk of death (adjusted hazard ratio: 1.39 [95% CI:1.28-1.52], $p < .001$). **Conclusions:** Lower physician volume is associated with increased risk of early discontinuation in older adults initiating rituximab for NHL. Due to the association between early discontinuation and mortality, physician volume may be an important factor in providing high quality NHL care.

6594 Poster Session (Board #416), Mon, 1:15 PM-4:45 PM

Patient safety: A progressive deprescribing model in patients with advanced solid tumors assisted at Instituto Oncológico Henry Moore (IOHM). *First Author: Ernesto Gil Deza, Instituto Oncológico Henry Moore, Buenos Aires, Argentina*

Background: "Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" (*Br J Clin Pharmacol* 80: 6, 1254. 2015). The aim of this paper is to present a model for deprescribing used at IOHM. **Methods:** Between 09/26/2012 and 09/26/2016, 10,053 pt filled out a Past Medical History Form, listing all the medications they were taking regularly. We selected all the pt. with advanced solid tumors (AST). In each pt the expected survival was established in order to evaluate the usefulness of the Tx. The drugs were classified in three groups: A) Green: Adequate (must be maintained); B) Yellow: Questionable (could be maintained or removed) or C) Red: Avoidable (must be removed). **Results:** We registered 2,103 pt who met the inclusion criteria. Sex F/M: 905 /1198. Median age 63 y (r = 19-99). A total of 1,629 pt. (77%) were taking medications on a regular basis. The total amount of medications was 5,679 . Median medications per patient: 3 (range: 1-14). Eighty percent of the pt (1,298 pt) were receiving questionable of avoidable medications. The following table shows the distribution of medications per group. **Conclusions:** A) In this cohort of 2,103 pt with AST, half of them had an average life expectancy of less than one year. B) 1,298 out of 1,629 pt (80%) were receiving a questionable medication C) 596/5,769 (10%) of the registered drugs, had to be suspended immediately and at least a thousand more could be eliminated. d) Obstacles to deprescribing were essentially medical ignorance, fear and inexperience.

Medication classification.

	(n = 5769)	
Green	**Yellow**	**Red**
Antihypertensives (1284)	NSAID (698)	Statins (233)*
Opioids (337)	Pump proton inh. (479)	Anti-platelets (203)*
Hypoglycemics (256)	Anti-spasmodic agents (357)	Tx. Osteoporosis (45)
Levothyroxine (182)	Benzodiazepines (331)	Anti-varicose (37)
Anticonvulsants (117)	Corticosteroids (248)	Memantine (25)
Inhalers (109)	Antibiotics (143)	Tx Alopecia (19)*
Anticoagulants (87)	Vitamins (114)	Alternative Med. (11)*
Others (170)	Others (261)	Others (23)
Total 2542 (44%)	Total 2631(46%)	Total 596 (10%)

* Presumably harmful

6595 Poster Session (Board #417), Mon, 1:15 PM-4:45 PM

Measuring cancer care experiences: Introducing SEER-CAHPS. *First Author: Maria Andrea Rincon, National Cancer Institute, Bethesda, MD*

Background: Care experience ratings are recognized as measures of healthcare quality. Here we introduce a new, public data resource, SEER-CAHPS, which links cancer registry data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program with Medicare claims and the Medicare Consumer Assessment of Healthcare Providers and Systems (MCAHPS) survey. **Methods:** The SEER-CAHPS resource includes cancer registry data from 1973-2011 (diagnosis, incidence, mortality, and sociodemographic data), Medicare CAHPS survey data from 1998-2013 (sociodemographic, health status, and care experience ratings), and Medicare fee-for-service (FFS) claims data from 2002-2013. The survey includes global ratings of overall care, personal doctor, specialist, health plan, and prescription drug plans, and composite ratings of doctor communication, care coordination, getting needed care, and getting care quickly. Data also contain survey weights to account for the Medicare CAHPS sampling design. Cross-sectional and longitudinal analyses are possible. **Results:** Currently, SEER-CAHPS includes 205,339 individuals with a history of cancer documented in SEER (FFS: 26,802 with a survey before cancer diagnosis, and 55,231 with a survey after cancer diagnosis; Medicare Advantage [MA]: 57,227 with a survey before cancer diagnosis and 71,436 with a survey after cancer diagnosis). The data resource also includes 724,965 MCAHPS respondents without cancer in SEER regions (FFS: 282,592; MA: 447,358). The data provide insights on topics including experiences of cancer patients in their last year of life; experiences of cancer survivors; and the associations of guideline-concordant follow-up care with patient experiences among cancer survivors. We will demonstrate project sample-size estimation and present instructions for submitting data access applications. **Conclusions:** SEER-CAHPS, a new, publicly available resource, provides population-based, cancer-specific data on patient experiences, health outcomes and healthcare utilization.

6596 Poster Session (Board #418), Mon, 1:15 PM-4:45 PM

Identifying determinants of quality of life in patients undergoing systemic therapy for solid tumors. *First Author: Frank Po-Yen Lin, The Kinghorn Cancer Centre, Department of Oncology, St Vincent's Hospital, Sydney, Australia*

Background: Knowing which factors compromise quality of life (QoL) in patients undergoing cancer treatments can help oncologists provide more effective care. To identify these factors, we conducted a single-centered cross-sectional study examining the relationships between patient-reported QoL, adverse events (AE), and treatment characteristics. **Methods:** Consecutive patients attending an outpatient chemotherapy unit completed two questionnaires (EORTC QLQ-C30 and National Cancer Institute PRO-CTCAE) per visit to identify factors contributing to the lowest global QoL score [QLQ-C30 QL2, range 0 (worst)–100 (best)] over a 6-week period. QL2 was correlated to each PRO-CTCAE item and treatment characteristic (tumor type, drug class, number of cycles, and treatment intent) using multiple regression, adjusted for age, sex, and use of concurrent radiotherapy. To determine whether QoL can be reliably modeled by machine learning, ten algorithms were compared for performance in classifying patients into dichotomized QL2 subgroups. **Results:** One hundred and fifteen of 130 patients (157/244 visits) completed up to 6 sets of questionnaires (median QL2: 67, IQR: 50–83). No difference was found between QL2 and treatment characteristics (at $\alpha_{Bonferroni}=5\times10^{-4}$). However, QL2 was significantly associated with AE in gastrointestinal, respiratory, attention, pain, sleep/wake, and mood categories. Using AE as covariates, support vector machine with radial basis kernel was the best at classifying patients into QoL groups (mean bootstrapped area under ROC curve 0.812, 95% CI 0.700–0.925). **Conclusions:** Patient-reported QoL is associated with multiple AE, but not with characteristics of systemic therapy. Machine learning analysis suggests that a combined AE analysis may reliably characterize a patient's QoL.

Top PRO-CTCAE items associated with detriment of QoL.

Item	QL2 decrease per PRO-CTCAE grade	99% CI
Fatigue	12.5	(6.1–19.0)
Concentration	10.8	(1.3–20.3)
Anorexia	10.1	(2.7–17.5)
Feeling discouraged	10.1	(2.1–18.1)
Pain	9.9	(4.7–15.0)
Constipation	9.4	(2.0–16.8)
Nausea	9.2	(2.4–16.0)
Abdominal pain	9.2	(2.3–16.1)
Dry mouth	8.9	(1.8–16.0)
Dyspnea	8.9	(0.8–17.0)

6597 Poster Session (Board #419), Mon, 1:15 PM-4:45 PM

Implementing cost transparency in oncology: A qualitative study of barriers, facilitators, and patient preferences. *First Author: Erin Aakhus, Leonard Davis Institute for Health Economics, Philadelphia, PA*

Background: As cancer drug prices rise and insurance plans shift toward greater cost sharing, studies link patients' high out-of-pocket (OOP) costs to non-adherence and early discontinuation of treatment. Meanwhile, few oncologists routinely discuss OOP costs with their patients. Using qualitative methods, we explored barriers and facilitators of cost transparency (i.e., disclosure of financial risks of cancer treatment). **Methods:** We performed semi-structured interviews with cancer patients (n = 22) and providers (n = 19) at an academic medical center and three affiliated community practices between August, 2015 and May, 2016. Two analysts coded the transcribed interview data using textual thematic methods, and hypotheses were generated employing grounded theory method. **Results:** We grouped themes that emerged into three major domains: 1) barriers, 2) facilitators, and 3) patient preferences. Patients and providers both expressed a strong aversion to making tradeoffs between financial and physical health outcomes. While patients feared being "profiled" based on their ability to pay, providers feared that cost transparency might threaten the doctor-patient relationship by exposing personal or institutional financial conflicts of interest. Pragmatic barriers included time constraints and difficulty in providing accurate cost estimates. Important facilitators were strong doctor-patient relationships and availability of support staff with financial expertise. We detected substantial heterogeneity in patient preferences. While some patients wanted to discuss costs with their provider, others feared "distracting" providers from their primary roles as health advocates. **Conclusions:** With implementation of OOP cost transparency, oncology practices will need to consider patient/provider aversion to financial/health tradeoffs, patients' sensitivity to socioeconomic "profiling," provider- and practice-level financial incentives, time constraints, accuracy of cost estimates, and variability in patient preferences. Meanwhile, strong provider-patient relationships and availability of support staff will facilitate OOP cost transparency.

6598 Poster Session (Board #420), Mon, 1:15 PM-4:45 PM

Examining the relationship between cost of novel oncology drugs and their clinical benefit over time. *First Author: Ronak Saluja, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: The average launch price of oncology drugs has increased by 10% annually from 1995 to 2013. The purpose of this study was to determine if the clinical benefit of novel oncology drugs has increased proportionally over time and is correlated with launch price. **Methods:** Novel oncology drugs fromrandomized controlled trials (RCTs) cited for clinical efficacy evidence in drug approvals between January 2006 and August 2015 were identified. For each drug, only the first FDA approved indication was included. To determine clinical benefit, all included RCTs were scored using the ASCO Value Framework and the ESMO Magnitude of Clinical Benefit Scale. The launch price for the FDA approval year of each drug was extracted from RedBook. Each drug's 28-day cost was determined using the dosage schedule outlined in the respective RCT and was adjusted to 2015 USD using the consumer price index. The relationships between 28-day drug cost and FDA approval year, and between incremental drug cost (difference in total drug cost between experimental and control arms accounting for treatment duration) and FDA approval year were examined using generalized linear regression models (gamma distribution and log link). Ordinary least square models were used to evaluate the relationship between ASCO/ESMO scores and FDA approval year. Spearman's correlation coefficients between 28-day/incremental drug costs and ASCO/ESMO scores were also calculated. **Results:** Forty RCTs were included in this analysis. The 28-day drug cost was significantly associated with FDA approval year ($p = 0.04$), with an average increase of 8.5% per year. Incremental drug cost was also significantly associated with FDA approval year ($p < 0.001$) with an increase of 28.6% per year. The mean ASCO and ESMO scores were 26 and 3, respectively. Both scores were not statistically associated with FDA approval year ($p = 0.73$ and $p = 0.86$, respectively) and were also not correlated with 28-day or incremental drug costs (all rho $< = 0.2$). **Conclusions:** Novel oncology drugs are not priced according to their clinical benefit. The rising cost of novel oncology drugs over time is not associated with an increase in their clinical benefit, suggesting a decrease in their value over time.

6599 Poster Session (Board #421), Mon, 1:15 PM-4:45 PM

Comprehensive genomic profiling (CGP) versus conventional molecular diagnostic testing of patients with advanced non-small cell lung cancer (NSCLC): Overall survival (OS) and cost in a U.S. health plan population. *First Author: James Signorovitch, Analysis Group, Inc., Boston, MA*

Background: Molecular diagnostic testing options in NSCLC include conventional testing (specific alterations in single genes or multi-gene panels), and CGP (all classes of genomic alterations—base pair substitutions, copy number, insertions/deletions, and rearrangements in multi-gene panels). Guidelines recommend broad molecular profiling to enable genomic matching with available compendia-based and investigational treatment options. This study estimated the incremental benefits and costs of CGP versus conventional testing of patients with advanced NSCLC. **Methods:** The impacts of increased use of CGP (via FoundationOne) versus conventional molecular testing on OS and on a commercial US health plan budget were estimated using a decision-analytic model. The number of patients needed to test with CGP to add 1 life year was also estimated. Model inputs were based on published literature (incidence rates, OS associated with drugs indicated for advanced NSCLC), real-world data (testing rates, and biopsy, conventional testing, and medical service costs from administrative claims data analyses), list price of FoundationOne, and assumptions for clinical trial participation. **Results:** Among 2 million covered lives, an estimated 532 had advanced NSCLC and 266 received molecular diagnostic testing. An increase in CGP use from 2% to 10% (+21 patients receiving CGP) was associated with +2 years in population OS and a budget impact of $0.018 per member per month (PMPM). The budget impact was primarily attributable to changes in drug use, longer treatment, and longer survival (collectively $0.013 PMPM) with the remainder due to CGP cost ($0.005 PMPM). Approximately 11 patients need to be tested with CGP versus conventional molecular diagnostic testing to add 1 life year. **Conclusions:** An increase in molecular diagnostic testing with CGP versus conventional testing to inform treatment decisions in patients with advanced NSCLC was associated with a gain in OS and a modest health plan budget impact, with most of the added costs attributable to increased use of effective treatments and prolonged survival.

6600 Poster Session (Board #422), Mon, 1:15 PM-4:45 PM

Are surrogate endpoints unbiased metrics compared to hazard ratio for death? An evaluation of clinical benefit scores (CBS) in the American Society of Clinical Oncology (ASCO) value framework. *First Author: Mahin Iqbal Qureshi, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada*

Background: Clinical benefit scores (CBS) are a key element of the American Society of Clinical Oncology (ASCO) value framework's Net Health Benefit valuation of cancer therapies. CBS are assigned based on a hierarchy of efficacy endpoints, from hazard ratio for death (HR OS), to median overall survival (mOS), HR for disease progression (HR PFS), median progression-free survival (mPFS), and response rate (RR). When HR OS is unavailable, other endpoints in the hierarchy are used as "surrogates" to calculate CBS via their scaling factors. We aim to examine whether surrogate-derived CBS offer unbiased scoring of clinical benefit compared to HR OS-derived CBS. **Methods:** CBS for advanced-disease settings were computed for randomized clinical trials (RCTs) of oncology drug approvals by the Food and Drug Administration, European Medicines Agency, and Health Canada, between 2006 and August 2015. Spearman's correlation assessed association between CBS derived from surrogates and HR OS. Mean bias (surrogate-derived CBS minus HR OS-derived CBS) evaluated the tendency for surrogate-derived CBS to over- or under- estimate clinical benefit. Mean absolute error (MAE), a measure of average deviation, assessed precision of surrogate-derived CBS in relation to HR OS-derived CBS. **Results:** Scored RCTs (n=104) yielded 69, 93, 88, and 89 paired CBS between HR OS and mOS, HR PFS, mPFS, and RR, respectively. See table for results. Restricting to RCTs reporting all endpoints (n=59) and RCTs without OS as primary endpoint (n=68) showed similar results. **Conclusions:** Findings suggest HR PFS-, mPFS-, and RR-derived CBS are poor "surrogates" as they are imprecise and weakly correlated to HR OS-derived CBS. HR PFS and particularly mPFS exhibit bias to overestimate CBS.

Analysis of surrogate-derived CBS minus HR OS-derived CBS.

	Surrogates			
	mOS	HR PFS	mPFS	RR
Correlation Coefficient (95% CI)	0.75(0.62-0.84)	0.20(-0.01-0.39)	0.07(-0.14-0.27)	0.09(-0.12-0.29)
Mean Bias	2.43	12.35	42.30	4.96
MAE	9.81	16.19	46.59	18.32
Maximum Overestimation	107	57	324	48
% Overestimation (>0 Points)	52.5	74.2	85.2	59.6
% Overestimation (>20 Points)	8.7	25.8	60.9	27.3

6601 Poster Session (Board #423), Mon, 1:15 PM-4:45 PM

Value frameworks for cancer care: Do they account for potential durable survival with immunotherapies? *First Author: Daniel A. Goldstein, Davidoff Cancer Center, Petah Tikva, Israel*

Background: Modern immuno-oncologic agents may have the potential to provide durable survival for some patients. Simultaneously, there is growing concern regarding the cost of cancer care, and multiple frameworks have been developed to assess value. The points based framework created by the American Society of Clinical Oncology (ASCO) has a specific threshold, and more points are awarded if substantial durable survival is demonstrated. The objective of this study was to assess if modern immuno-oncologic agents reach defined efficacy thresholds in this framework. **Methods:** We reviewedall FDA approvals for immuno-oncologic agents since the first approval in 2011. We collected data regarding study endpoints, specifically the parameters defined in the updated ASCO value framework: improvement in proportion of patients alive with the test regimen, and survival rate with standard. We assessed whether bonus points would be rewarded as per the updated ASCO value framework for durable responses demonstrated on the tails of the Kaplan-Meier curves. These parameters were used as an input to check whether each drug reaches the required achievement defined in the framework. **Results:** 17 indications for four immunotherapy active ingredients were approved by FDA between 2011-2016: ipilimumab, pembrolizumab, nivolumab and atezolizumab. 59% of the approvals rely on survival endpoints such as overall, progression-free, or relapse-free survival. 41% are based on objective response rates. Only one drug (nivolumab indicated for melanoma first-line treatment) was found to fulfill the threshold defined for the survival rate of standard care (above 20%). Six drugs achieved the required level of improvement in proportion of patients alive in the test regimen compared to the standard (above 50%). As there was no overlap between these two groups of drugs, no drug was found to gain the durable survival bonus points defined by the ASCO framework. **Conclusions:** Durable survival and responses of modern immuno-oncology agents are currently not recognized to be significant by the ASCO value framework. This may be due to insufficient demonstration of efficacy of such agents, or may be due to an inappropriately calibrated value framework.

6602 Poster Session (Board #424), Mon, 1:15 PM-4:45 PM

Total and out-of-pocket costs of different primary management strategies in ovarian cancer. *First Author: Rudy Sam Suidan, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Communicating healthcare costs to pts is an important component of delivering high-quality value-based care, yet cost data are lacking. This is especially relevant for epithelial ovarian cancer (OC), where no clinical consensus on optimal first-line treatment exists. Our objective was to generate cost estimates of different primary management strategies in OC. **Methods:** All women who underwent primary treatment for OC from 2006 – 2015 were identified from MarketScan, a claims database of commercially insured US pts (n = 12,761). Pts were classified based on: 1) whether they underwent primary debulking surgery followed by postoperative chemotherapy, or neoadjuvant chemotherapy followed by interval debulking; 2) type of chemotherapy regimen administered (intravenous [IV] every 3 weeks [Standard], IV every week [Dose-dense], or intraperitoneal [IP]/IV); and 3) if regimens included bevacizumab (Bev). Total and out-of-pocket (OOP) costs were calculated using all claims within 8 months from initial treatment and were normalized to 2015 US dollars. A generalized linear model was used to assess cost by strategy adjusting for clinical and demographic factors. **Results:** Mean adjusted total and OOP costs for the different treatment strategies/regimens are shown in the table. Among pts who did not receive Bev, 25% paid ≥$3964 and 10% paid ≥$5875. For pts who received Bev, 25% paid ≥$4201 and 10% paid ≥$6222. Among pts enrolled in high-deductible health plans, mean OOP costs were $4680, with 25% of pts paying ≥$6264 and 10% paying at least $9144. **Conclusions:** Costs vary across different treatment strategies and pts bear a significant OOP burden, especially those enrolled in high-deductible plans. As no consensus exists on optimal first-line management for OC, these data may help inform value-based discussions between providers and pts.

		Total Costs		OOP Costs	
	n	Adjusted Mean	p	Adjusted Mean	p
Primary Debulking	11,091	$100,483	< .001	$2791	< .001
Neoadjuvant Chemotherapy	1670	$106,614		$2362	
IV Standard Chemotherapy	9739	$98,516	< .001	$2661	< .001
IV Dose-dense Chemotherapy	1679	$107,929		$3193	
IP/IV Chemotherapy	1343	$114,166		$2707	
Regimens without Bev	11,912	$97,983	< .001	$2717	.02
Regimens with Bev	849	$160,781		$2931	

6603 Poster Session (Board #425), Mon, 1:15 PM-4:45 PM

Validity and reliability of four value frameworks for cancer drugs. *First Author: Tanya GK Bentley, Partnership for Health Analytic Research, LLC, Beverly Hills, CA*

Background: Little is known about the validity and reliability of value assessment frameworks. **Methods:** Eight panelists used the ASCO, ESMO, ICER, and NCCN frameworks to conduct value assessments of 15 drugs for advanced lung and breast cancers and castration refractory prostate cancer. Panelists received instructions and published clinical data to complete the assessments, assigning each drug a numeric or letter score. We used Kendall's *W* coefficient to measure convergent validity by cancer type among frameworks and intraclass correlation coefficients (ICC) to measure framework inter-rater reliability across cancers. Panelists were surveyed on their experiences. **Results:** Kendall's *W* for breast, lung, and prostate cancer drugs were 0.560 (p= 0.010), 0.562 (p= 0.010), and 0.920 (p< 0.001), respectively. Pairwise and subdomain *W* are shown in the table. ICC (95% CI) for ASCO, ESMO, ICER, and NCCN were 0.800 (0.660-0.913), 0.818 (0.686-0.921), 0.652 (0.466-0.834), and 0.153 (0.045-0.371), respectively. Panelists generally agreed the frameworks were logically organized and easy to use. **Conclusions:** Convergent validity among the frameworks was fair to excellent, increasing with clinical benefit subdomain concordance and simplicity of drug trial data. Inter-rater reliability, highest for ASCO and ESMO, improved with clarity of instructions and specificity of score definitions. Continued use, analyses, and refinements of the frameworks will bring us closer to using value-based treatment decisions to improve patient care and outcomes.

	High *W (p)*		Low *W (p)*	
Breast				
Pairwise	ESMO-ICER, ICER-NCCN	0.950 (0.019)	ASCO-NCCN	0.300 (0.748)
Subdomain	Certainty (ICER, NCCN)	0.908 (0.046)	Clinical benefit (ASCO, ESMO, NCCN)	0.345 (0.436)
Lung				
Pairwise	ESMO-ICER	0.974 (0.007)	ASCO-NCCN	0.218 (0.839)
Subdomain	Toxicity (ASCO, ESMO, NCCN)	0. 944 (< 0.001)	Certainty (ICER, NCCN)	0.230 (0.827)
Prostate				
Pairwise	ICER-NCCN	1.000 (<0.001)	ESMO-ICER, ESMO-NCCN	0.900 (0.052)
Subdomain	Quality of life (ASCO, ESMO)	0.986 (0.003)	Toxicity (ASCO, ESMO, NCCN)	0.200 (0.711)

6604 Poster Session (Board #426), Mon, 1:15 PM-4:45 PM

Challenges of diagnostic concordance of lung cancer cases in Qualified Clinical Data Registry (QCDR) measure collection by CMS in calculating MACRA's rewards and penalties. *First Author: Shawn Dana Glisson, Norton Healthcare's Norton Cancer Institute, Louisville, KY*

Background: QCDR was introduced for the Physician Quality Reporting System (PQRS) beginning in 2014. A QCDR is a CMS-approved entity that collects medical and/or clinical data for the purpose of patient and disease tracking to foster improvement in the quality of care provided to patients. Those who satisfactorily participate in PQRS through a QCDR may avoid the 2018 negative payment adjustment -2.0% of total Medicare payments. PQRS #396 is an example of a measurement by which oncologists may be evaluated. A physician's QCDR score is determined by his/her numerator and denominator per patient based on total data submitted by various healthcare providers. **Methods:** IRB approval was obtained for a retrospective review of 60 randomly selected NSCLC pathology reports that were diagnosed at UTMB. The Denominator was determined by CMS to be: The patients were between the ages of 18-75; the diagnosis of NSCLC was coded by the appropriate ICD and CPT codes. The Numerator was determined by CMS to be: Pathology reports with a diagnosis that included pT pN for NSCLC with histologic type vs those not documented for medical reasons vs those specimens that were not of lung origin, or were classified as NSCLC-NOS. **Results:** The study consisted of 60 NSCLC pathology reports of which 2 were determined in retrospect not to have been lung cancer cases. Another 10 were considered to be incomplete. A final 2 were diagnosed as a different histological lung cancer type. As [60 - (2+10+2)]/60 = 76.67%, adherence to the quality standard was less than perfect even though excellent medical care was delivered. This score puts the institution at risk of a 2% Medicare Payment Reduction in 2018 if a majority of other institutions score even slightly higher. **Conclusions:** Physician remuneration will be reduced by current information submitted to CMS. As the quality scores will be made public, reputations may be negatively impacted. Coding and billing operations may be hindered in their attempt to accurately submit data to CMS. Healthcare Systems may be less inclined to request outside consults (including NGS) that may provide a different diagnosis that could confuse the QCDR.

6605 Poster Session (Board #427), Mon, 1:15 PM-4:45 PM

Estimated cost of anticancer therapy directed by comprehensive genomic profiling (CGP) in a single-center study. *First Author: James Signorovitch, Analysis Group, Inc., Boston, MA*

Background: Accumulating evidence supports the clinical benefit of targeted therapies matched to cancer patients based on genomic alterations. CGP, which detects all classes of alterations (base pair substitutions, copy number, insertions/deletions, and rearrangements), can match more patients with available and investigational therapies. This study estimated anticancer drug costs and overall survival (OS) for matched vs. unmatched therapy. **Methods:** Costs were estimated for patients with complete data (N = 188/500) from a prospective, nonrandomized, phase I oncology center study of patients with diverse refractory cancers who underwent CGP and were treated with matched or unmatched therapy (PMID: 27197177). Average time to treatment failure and average OS were assessed during the observation period. Patient-specific drug and administration costs were imputed for the first regimen after CGP based on drug classes, unit costs, and times to treatment failure. **Results:** Patients onmatched (N = 122) vs. unmatched (N = 66) therapy had, on average, longer time on treatment (+1.5 mos), longer observed survival (+2.4 mos), and higher anti-cancer drug costs (+$38K) (all $p < 0.01$); 66% of increased drug costs were attributable to longer time on treatment as opposed to higher monthly drug costs. Combination therapy was used for 71% of matched and 53% of unmatched patients. Those undergoing CGP in earlier-line (1-3; N = 58) vs. later-line (4+; N = 130) therapy had numerically larger incremental increases in average times on treatment (+1.9 vs. +1.2 mos) and survival (+2.5 vs. +2.1 mos), and numerically lower incremental drug costs (+$27K vs. +$43K), with matched vs. unmatched therapy. **Conclusions:** For patients cared for in a phase I clinic, matched vs. unmatched therapy was associated with longer treatment durations, longer survival times, and manageable incremental costs. Despite frequent use of combination therapy, most of the increased costs of matched therapy were due to longer treatment times rather than higher monthly drug costs. Benefits of matching were numerically greater in earlier- vs. later-lines, consistent with the value of earlier-line use of CGP to guide treatment.

6606 Poster Session (Board #428), Mon, 1:15 PM-4:45 PM

Can we satisfactorily measure the clinical value of new oncology agents with a single summary measure? *First Author: Clare Frances Jones, PRMA Consulting Ltd, Fleet, Hampshire, United Kingdom*

Background: Current value frameworks (VFs) assess clinical value primarily through using clinical trial endpoints as survival metrics (e.g., median and hazard ratio (HR)). But, if key assumptions do not hold, the interpretation of these summary statistics can become problematic and fail to adequately capture the expected benefit to a patient. This has been observed with innovative oncology treatments. As a proof of concept analysis, we reviewed how two VFs (ASCO and ESMO) dealt with cases where the assumption of proportional hazards (PH) does not hold. **Methods:** Oncology agents approved by the FDA since 2011 were reviewed and three agents were identified with survival profiles where the assumption of PH was found not to hold because, on visual inspection, the survival curves displayed non-standard patterns: Divergence followed by convergence – panobinostat OS in RRMM; Curves initially track together then diverge – nivolumab OS in NSCLC; Curves diverge steadily then a plateau emerged in the active treatment curve – pembrolizumab PFS in refractory melanoma. We evaluated these agents to assess which measures of clinical benefit were most valued under each VF and how the issue of non-PH influenced the outcome. **Results:** Clinical benefit/value scores varied: ASCO: 14-27 (maximum 100), ESMO: grade 1-3. The ASCO VF uses a hierarchical approach (incorporating HR and median survival benefit, always prioritising the former) adding a bonus for survival benefit in the tail of the distribution. The combination of HR, median survival benefit 2 and 3 year survival rates in the ESMO non-curative VF can potentially capture aspects of clinical benefit in some cases of non-PH. Overall, the ASCO VF appears less flexible to accommodate non-PH than the ESMO VF. **Conclusions:** Despite VFs using summary statistics which cannot be easily interpreted under conditions of non-PH, the case of non-PH is not explicitly catered for. Additionally, both VFs may miss important interpretation where value is differentiated across patients groups with different response profiles which may underlie non-standard survival curves. In these situations, a more flexible approach to assessing clinical value may render VFs more relevant for clinical decision making.

6607 Poster Session (Board #429), Mon, 1:15 PM-4:45 PM

Impact of intravenous cancer drug wastage on economic evaluations. *First Author: Judy Truong, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Intravenous drugs administered through body-surface area (BSA) or weight-based dosing may cause wastage due to large and/or limited fixed vial sizes, and vial sharing restrictions. Drug wastage leads to incremental costs without incremental value to patients. Bach et al. (2016) estimated 10% of revenue ($1.8 billion) from cancer drugs would result from wastage in 2016. The pan-Canadian Oncology Drug Review (pCODR) committee provides recommendations on which drugs to publicly reimburse by reviewing clinical and economic evidence. There is considerable potential that drug wastage could impact the economic evaluations. We sought to determine the impact of modeling cancer drug wastage on the results of economic evaluations. **Methods:** Economic evaluations submitted by drug manufacturers and reviewed by the pCODR Economic Guidance Panel (EGP) were assessed for frequency of wastage reporting and modeling. Cost-effectiveness analyses and budget impact analyses were conducted for scenarios in which "no wastage" and "wastage" of drugs occurred. Sensitivity analyses were performed to determine the effects of BSA and weight variation. **Results:** 12 drugs for use in 17 indications were analyzed. Wastage was reported in 71% and incorporated in 53% of manufacturer's models, resulting in a mean incremental cost-effectiveness ratio (ICER) increase of 6.1% (range: 1.3% to 14.6%). EGP reported and incorporated wastage for 59% of models, resulting in a mean ICER increase of 15.0% (2.6% to 48.2%). When maximum wastage (i.e. the entire unused portion of each vial is discarded) was incorporated in our independent analysis, the mean ICER increased by 24.0% (0.0% to 97.2%) and the mean 3-year total incremental costs increased by 26.0% (0.0% to 83.1%). Over a 3-year period, wastage can increase the total incremental drug budget cost by CAD $102 million nationally. Changing the mean BSA or body weight caused 45% of the drugs to use a different vial size (if available) and/or quantity, resulting in further increased drug costs. **Conclusions:** Wastage can have an under-recognized and significant impact on economic evaluations of intravenous chemotherapy drugs. Guidelines are needed to promote uniform and optimal modeling of drug wastage in economic evaluations.

6608 Poster Session (Board #430), Mon, 1:15 PM-4:45 PM

Cost-effectiveness of ovarian cancer screening: An analysis of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) from a U.S. health system perspective. *First Author: Haley Moss, Duke University Medical Center, Durham, NC*

Background: UKCTOCS is the largest randomized controlled trial to evaluate screening's impact on ovarian cancer mortality, assigning women to multimodal screening (MMS) with serum CA125 interpreted with a risk algorithm; annual transvaginal ultrasound; or no screening (NS). There was a non-statistically significant 15% reduction in mortality over 11 years in MMS group. As most of the potential benefit of screening was seen after 7 years, follow-up is ongoing to determine if an observed stage shift translates into significant mortality reduction. The current study estimates the cost-effectiveness of an MMS screening program in the US. **Methods:** A modified Markov model was constructed using data from UKCTOCS to compare MMS to NS. Published estimates of the long term effect of MMS screening on ovarian cancer mortality were used to simulate mortality over 40 years from the start of screening. Base case costs included CA125, ultrasounds, clinical evaluations and false-positive surgeries, with an annual weighted cost of $35 in addition to an estimated risk algorithm cost of $100. The utility and costs of ovarian cancer treatment were incorporated into the model. Incremental cost-effectiveness ratios (ICERs) were calculated in 2016 U.S. dollars per quality-adjusted year of life saved (QALY). Additional sensitivity analyses were performed. **Results:** MMS is both more expensive and more effective in reducing ovarian cancer mortality over a lifetime than NS. Screening women from age 50 to 75 with MMS reduced mortality by 24% with an ICER of $98,062/QALY. If screening begins at age 60, MMS reduces mortality by 12%, with ICER below the willingness to pay threshold of $100,000/QALY only if the algorithm costs $< $50. In probabilistic sensitivity analyses, the probability that screening from age 50-75 at an algorithm cost of $100 was less than $100,000/QALY was 41%. **Conclusions:** Ovarian cancer screening is potentially cost-effective in the US depending on final significance of mortality reduction and cost of the CA-125 risk algorithm. These results are limited by uncertainty around the effect of screening on ovarian cancer mortality beyond the 11 years of UKCTOCS.

6609 Poster Session (Board #431), Mon, 1:15 PM-4:45 PM

Delivery of meaningful cancer care: Evaluating benefit and cost of cancer therapies using ASCO and ESMO frameworks. *First Author: Joseph Del Paggio, Department of Medicine, University of Toronto, Toronto, ON, Canada*

Background: ASCO and ESMO have developed frameworks to evaluate the benefit of cancer therapies. Here, we apply the frameworks to a cohort of contemporary randomized controlled trials (RCTs) to explore agreement and to evaluate the relationship between treatment benefit and cost. **Methods:** Characteristic and outcome data from RCTs evaluating systemic therapies in non-small cell lung cancer (NSCLC), breast cancer, colorectal cancer (CRC), and pancreatic cancer published and cited in *PubMed* between 2011-2015 were abstracted. Trial endpoints were evaluated using ASCO and ESMO frameworks. Cohen's kappa statistic was calculated to determine agreement between the two frameworks, using the median ASCO score as a benefit threshold. Differences in monthly drug cost between RCT experimental and control arms were derived from 2016 average wholesale prices. Analyses included Pearson chi-square tests, Fisher's Exact tests, independent samples t-tests, and Pearson correlation to assess the association between continuous variables. **Results:** Fifty percent (136/271) of published RCTs favoured the experimental arm; scoring rubrics were applicable to 109 RCTs (39% NSCLC, 33% breast, 23% CRC, 5% pancreas). ASCO scores ranged from 2 to 72; median score was 25. Thirty seven percent (40/109) of RCTs met benefit thresholds using the ESMO framework. Agreement between frameworks was fair at best ($\kappa = 0.28$, $p = 0.002$). When stratified by treatment intent (19 curative, 90 palliative RCTs), agreement remained poor ($\kappa = 0.23$, $p = 0.115$; $\kappa = 0.34$, $p < 0.001$). Major differences leading to limited agreement includes the relative weights each framework places on HR, endpoints, and toxicity/QOL analysis. Smaller RCT sample size was the only trial characteristic associated with higher ASCO scores ($p = 0.015$). Among the 100 RCTs for whom drug costing data were available, there was no association between ASCO benefit score and monthly drug costs ($r = -0.12$, $p = 0.22$); those meeting ESMO thresholds had a lower mean drug cost than those who did not ($p = 0.046$). **Conclusions:** There is only fair correlation between ASCO and ESMO clinical benefit frameworks. Drug costs are not associated with ESMO/ASCO measures of magnitude of clinical benefit.

6610 Poster Session (Board #432), Mon, 1:15 PM-4:45 PM

Cost of surveillance imaging in head and neck cancer patients treated with definitive radiotherapy. *First Author: Sweet Ping Ng, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The goal of surveillance is to detect potentially salvageable recurrence, allowing early salvage treatment and thereby improving clinical outcomes. Currently, there is limited data on the optimal frequency of imaging for head and neck cancer patients treated with definitive radiotherapy. This study aims to evaluate the cost-effectiveness of surveillance imaging in this group of patients. **Methods:** Eligible patients included those with a demonstrable disease free interval ($\geq$ 1 follow up scan without evidence of disease and a subsequent visit/scan) treated between 2000-2010. Age, tumor site and stage, induction chemotherapy use, dose/ fractionation, mode of detection of recurrence, salvage therapy, number and modality of scans were recorded. Deaths from disease recurrence or from other causes were also recorded. Imaging costs were calculated based on the 2016 Medicare fee schedule. **Results:** 1508 patients were included. Mean age was 55.8 years (range: 17-87). Median overall survival was 99 months (range: 6-199). Mean imaging follow up period was 70 months. 190 (12.6%) patients had disease recurrence – 107 locoregional (LR) and 83 distant. 119 (62.6%) of the relapsed group were symptomatic and/or had an adverse clinical finding associated with recurrence. 80.4% of LR relapses presented with a clinical finding, while 60.2% of distant relapses were detected via imaging alone in asymptomatic patients. There was no difference between the successful salvage rates and overall survival between those with relapses detected clinically or via imaging alone. 70% of relapses occurred within the first 2 years post-treatment. In those who relapsed after 2 years, the median time to relapse was 51 months (2 LR and 11 distant relapses). After 2 years, the average cost for detecting a salvageable recurrence for image-detected group was $741 447.41, and the cost for preventing 1 recurrence-related death for image-detected disease was $889 736.89. The number of scans required to detect a salvageable recurrence in an asymptomatic patient after 2 years was 3512. **Conclusions:** Surveillance imaging in asymptomatic patients without clinically suspicious findings beyond 2 years requires judicious consideration.

6611 Poster Session (Board #433), Mon, 1:15 PM-4:45 PM

Differences in medical care costs for recurrent versus de novo stage IV cancer by age at diagnosis. *First Author: Matthew P. Banegas, Kaiser Permanente Center for Health Research, Portland, OR*

Background: To address the paucity of data on costs of cancer recurrence, this study estimated medical care costs of patients diagnosed with recurrent breast, colorectal or lung cancer, and compared costs to patients diagnosed with de novo stage IV disease. **Methods:** Data from patients enrolled in three health plans who were diagnosed with de novo stage IV or recurrent breast ($n_{stage\ IV} = 352$; $n_{recurrent} = 765$), colorectal ($n_{stage\ IV} = 1072$ and $n_{recurrent} = 542$) and lung ($n_{stage\ IV} = 4042$ and $n_{recurrent} = 339$) cancers between 2000-2012 were used to estimate total medical care costs in the 12 months preceding (pre-index), month of index, and 12 months following (post-index) diagnosis/recurrence date. Cancer patients were identified using tumor registry data. Recurrent cancers were validated by medical record abstraction and the RECUR algorithms –innovative tools to detect recurrence using claims and electronic health record data. We used generalized linear repeated measures regression models controlling for demographic and comorbidity variables to estimate costs (2012 US$), stratified by age at diagnosis (ages $<$ 65, $\geq$65). **Results:** Medical care cost differences in the pre-index period indicate higher costs for recurrent cancer patients than for stage IV breast (Age $<$ 65:+$2550; Age $\geq$65: +$1254), colorectal (Age $<$ 65:+$3295; Age $\geq$65: +$1653), and lung cancer patients (Age $<$ 65: +$3232; Age $\geq$65: +$2340). Conversely, in the index and post-index periods, costs for stage IV cancers were higher than recurrent cancer costs. Specifically, post-index period cost differences indicate higher costs for stage IV patients than for recurrent breast (Age $<$ 65:+$683; Age $\geq$65: +$1172), colorectal (Age $<$ 65:+$3104; Age $\geq$65: +$1557), and lung cancer patients (Age $<$ 65:+$1136; Age $\geq$65: +$1103). **Conclusions:** Our study provides medical care cost estimates of recurrent and de novo stage IV cancers. Cost differences between recurrent and stage IV cancers reveal heterogeneity in care patterns that merits further investigation. The reported study costs, measured in capitated care systems using standardized fee-for-service reimbursement coefficients, may serve as a benchmark for stage-specific phase-of-care oncology episode payment models.

6612 Poster Session (Board #434), Mon, 1:15 PM-4:45 PM

Economic impact of immune checkpoint inhibitor therapy in Brazil and strategies to improve access. *First Author: Pedro Nazareth Aguiar, Federal University of São Paulo (UNIFESP), São Paulo, Brazil*

Background: Immunotherapy was elected by ASCO as the most important advance in Oncology for the last 2 consecutive years. Nevertheless, the costs of immune checkpoint inhibitors is a limitation to their incorporation in several countries, including Brazil. The objective of this study is to estimate the economic impact of immunotherapy and make suggestions in order to improve the access for patients who benefit the most from treatment. **Methods:** We assessed Brazilian cancer epidemiology data and the international literature to estimate the number of eligible patients each year. The authors estimated the economic impact according to the medication acquisition costs converted to US dollars. The median duration of the treatment was based upon the clinical trials. **Results:** We assessed 3 different agents (and one combo) for 7 indications. The results are summarized in the table below. **Conclusions:** The current cost of immune checkpoint inhibitors is prohibitive in the public health system in Brazil. While the country's GDP per capita is 78% lower than that of the US, immune checkpoint inhibitors have similar prices in both. Biomarker selection, posology, and lower cost drugs help decrease the total economic impact of therapy. Price discrimination and volume discounts would help improve access. Further studies and discussion with all stakeholders is needed to identify patients who would benefit the most and to implement strategies to increase access to these potentially life-saving therapies.

Drug	Melanoma 1L	NSCLC 1L	NSCLC 2L	Kidney 2L	Bladder 2L	H&N 2L	Gastric 2L	TOTAL	Number of Eligible Patients (% of all cancer patients)	Increase in Cancer Drug Total Expenditure Cost in the Public Health System	Additional Cost Per Citizen
Ipi+ Nivo	45.5 mi	NA	NA	NA	NA	NA	NA	45.5 mi -10%: 40.9 -20%: 36.3	311 (0.1)	+5.7% +5.1% +4.5%	0.2 0.2 0.2
Nivo	17.6 mi	NA	173.0 mi All Comers	35.9 mi	10.0 mi	115.0 mi	31.0 mi	382.5 mi -10%: 340.6 -20%: 298.7	13,455 (3.4)	+48% +43% +37%	1.9 1.7 1.5
Pembro	12.7 mi	354.0 mi PD-L1>50%	100.0 mi PD-L1>1%	16.5 mi	7.2 mi	89.2 mi	22.6 mi	602.3 mi -10%: 532.3 -20%: 462.3	25,084 (6.4)	+75% +67% +58%	3.0 2.7 2.3
Atezo	NA	NA	255.6 mi All Comers	59.5 mi	16.8 mi	178.7 mi	51.6 mi	562.2 mi -10%: 502.4 -20%: 442.6	13,144 (3.3)	+70% +63% +55%	2.8 2.5 2.2

6613 Poster Session (Board #435), Mon, 1:15 PM-4:45 PM

Barriers to MACRA among a cohort of community oncologists. *First Author: Chadi Nabhan, Cardinal Health, Dublin, OH*

Background: Value Based Care (VBC) initiatives specifically the Medicare and CHIP Reauthorization Act (MACRA), which includes Medicare Incentive Payment System (MIPS) and Alternative Payment Models (APMs), present challenges for community oncologists. Understanding barriers associated with implementation and compliance are essential for optimal execution. **Methods:** Using audience response technology, 52 community oncologists and 26 practice managers (PMs) of diverse geography, practice type and affiliations were surveyed in November 2016. **Results:** Of the attendees, 43% were participating in commercial payer VBC while 33% were participating in the Oncology Care Model (OCM), an APM. Reasons for non-participation: Cost of drugs 58%; data transparency 42%; human resources 33%; technology 29%. The majority of attendees stated limited awareness of MACRA reporting requirements. Once reporting was explained, the stated challenges to MACRA implementation included: inability to measure and track costs 76%; problematic quality improvement activities 56%; lack of patient engagement tools 52%; concern about interpreting CMS reports 52%; meeting meaningful use requirements 33%. In regard to preparation: 52% had survivorship or palliative care plans, 39% made infrastructure investments, and 23% were utilizing clinical pathways. Although 54% stated use of data analytics to maximize efficiency and profitability, half of these were not satisfied with ease of data extraction or output. One third opined that patient satisfaction was irrelevant to quality of care. In the end, nearly half stated reporting requirements could be managed; but 98% stated they were unwilling to assume downside financial risks for hospital and emergency room visits. **Conclusions:** Identifying and eliminating barriers to MACRA (MIPS/APMs) implementation may be critical to program success. The main reasons for OCM non-participation were costs of drugs and data transparency. There is significant dissatisfaction with available reporting and data extraction tools. Willingness to assume 2-sided risk for total cost of care was identified as the greatest risk to APM adoption.

6614 Poster Session (Board #436), Mon, 1:15 PM-4:45 PM

Trends in aggressive care at the end-of-life for stage IV lung cancer patients. *First Author: Chebli Mrad, Department of Medicine, Mount Sinai St. Luke's and Mount Sinai West Hospitals, Icahn School of Medicine, New York, NY*

Background: Prior studies have demonstrated that high-intensity end-of-life care improves neither survival nor quality of life for cancer patients. The National Quality Forum endorses dying from cancer in an acute care setting, ICU admission in the last 30 days of life, and chemotherapy in the last 14 days of life as markers of poor quality care. **Methods:** Discharge data from the National Inpatient Sample database was analyzed for 3,030,866 acute care hospitalizations of metastatic lung cancer patients between 1998 and 2014. Longitudinal analysis was conducted to determine trends in aggressive care at the end-of-life and multivariate logistic regression was performed to determine associations with age, race, region, hospital characteristics, and aggressive care. **Results:** In-hospital mortality for metastatic lung cancer patients decreased from 17% to 11%. Among terminal hospitalizations, utilization of radiation therapy and chemotherapy decreased from 4.6% to 3.0% and from 4.8% to 3.0%, respectively. However, the proportion admitted to the ICU increased from 13.3% to 27.9% and invasive procedures increased from 1.2% to 2.0%. Reflecting this aggressive end-of-life care, mean total charges for a terminal hospitalization rose from $29,386 to $72,469, adjusted for inflation. Among patients who died in the inpatient setting, the ICU stay translated into higher total costs (+$16,962, CI: $15,859 to $18,064) compared to patients who avoided the ICU. Promisingly, palliative care encounters for terminal hospitalizations increased during this period from 8.7% to 53.0% and was correlated with a decrease in inpatient chemotherapy (OR = 0.56, CI: 0.47 to 0.68), radiotherapy (OR = 0.77, CI: 0.65 to 0.92), and ICU admissions (OR = 0.48, CI: 0.45 to 0.53) but had only a modest impact on terminal hospitalization cost (-$2,992, CI: -$3,710 to -$2,275). Multivariable analysis showed variation by patient and hospital characteristics in aggressive care utilization. **Conclusions:** Among patients with metastatic lung cancer there has been a substantial increase in ICU use during terminal hospitalizations, resulting in high cost for the health care system. Inpatient palliative care has the potential to reduce aggressive end-of-life interventions.

6615 Poster Session (Board #437), Mon, 1:15 PM-4:45 PM

Validation of a financial toxicity (FT) grading system. *First Author: Jonas A. De Souza, The University of Chicago Medicine, Chicago, IL*

Background: FT is an important adverse event (AE) that should be objectively measured in clinical practice. We previously developed an evidence-based FT grading system based on differences in HRQoL, analogous to the NCI-Common Terminology Criteria for Adverse Events (grade 1, mild AE; grade 2, moderate AE; grade 3, severe AE ,de Souza et al - ASCO 2015). We aimed to validate this grading system using a new sample of cancer patients (pts) and report its association with bankruptcy. **Methods:** FT was assessed by the COST (COmprehensive Score for financial Toxicity) in 2 sets of cancer pts. In the previously reported Development Set (DS), gradations of FT were determined by ROC analyses based on conventions for clinically meaningful small (0.2), medium (0.5) and large (0.8) effect sizes (e.s.) for independent FACT-G differences attributable to FT in pts with Stage IV cancers on chemotherapy. In the Validation Set (VS), differences in HRQoL and the odds ratio for a pt to have declared bankruptcy after the cancer diagnosis were assessed in a larger cohort of cancer pts on chemotherapy. **Results:** The grading system was developed in 888 cancer pts with cancer (233 pts in the DS and 655 in the VS). In the DS, ROC analyses produced 4 FT grades (G): G0, no FT, COST $\geq$26 (99 pts, 42%); G1, mild FT: $\geq$ 14-26 (71 pts, 31%); G2, moderate FT: $>$ 0-14 (58 pts, 25%); and G3, severe FT: COST = 0 (5 pts, 2%). Applying the FT grading to the 655 pts in VS, we had: G0, 146 pts (22%); G1, 281 (43%); G2, 215 (33%); and G3, 13 (2%). The decreases in FACT-G HRQoL measured in e.s. per FT grading in comparison with G0 were small for G1: -0.4 (95%CI: -0.6 – -0.25); large for G2: -0.9 (95%CI: -1.1 – -0.7); and even larger for G3: -1.5 (95%CI: -2.0 – -0.9), all with $p <$ 0.001. In the VS, 23 pts (4%) had declared bankruptcy after their cancer diagnosis. Compared to FT G0, the odds of having declared bankruptcy were 8.6 (95%CI: 1.1 – 67, p = 0.04) times higher for pts with FT G2, and 29 times higher (95% CI: 2.4 – 355, p = 0.008) for those with G3 FT. **Conclusions:** We developed a FT grading system anchored on independent differences in HRQoL. We applied the system in a different set of cancer pts and it retained its validity. We also found an larger incidence of bankruptcy after the cancer diagnosis in higher grades of FT, adding to the grading's meaningful use.

6616 Poster Session (Board #438), Mon, 1:15 PM-4:45 PM

Bias in valuation of health care benefits in metastatic prostate cancer: A contingent valuation of willingness to pay. *First Author: Nuno Sousa, Instituto Português de Oncologia de Lisboa, Senhora Da Hora, Portugal*

Background: Willingness to pay (WTP) studies assess societal valuation of healthcare interventions. Prostate cancer (PC) is the most common cancer diagnosis in men. We explore factors that may bias valuation of health care benefits through contingent valuation of WTP for therapeutic innovation in metastatic castration-resistant PC. **Methods:** Cross-sectional study of Portuguese Society (SOC) and Healthcare Providers (HCP). Monthly WTP assessed through biding and open-ended questions by standardized survey with 2 baseline scenarios: ScA 12-month median survival, ScB 30-month median survival. Respondents considered own financial resources and expenses and for each therapeutic scenario reported WTP, out-of-pocket, and expected National Healthcare System (NHCS) WTP. Impact of demographic, personal medical history and household income assessed by tweedie generalized linear model. **Results:** 1000 subjects on societal cohort and 100 physicians provided valid responses. Subjects reported higher WTP values when NHCS was to provide treatment compared to out-of-pocket cost. For NHCS perspective median WTP for ScA was 2,133€ for HCP vs 5,510€ for SOC and ScB 1 963€ for HCP vs 5,479€ for SOC. Overall, societal cohort's NHCS mean WTP was 2.6 (ScA) and 2.8 (ScB) times higher ($p < .001$) than healthcare providers, but with no difference for out-of-pocket WTP. This difference remained significant when adjusted for all other factors. Additionally, subjects with prior personal or familial history of cancer and subjects with higher household income provided higher WTP estimates. In HCP cohort, urologists reported higher WTP compared to Medical Oncologists. **Conclusions:** This study provides critical insight into differing valuation of cancer treatments between physicians and society and potential biases in individual valuation of healthcare benefits. Improvement of societal's perception and understanding of cost-benefit assessments is critical to designing an equitable healthcare system.

6617 Poster Session (Board #439), Mon, 1:15 PM-4:45 PM

Financial impact of flat dosed (FD) monoclonal antibodies (MABs) at a single institution in 2016. *First Author: Michael P. Kane, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Immuno-oncology (I/O) agents represent an important, accelerated breakthrough in cancer therapy. Like other MABs, these agents have been adjusted after FDA approval to have a flat-dose. Purportedly, flat dosing simplifies prescribing, dispensing, inventory and billing. Nivolumab (N) and Pembrolizumab (P) achieved FDA approval in several malignancies. Original studies determined the dosing of N @ 3 mg/kg q2-weeks and P @ 2 mg/kg q3-weeks. Based on simulations from population pharmacokinetics models, the FDA approved a FD of N 240 mg in melanoma, RCC and NSCLC. The financial impact of this FD methodology in our patient population was compared with weight based dosing (3mg/kg) of N with a cap of 240 mg versus flat dosing. The potential impact of this change was also evaluated for P, including if a 50 mg vial of P was still available. **Methods:** Applicable dispensed doses (N & P) and patients' weights for 2016 were mined from the electronic health record. Wholesale Acquisition Costs at end of year were used for financial comparison. **Results:** see table. **Conclusions:** Weight based dosing with a cap (N 240mg; P 200mg) versus flat dosing would have saved $198,567 and $80,037, respectively. Additionally, $760,351 would have been saved if 50 mg vials of P were available. With the current drug pricing structure, wide-scale adoption of flat dosing for I/O mABs may result in higher drug costs. Labeling I/O mABs with both weight-based and FD options and ensuring the availability of proper vial sizes, particularly multi-dose vials, to fit the population and dosing schema would restrain the costs of care.

N: 54 patients, 510 doses; (Mean 77.3kg, SD 16.15, (44.90-127.89kg)); 33 patients less than 80kg (302 doses).

2016 WAC of N	All weight based doses (3 mg/kg)	Flat Dose (240 mg)	Weight Based 3 mg/kg Capped at 240 mg
Cost	$3,147,460.20	$3,069,225.90	$2,870,628.51

P: 103 patients, 605 doses; (Mean 80.14kg, SD 19.89, (39.46-164.17kg)); 89 patient less than 100kg (528 doses).

2016 WAC of P	All weight based doses (2 mg/kg)	Weight Based If 50 mg vials were available	Flat Dose (200 mg)	Weight Based 2 mg/kg Capped at 200 mg	Weight Based Capped at 200 mg If 50 mg Vials Were Available
Cost	$5,615,929.50	$4,811,113.00	$5,380,265.00	$5,300,228.00	$4,619,913.50

6618 Poster Session (Board #440), Mon, 1:15 PM-4:45 PM

Spending on antineoplastic agents in the United States: 2011-2016. *First Author: Edward C. Li, University of New England College of Pharmacy, Portland, ME*

Background: Novel antineoplastic therapies confer advantages in efficacy and safety over traditional cytotoxic agents, but they are costly. There is little information on recent trends in actual antineoplastic expenditures representative of the overall U.S. health care system or by healthcare sector. The objective of this study was to describe antineoplastic expenditures by year and healthcare sector in the U.S. **Methods:** Quintiles IMS National Sales Perspective data for the period of Jan 1, 2011, to Dec 31, 2016, were evaluated to describe antineoplastic agent expenditures. Actual expenditures were totaled by health care sector and calendar year, and then adjusted for U.S. medical-cost inflation (part of the overall consumer price index) to 2016 dollars. Growth was calculated as the percentage increase from previous years. Descriptive statistical analysis was used. **Results:** Total antineoplastic expenditures increased from $26.8 billion in 2011 to $38.9 billion in 2016. Compared to the previous year, spending increased by 13.7%, 15.6%, 13.4%, 6.3%, and 0.4% in 2016, 2015, 2014, 2013, and 2012, respectively. In hospitals and clinics, spending on biologics grew by 80% from 2011 to 2016. Rituximab, bevacizumab, and trastuzumab expenditures continue to be high ($3.7, $3.0, and $2.6 billion in 2016, respectively) while nivolumab spending increased from $765 million in 2015 to $2.6 billion in 2016. Cytotoxic drug spending remained flat during the study period due to the availability of multiple generic products. Large percentage decreases in spending were seen for oxaliplatin (-97%), docetaxel (-98%), gemcitabine (-92%), bendamustine (-56%) and decitabine (-94%) in 2016 compared to 2011. **Conclusions:** Antineoplastic expenditures increased significantly since 2011 and are expected to continue to do so with the anticipated approval of additional novel but costly cancer therapies, and because of an aging population.

Top 5 antineoplastic expenditures by year (USD – in millions).

	2011	2012	2013	2014	2015	2016
Rituximab	$3,252	$3,372	$3,452	$3,519	$3,599	$3,737
Bevacizumab	$2,939	$2,829	$2,840	$2,948	$3,114	$2,965
Nivolumab				$0.85	$765	$2,586
Trastuzumab	$1,842	$1,999	$2,056	$2,256	$2,524	$2,586
Pertuzumab		$61	$244	$617	$854	$932

6619 Poster Session (Board #441), Mon, 1:15 PM-4:45 PM

Cost-effectiveness analysis of first-line treatments for early-stage, low-grade follicular lymphoma. *First Author: Joanna C. Yang, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Low-grade follicular lymphoma (FL) can present as localized stage I to II disease in up to one-third of patients. Upfront involved-site radiation therapy (RT) to 24-30Gy is the preferred first-line management strategy for these patients. However, the National LymphoCare Study found that less than one quarter of patients with early-stage, low-grade FL received upfront RT, while more than half received either chemoimmunotherapy or observation. **Methods:** We performed a cost-effectiveness analysis using a Markov state-transition model to simulate the progression of early-stage, low-grade FL in a cohort of 60-year-old men. The following first-line treatments were compared: RT, observation, rituximab induction (RI), rituximab and bendamustine (BR), and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP). Patients who relapsed received second-line therapies that were dependent on their first-line treatment: RT for RI and observation, RCHOP for RT and BR, and BR for RCHOP. Disease-progression probabilities and other model inputs were from published trials. **Results:** First-line RT followed by RCHOP for relapses had a quality-adjusted life expectancy (QALE) of 11.4 years, superior to first-line observation, RI, BR, and RCHOP strategies. First-line RT strongly dominated observation, BR, and RCHOP. Compared with RI, first-line RT resulted in an incremental cost-effectiveness ratio of $2,740 per quality-adjusted life year. The probability of dying from other causes, the probability of a complete response to RT, and the probability of relapse had the greatest impact on both cost and effectiveness expected values. **Conclusions:** In contrast to current practice patterns, first-line RT is the most effective upfront treatment for patients with early-stage, low-grade FL. Further, first-line RT paired with RCHOP for relapses is a cost-effective treatment paradigm, relative to other strategies.

First-Line Treatment	Second-Line Treatment	Cost (2016 USD)	Effectiveness (Years)	Incremental Cost-Effectiveness Ratio
RI	RT	$585,430	7.3	
RT	RCHOP	$596,656	11.4	$2,740
Observation	RT	$750,548	5.3	Dominated
BR	RCHOP	$1,956,411	7.0	Dominated
RCHOP	BR	$2,017,066	8.6	Dominated

6620 Poster Session (Board #442), Mon, 1:15 PM-4:45 PM

Algorithmic matching of genomic profiles to precision cancer medicine clinical trials at DFCI. *First Author: James Lindsay, Dana-Farber Cancer Institute, Boston, MA*

Background: Genomic profiling and access to precision medicine clinical trials are now standard at leading cancer institutes and many community practices. Interpreting patient-specific genomic information and tracking the complex criteria for precision medicine trials requires specialized computational tools, especially for multi-institutional basket studies such as NCI-MATCH and TAPUR. **Methods:** To address this challenge we have developed an open source computational platform for patient-specific clinical trial matching at Dana-Farber Cancer Institute (DFCI) called MatchMiner, which aides in both patient recruitment to precision medicine trials, as well as decision support for oncologists. Trial matches are computed based on genomic criteria, including mutations, CNAs, and SVs, as well as clinical and demographic information, including cancer type, age, and gender. A formal standard called clinical trial markup language (CTML) to encode complex clinical trial eligibility criteria has also been created. **Results:** MatchMiner is now available at DFCI. Currently 123 precision medicine clinical trials have been transformed into CTML and 13,000 patient records are available, with over 88% of current patients having at least 1 match (average 2.6). A total of 103 genes are specified as criteria for at least 1 trial. KRAS, TP53, PTEN, PIK3CA and BRAF are the genes driving the most number of matches. General usage statistics and trial enrollment rates are currently being monitored to determine the system effectiveness. As this is an open source initiative, the software is also now publically available at https://github.com/dfci/matchminer. **Conclusions:** We have developed an open source computational platform that enables patient-specific matching and recruitment to precision medicine clinical trials at DFCI. We are actively seeking collaborators and plan to make CTML a multi-institution standard for encoding complex clinical trial eligibility in a computable form.

6621 Poster Session (Board #443), Mon, 1:15 PM-4:45 PM

Determinants of spending for metastatic breast, lung, and colorectal cancer in SEER-Medicare. *First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA*

Background: A substantial proportion of cancer spending is directed towards patients with metastatic disease. Past efforts to characterize spending for metastatic cancer have been limited, because they have not included patients with recurrent disease or analyzed spending across the entire episode of care. Spending for stage IV and recurrent metastatic cancer patients may differ. **Methods:** Using SEER-Medicare data from 2008-13, we identified breast (BC), colorectal (CRC), and lung (LC) cancer patients who were continuously enrolled in parts A, B and D, and had either stage IV or recurrent disease (i.e., return of cancer after resection of stage I-III disease). Mean total Medicare spending/patient per month and per year (2012$US) were estimated from 12 months prior to 12 months after diagnosis, and described for relevant patient sub-groups. **Results:** In a cohort of 27,847 patients, total spending for stage IV vs. recurrent cancer was 61-73% lower in the year before diagnosis ($11,339 vs. $28,796 for BC; $13,359 and $49,804 for CRC; $15,118 and $49,555 for LC), and 28-88% higher in the year after diagnosis ($68,787 and $42,091 for BC; $111,304 and $58,657 for CRC; $92,181 and $72,354 for LC). When considering the 2 year-period spanning the diagnosis, spending was similar (≤14%) between groups. The primary drivers of spending differences between patients with stage IV and recurrent disease were cancer type and time from diagnosis (Table). Younger age, higher comorbidity, and SEER region were also drivers of higher spending, especially after diagnosis. **Conclusions:** Spending patterns differ for patients with stage IV vs. recurrent cancer, suggesting different patterns of care that warrant further investigation. Spending differences after diagnosis were driven largely by part B spending, which was due in part to differential chemotherapy use.

Diff avg mo spending (2012 US$): Recur—stage IV

		Pre-advanced Dx		Post-advanced Dx	
	Medicare File	12 → 7 mos	6 → 1 mos	0 → 5 mos	6 → 11 mos
Breast	A+B+D	1281	1629	-2917	-1532
	A	326	429	-1756	-419
	B	813	1046	-1159	-1053
	D	141	153	-2	-60
CRC	A+B+D	2522	3552	-6066	-2541
	A	1554	2125	-3846	-454
	B	918	1365	-2237	-2076
	D	51	62	17	-12
Lung	A+B+D	2098	3641	-2885	-526
	A	1006	1749	-1684	204
	B	1015	1754	-1204	-642
	D	77	138	3	-88

6622 Poster Session (Board #444), Mon, 1:15 PM-4:45 PM

Cost-effectiveness of front-line trials in metastatic colorectal cancer: Integrating the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) with the costs of drugs. *First Author: Andrea Bonetti, Mater Salutis Hospital AULSS 9 of the Veneto Region, Legnago, Italy*

Background: In Western Countries, colorectal cancer (CRC) is the second most common cause of death from cancer. In light of the relevant expenses of drugs it might be interesting to make a balance between the cost of the drugs and clinical parameters of interest such as progression free survival (PFS). **Methods:** Phase III randomized clinical trials (RCTs) that compared at least two front-line chemotherapy regimens for mCRC patients were evaluated. Differences in PFS between the different arms were calculated and compared with the pharmacological costs (at the Pharmacy of our Hospital) needed to get one month of PFS. Subsequently we applied the ESMO-MCBS (a 1 to 5 scale) to the above phase III RCTs. **Results:** Overall 28 phase III RCTs, including 19 958 patients, were analyzed. The FOLFOX resulted the least expensive (56 € per month of PFS gained) while the addition of irinotecan to FOLFOX (FOLFOXIRI) increased only marginally the costs (90 € per month of PFS gained). Treatments including the monoclonal antibodies showed a cost per month of PFS gained of 2823 € (FOLFIRI with cetuximab in KRAS wild-type patients and liver-only metastases), of € 15 822 (FOLFOX with panitumumab in KRAS wild type) and of 13 383 € (FOLFOX with bevacizumab). According to the ESMO-MCBS the treatments including an EGFR-inhibitor (cetuximab or panitunumab) were associated with a score of 4 while the inclusion of bevacizumab reached a score of 3. The remaining phase III RCTs obtained a low (grade 1-2) score.Dividing the costs per month of PFS gained with the grade of ESMO-MCBS, for each RCTs, we obtained the costs of each point of ESMO-MCBS per month of PFS gained. FOLFOX was confirmed as being the least expensive (18.7 €) while among treatments including a targeted biological agent panitunumab in combination with FOLFOX in K-RAS wild type patients was less expensive (3955 €) than the combinations FOLFOX-bevacizumab (13 383 €) and FOLFIRI-cetuximab in K-RAS wild type patients (21 854.6 €). **Conclusions:** Our data demonstrate a huge difference in cost per month of PFS gained and per each point of the ESMO-MCBS in modern front line treatments in mCRC.

6623 Poster Session (Board #445), Mon, 1:15 PM-4:45 PM

Access and price of cancer drugs: What is happening in France? *First Author: Mathilde Grande, French National Authority for Health, La Plaine Saint-Denis, France*

Background: The French National Authority for Health (HAS) is responsible for health technology assessment (HTA), providing opinion on drugs for reimbursement and pricing purposes. For all indications with a positive opinion for reimbursement, HAS assesses the clinical added value (CAV) on a 5-point scale for pricing negotiations based on clinical data. A major to moderate CAV leads to the highest prices, a minor CAV leads to a higher price than the comparator, and no CAV leads to lower price than the cheapest comparator. Countries increasingly face the policy challenge of harnessing the benefits of cancer drugs while managing healthcare budgets. In this context, we aimed to analyze cancer drugs assessment by HAS. **Methods:** a retrospective and descriptive analysis comparing all new hematology/oncology cancer indications versus all others new indications assessed by HAS between 2010 and 2015 has been conducted. **Results:** 87 cancer indications (60 drugs) have been evaluated, representing 17% (87/510) of all new drugs indications assessed by HAS. Almost all cancer indications (92%) obtained a favorable opinion for reimbursement. Seven (8%) had an unfavorable opinion versus 20% in other therapeutic areas. However, 5 of these 7 indications were related to a drug included on the list of reimbursed drugs for another indication and consequently drugs are available. Overall, only 2 drugs were not reimbursed: nintedanib in non small cell lung cancer and tegafur/gimeracil/oteracil in gastric cancer (no impact on survival and lack of results transposability). Of the 80 indications with a favorable opinion, 20 had a major to moderate CAV (25%), 32 a minor CAV (40%) and 28 have no CAV (35%). Major to moderate CAV are mostly composed of hematology drugs (12, 60%). The proportion of major to moderate CAV assessment is higher in oncology than in other therapeutic areas (66% vs. 30%). **Conclusions:** France benefits from a universal healthcare system offering wide coverage and large access to drugs. Almost all of the new hematology/oncology cancer drugs assessed had a favorable opinion and are fully reimbursed (100%) by health insurance. A high proportion (66%) of CAV is recognized in oncology. Nevertheless, the over DRG list can inadvertently limit access to these new cancer drugs.

6624 Poster Session (Board #446), Mon, 1:15 PM-4:45 PM

Price trajectories assessment for Medicare Part B generic anti-cancer drugs. *First Author: Noa Gordon, Davidoff Cancer Center, Petah Tikva, Israel*

Background: Patented anti-cancer drugs launch prices have increased in recent years with subsequent increases after launch. Recently, large price increases of generic drugs were at the center of public attention in the United States. Our aim was to assess price changes with time for Medicare part B anti-cancer generic drugs and to understand how drug characteristics and market structure influence price trajectories. **Methods:** We included all Medicare part B anti-cancer drugs with price reported in both 2006 and 2016. Patent expiration dates were attached using the Medicare Drug Patent Expiration engine and drugs with a patent expiration date later than 2006 were excluded. Generic manufacturers' FDA approvals for each drug were extracted from the FDA Orange Book. For each drug we extracted the Average Sales Price (ASP) history from October 2006 to October 2016, published by the Center for Medicare and Medicaid services (CMS). Prices were adjusted for inflation, using information obtained from the United States Department of Labor. For each drug we calculated the cumulative ASP change during the follow-up period. Data were analyzed using IBM SPSS Statistics software. **Results:** We identified 31 anti-cancer generic drugs that met the inclusion and exclusion criteria. During the follow-up period, 15 (48%) drugs had increases in price (median 139%, range 18-2632%). Seven (23%) drugs increased by more than 200% (Table 1). Both gradual price and acute price increases were observed. Some of the drugs which had substantial price increases had no market competition market. **Conclusions:** Generic drug prices may change substantially with time. Gradual or rapid price increases may be due to lack of generic drug competition, substitution shortages or marketing reasons. New regulations may be needed to prevent further increases in generic drug costs, while balancing the need to maintain financial incentives for drug production and competition.

Top price increases.

Description	# Generic substitutions (# discontinued)	Change (%) inflation adjusted
carmustine 100mg	1	2632
cyclophosphamide 100mg	3 (2)	2175
busulfan oral 2mg	1	988
mitomycin 5mg	6 (3)	443
methotrexate oral 2.5mg	9	278
vinblastine sulfate 1mg	5 (3)	245
cyclophosphamide oral 25mg	3 (1)	216

TPS6625 Poster Session (Board #447a), Mon, 1:15 PM-4:45 PM

Biospecimen donors' views about biobank closure. *First Author: Rebecca D. Pentz, Emory University School of Medicine, Atlanta, GA*

Background: The future of biobanks is often uncertain due to sporadic funding. A survey of 456 biobank administrators found that they consider the loss of funding to be either a "massive (40%)" or "moderate (31%)" concern. Only 26% of biobanks reported having a plan in the event of closure (Cadigan et al., *Life Sciences, Society and Policy*, 2013). Biospecimen donors' views on how they want their tissue handled following biobank closure is unknown. Our study will be the first to determine how biospecimen donors want their data and biological materials handled if their biobanks were to close. We believe this report of 100 biospecimen donors' views will be useful to researchers and tissue bank administrators in creating contingency tissue bank closure plans that incorporate biospecimen donors' perspectives. **Methods:** We will complete accrual of 100 oncology biospecimen donors (current accrual is 65 patients) at one institution by interviewing them about their views of bank closure and preferences for the handling of their tissue post-closure. The interview asks participants if they have a preference for the handling of their tissue and information in the event of bank closure, and if so, if they prefer transfer of their materials to another tissue bank or destruction. Feelings about closure are captured in three categories: sad/disappointed, angry/frustrated, and other negative emotions. The effect of tissue bank closure upon trust in medical research is captured in three categories: decreases trust, does not decrease trust, and may decrease trust under certain circumstances. We ask the participants to rank the following options for transfer of their tissue and information: transfer to another local academic tissue bank, to a for-profit or pharmaceutical bank, to an international bank, or to a national bank. We also ask if any of these options are deemed absolutely unacceptable. Results: NA Conclusions: NA

TPS6626 Poster Session (Board #447b), Mon, 1:15 PM-4:45 PM

Objective assessment of physical activity during chemotherapy for breast cancer. *First Author: Michelle E. Melisko, University of California, San Francisco, San Francisco, CA*

Background: Exercise can alleviate side effects of chemotherapy, improve quality of life (QOL), and positively impact disease specific and overall survival. Despite the benefits of physical activity (PA), many patients' activity levels decrease during chemotherapy. Wearable devices, such as the Fitbit, can provide insight into patterns of activity, and help encourage behavior change. The aims of this study are: 1) determine the feasibility/acceptability of using a Fitbit to measure PA and sleep throughout chemotherapy for breast cancer; 2) describe patterns of PA, sedentary time, and sleep during chemotherapy; 3) explore associations of activity and sleep with QOL. **Methods:** Non-metastatic breast cancer patients from UCSF and UCSD will be enrolled prior to starting chemotherapy. Eligibility criteria include ability to speak/read English, walk unassisted, and access to internet or Fitbit compatible smart phone. Patients sign informed consent, receive a Fitbit Charge HR and guidance on how to use the device. Patients are instructed to wear the Fitbit throughout their adjuvant or neoadjuvant chemotherapy and 6 months post therapy and to sync the Fitbit at least weekly. Patients complete surveys at start, midpoint, end, and 6 months post chemotherapy. Questionnaires include PROMIS anxiety, depression, physical function, fatigue, cognitive function, social roles, comfort with technology and usefulness of the Fitbit. Fitabase database collects minute level activity, sleep, and heart rate. To assess feasibility, we will evaluate if a participant wears FitBit for at least 10 hour per day for $\geq$ 80% of the days during chemotherapy. We will use mixed effects regression models to assess patterns of PA and associations between activity and QOL. All models will include activity time and Fitbit wear time and will control for the potential confounding effects of age and other demographic or clinical variables. As of February 6 2017, 48 out of a planned 80 patients are enrolled. Acknowledgment: Athena Breast Health Network investigators and patients; support at UCSD by NCI (U54 CA155435-01) and by gift from Carol Vassiliadis and family; NCI grant K07CA181323 to SH; UCSF M Zion Health Fund Award, GBCTB unrestricted funding and TriValley SOCKS to MM. Clinical trial information: NCT03041545.

7000 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Phase 3 trial of momelotinib (MMB) vs ruxolitinib (RUX) in JAK inhibitor (JAKi) naive patients with myelofibrosis (MF). *First Author: Ruben A. Mesa, Mayo Clinic Cancer Center, Scottsdale, AZ*

Background: MMB, an oral JAKi, has been shown in early trials to reduce spleen volume, improve disease associated symptoms (Sx) and improve RBC transfusion (Tx) requirements in patients (pts) with MF. This study was designed to test non-inferiority of MMB vs RUX in splenic volume reduction and Sx amelioration, and superiority in Tx requirement, in JAKi naïve MF pts. **Methods:** Eligibility: MF, IPSS high risk, Int-2, or symptomatic Int-1; palpable spleen ≥5cm; platelets ≥ 50 K/μl, and no Gr ≥2 peripheral neuropathy (PN). Stratification by Tx dependency and platelets (<100, 100-200 and >200 K/μl). Pts were randomized 1:1 to 24 wks of MMB 200 mg qd + RUX placebo or RUX 20 mg bid (or modified per label) + MMB placebo, after which all pts could receive open label MMB. Assessments: spleen volume by MRI, and pt reported Sx using a daily eDiary of modified MPN-SAF Total Sx Score (TSS). Primary endpoint was splenic response rate (SRR; ≥35% reduction in volume from baseline) at 24 wks. Secondary endpoints, evaluated sequentially at 24 wks, were rates of TSS response (≥50% reduction from baseline), RBC Tx independence (TI), RBC Tx dependence (TD) and of RBC Tx. **Results:** 175 of 215 (81%) and 201 of 217 (93%) pts randomized to MMB and RUX, respectively, completed the 24 wk DB phase. Efficacy results are shown in Table. Most common Gr ≥3 AEs in the DB phase with MMB were thrombocytopenia (7%) and anemia (6%), and with RUX were anemia (23%), thrombocytopenia (5%) and neutropenia (5%). Gr ≥3 infections occurred in 7% of MMB and 3% of RUX pts. Treatment emergent PN occurred in 22 (10%) of MMB (all Gr ≤2) and 10 (5%) of RUX (9 Gr ≤2, 1 Gr 3) pts in DB phase, none discontinuing study drug for PN. Overall, AEs led to study drug D/C in 13% of MMB and 6% of RUX pts in DB phase. **Conclusions:** In pts with JAKi naive MF, 24 weeks of MMB is non-inferior to RUX for spleen response but not for symptom response. MMB treatment is associated with a reduced transfusion requirement. NCT01969838.

Endpoints	MMB	RUX	P-Value
Spleen response rate, %	26.5	29.0	0.011[a]
TSS response rate, %	28.4	42.2	0.98 [a]
TI rate, %	66.5	49.3	< 0.001[b]
TD rate,%	30.2	40.1	0.019[b]
Tx rate (units/month), median	0.0	0.4	< 0.001[b]

[a]Test for non-inferiority; [b]Test for superiority, all values nominally significant.

7001 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Phase 3 randomized trial of momelotinib (MMB) versus best available therapy (BAT) in patients with myelofibrosis (MF) previously treated with ruxolitinib (RUX). *First Author: Claire N. Harrison, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom*

Background: MMB, an oral JAK inhibitor, has been shown in early trials to reduce spleen volume, improve disease associated symptoms (Sx) and improve RBC transfusion requirements in patients (pts) with MF. This study of previously RUX treated pts with MF tested the superiority of MMB vs BAT in splenic volume reduction, Sx amelioration, and transfusion requirement at 24 weeks. **Methods:** Eligibility included primary or post-ET/PV MF; DIPSS high risk, Int-2, or symptomatic Int-1; prior RUX ≥4 weeks who either required transfusions or dose reduction to <20 mg BID with at least one of Gr ≥3 thrombocytopenia, anemia, or bleed; palpable spleen ≥5cm; and no Gr ≥2 peripheral neuropathy. Stratification was by transfusion dependency and baseline TSS (modified MPN-SAF Total Sx Score) <18 or ≥18. Pts were randomized 2:1 to 24 weeks of open-label MMB 200 mg QD or BAT. Assessments included spleen volume by MRI, and patient-reported Sx using a daily eDiary for TSS. 1° endpoint was splenic response rate (SRR; ≥35% reduction in volume from baseline). 2° endpoints, evaluated sequentially, were rates of TSS response (TSS RR; ≥50% reduction from baseline), RBC transfusion, RBC transfusion independence (TI) and RBC transfusion dependence (TD). **Results:** 73 of 104 (70%) and 40 of 52 (77%) pts receiving MMB or BAT, respectively, completed the 24 week randomized treatment phase. BAT for 88% of pts included RUX, and 27% of pts were on RUX in combination with other drugs. Efficacy results are in Table. The most common Gr ≥3 adverse events in MMB pts were anemia (13%) and thrombocytopenia (7%), and in BAT pts, anemia (13%), thrombocytopenia (6%) and abdominal pain (6%); treatment emergent peripheral neuropathy occurred in 11 (11%) of MMB (1 Gr3) and in no BAT pts. **Conclusions:** In previously RUX-treated patients with MF, 24 weeks of MMB was not superior to BAT for SRR, but significantly better in improving disease related symptoms and transfusion independence. Clinical trial information: NCT02101268.

Endpoints	MMB	BAT	*p*-value
SRR, %	6.7	5.8	0.90
TSS RR, %	26.2	5.9	<0.001[a]
Transfusion rate (units/month), med	0.5	1.2	0.39
TI rate, %	43.3	21.2	0.001[a]
TD rate, %	50.0	63.5	0.10

[a] p-values nominally significant

7002 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Bosutinib (BOS) versus imatinib (IM) for newly diagnosed chronic myeloid leukemia (CML): Initial results from the BFORE trial. *First Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BOS is a potent, dual SRC/ABL tyrosine kinase inhibitor approved for treatment (tx) of adults with Ph+ CML resistant/intolerant to prior therapy. We assessed the efficacy and safety of BOS vs IM for first-line tx of chronic phase (CP) CML. **Methods:** In this ongoing, multinational, phase 3, open-label study, 536 patients (pts) with newly diagnosed CP CML were randomized 1:1 to BOS 400 mg QD (n = 268) or IM 400 mg QD (n = 268 [3 not treated]). Per protocol, efficacy was assessed in a modified intent-to-treat (ITT) population of 487 Ph+ pts (BOS, n = 246; IM, n = 241) with e13a2/e14a2 transcripts; results in full ITT will also be presented. **Results:** After≥12 mo of follow-up, 78% of BOS and 73.2% of IM pts remain on tx with median tx durations of 14.1 and 13.8 mo, respectively. Major molecular response (MMR) rate at 12 mo (primary endpoint) was significantly higher with BOS vs IM (47.2% vs 36.9%; P= 0.02). Time to MMR was shorter for BOS (hazard ratio [HR] 1.34; P< 0.02). Rate of complete cytogenetic response (CCyR) by 12 mo was also significantly higher with BOS vs IM (77.2% vs 66.4%; P< 0.008), with time to CCyR shorter for BOS (HR 1.38; P≤0.001). Rates of BCR-ABL transcripts≤10% (Intl Scale) at 3 mo (75.2% vs 57.3%), MR^4 at 12 mo (20.7% vs 12%) and $MR^{4.5}$ at 12 mo (8.1% vs 3.3%) were higher with BOS vs IM, respectively (all P< 0.025). 1 BOS pt and 4 IM pts discontinued tx due to progression to accelerated or blast phase. There were no deaths within 28 d of last dose of BOS and 4 with IM. Safety data were consistent with known safety profiles of BOS and IM. 12.7% of BOS and 8.7% of IM pts discontinued due to drug-related toxicity. Gr≥3 diarrhea (7.8% vs 0.8%) and increased alanine (19% vs 1.5%) and aspartate (9.7% vs 1.9%) aminotransferase levels were more common with BOS. Cardio-, peripheral- and cerebrovascular events were infrequent (3%, 1.5% and 0% BOS vs 0.4%, 1.1% and 0.4% IM; gr≥3: 1.5%, 0% and 0% vs 0%, 0% and 0.4%). **Conclusions:** Pts on BOS had significantly higher rates of 12-mo MMR and CCyR and achieved responses faster than those on IM, but had higher incidence of gastrointestinal events and transaminase elevations. Results suggest BOS may be an important tx option for pts with newly diagnosed CP CML. Funding. Avillion, Pfizer. Clinical trial information: NCT02130557.

7003 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Deep molecular response to gilteritinib to improve survival in FLT3 mutation-positive relapsed/refractory acute myeloid leukemia. *First Author: Jessica K. Altman, Northwestern University, Chicago, IL*

Background: Gilteritinib, a highly selective FLT3/AXL inhibitor, has displayed antileukemic activity in FLT3 mutation-positive ($FLT3^{mut+}$) relapsed/refractory (R/R) AML in the CHRYSALIS Phase I/II study (NCT02014558), specifically at doses ≥80 mg/d. This exploratory analysis assessed molecular response to gilteritinib in a CHRYSALIS subpopulation. **Methods:** Molecular response was assessed from bone marrow aspirates obtained at baseline and at ≥1 additional time point from $FLT3^{mut+}$ patients (≥18 y) treated with 120 or 200 mg/d gilteritinib. These doses were identified due to their ability to induce consistent, potent FLT3 inhibition and high clinical response rates. *FLT3-ITD* and total *FLT3* were quantified by NGS to assess molecular response. A Cox regression model of overall survival (OS) by Kaplan-Meier estimation established a *FLT3-ITD*:total *FLT3* ratio (ITD signal ratio) of 10^{-2}as the threshold for improved survival. **Results:** Of 147 $FLT3\text{-}ITD^{mut+}$ patients who received gilteritinib 120 or 200 mg/d, 80 were included in this analysis. Composite response rate for these 80 patients was 55%. During response, 20 patients (25%) had an ITD signal ratio of $\leq 10^{-2}$. Of these 20 patients, 18 had a ratio of $\leq 10^{-3}$ (major molecular response [MMR]) and 13 had a ratio of $\leq 10^{-4}$ (minimal residual disease [MRD] negative). Median time to achieve minimum signal ratio was 54 days. Elimination of morphologic leukemia was observed in 80% of patients with ITD signal ratios $<10^{-2}$. Patients who had a signal ratio $\leq 10^{-2}$, MMR, or were MRD negative had significantly longer median OS than those who did not (Table). **Conclusions:** Molecular responses to gilteritinib in $FLT3\text{-}ITD^{mut+}$ R/R AML correlated with clinical response and improved OS. This is the first demonstration of molecular response to a FLT3 inhibitor in AML. These data suggest ITD signal ratio may predict durable clinical benefit of gilteritinib. Clinical trial information: NCT02014558.

	Achieved a Molecular Response		Did not Achieve a Molecular Response		
Molecular Response	n	Median OS, Days (95% CI)	n	Median OS, Days (95% CI)	*P*-value
ITD signal ratio $\leq 10^{-2}$	20	417 (246–NA)	60	199 (142–234)	<.001
MMR	18	417 (228–NA)	62	213 (143–264)	.003
MRD negative	13	417 (228–NA)	67	213 (144–264)	.002

7004 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Enasidenib in mutant-*IDH2* relapsed or refractory acute myeloid leukemia (R/R AML): Results of a phase I dose-escalation and expansion study. *First Author: Eytan M. Stein, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: Recurrent mutations in *isocitrate dehydrogenase 2* (m*IDH2*) occur in 8-15% of AML pts. mIDH2 proteins synthesize an oncometabolite, 2-hydroxyglutarate (2HG), causing DNA and histone hypermethylation and blocked myeloid differentiation. Enasidenib (AG-221) is an oral, selective, small-molecule inhibitor of mIDH2 protein. **Methods:** This phase 1/2 study assessed the maximum tolerated dose (MTD), pharmacokinetic and pharmacodynamic profiles, safety, and clinical activity of enasidenib in pts with m*IDH2* myeloid malignancies. Safety for all pts and efficacy outcomes for R/R AML pts from the phase 1 dose-escalation and expansion phases are reported. **Results:** In all, 239 pts received enasidenib. In the dose-escalation (n=113), the MTD was not reached at doses up to 650 mg daily. Median 2HG reductions from baseline were 92%, 90%, and 93% for pts receiving <100 mg, 100 mg, and >100 mg daily, respectively. Enasidenib 100 mg QD was chosen for the expansion phase (n=126) based on PK/PD profiles and demonstrated efficacy. Median number of enasidenib cycles was 5 (range 1–25). Grade 3-4 drug-related investigator reported AEs included indirect hyperbilirubinemia (12%) and IDH-inhibitor-associated differentiation syndrome (ie, retinoic acid syndrome; 7%). For R/R AML pts, overall response rate (ORR) was 40.3%, including 34 (19.3%) complete remissions (CR; Table). Response was associated with cellular differentiation, typically with no evidence of aplasia. Median overall survival (OS) for R/R AML pts was 9.3 months (mos). For pts who attained CR, OS was 19.7 mos. Pts who had received ≥2 prior AML regimens (n=94; 53%) had median OS of 8.0 mos. **Conclusions:** Enasidenib was well tolerated, induced CRs, and was associated with OS of >9 mos in pts who had failed prior AML therapies. Differentiation of myeloblasts, not cytotoxicity, appears to drive the clinical efficacy of enasidenib. Clinical trial information: NCT01915498.

	R/R AML Pts	
Response	All (N=176) (%)	100 mg/day (n=109) (%)
ORR*	40.3	38.5
CR	19.3	20.2
CR with incomplete hematologic recovery (CRi)	6.4	6.8
Morphologic leukemia-free state (MLFS)	8.0	9.2
Partial remission (PR)	6.3	2.8
Median response duration	5.8 mos	5.6 mos
Stable disease	48.3	53.2

*CR/CRi/PR/MLFS

7005 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Distinct patterns of somatic mutation clearance and association with clinical outcome in patients with AML. *First Author: Koichi Takahashi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Persistence of somatic mutations at the time of complete remission (CR) was associated with poor outcome in patients (pts) with AML. **Methods:** We studied 95 pts with AML who were treated with frontline induction and subsequently achieved CR. We sequenced pre-treatment and CR bone marrow samples by targeted capture sequencing of 295 genes (median 280x coverage). We defined 3 levels of mutation clearance (MC) based on variant allele frequency (VAF): MC2.5, persistent mutation with VAF<2.5%; MC1.0, persistent mutation with VAF<1%; and complete mutation clearance (CMC). **Results:** In the pre-treatment samples, we detected 597 mutations in 78 genes in 87 (92%) patients. In the matching CR samples, 62 (10%) and 82 (14%) mutations persisted at VAF≥2.5% and ≥1%, respectively, which corresponded to 43 (49%), 34 (39%), and 30 (34%) patients achieving MC2.5, MC1.0 and CMC, respectively. Table 1 shows the differential patterns of MC based on the mutations and pathways. Mutations associated with clonal hematopoiesis of indeterminate potential (CHIP), DNA methylation, and splicing pathways had low rate of MC, whereas mutations in transcription factors or receptor tyrosine kinase (RTK) had high rate of MC. Pts who achieved MC1.0 (median 31.2 vs. 12.5 months, P = 0.04) or CMC (median 31.2 vs. 12.5 months, P = 0.049) had significantly better relapse-free survival (RFS). **Conclusions:** Somatic mutations associated with CHIP, DNA methylation, and splicing pathways persisted frequently in CR samples suggesting preleukemic origin. Pts with deeper MC had significantly better RFS. Somatic mutation clearance may help risk prediction of AML.

Gene	MC2.5 (%)	MC1.0 (%)	CMC (%)	Pathway	MC2.5 (%)	MC1.0 (%)	CMC (%)
DNMT3A	21%	17%	14%	CHIP associated	33%	24%	22%
NPM1	100%	96%	96%	DNA methylation	39%	29%	26%
TET2	35%	35%	35%	RTK pathway	88%	87%	83%
FLT3	100%	100%	100%	Transcription Factors	94%	83%	77%
CEBPA	100%	89%	89%	Chromatn-Cohesin	67%	53%	53%
IDH2	38%	44%	38%	Splicing	33%	17%	17%
GATA2	100%	100%	91%				
NRAS	92%	92%	92%				
RUNX1	67%	44%	56%				
WT1	75%	75%	63%				
PTPN11	89%	89%	89%				
TP53	25%	0%	0%				
ASXL1	0%	0%	0%				
NF1	63%	50%	38%				
STAG2	57%	43%	43%				
BCOR	100%	50%	50%				
SRSF2	17%	17%	17%				
IDH1	100%	40%	40%				
SMC3	100%	100%	100%				
KRAS	100%	100%	75%				
SF3B1	100%	33%	33%				

7006 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Allogeneic hematopoietic cell transplant (alloHCT) for hematologic malignancies in human immunodeficiency virus infected (HIV) patients (pts): Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0903)/AIDS Malignancy Consortium (AMC-080) trial. *First Author: Richard F. Ambinder, Bunting Blaustein Cancer Research Building, Baltimore, MD*

Background: AlloHCT has been regarded as risky in HIV pts, with concern about fatal infection. We set out to assess feasibility and safety of alloHCT in this first prospective multicenter trial. **Methods:** The primary endpoint was 100-day non-relapse mortality (NRM). Pts had drug-susceptible HIV; age ≥ 15 yr; adequate organ function; acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL), high risk myelodysplastic syndrome (MDS), or Hodgkin (HL) or non-Hodgkin lymphoma (NHL) beyond first CR; an 8/8 HLA-matched related or at least a 7/8 unrelated donor. Pts received myeloablative (MA) or reduced intensity (RI) regimens. HIV outgrowth assays (VOA) were performed with resting CD4+T-cells in pts who had clinically undetectable HIV plasma RNA at 1 yr. **Results:** Between 5/2012 and 12/2015, 17 pts underwent alloHCT. Pts were: male (17); white (11), African American (3), Other/Unknown (3); median age 47 yrs (25-64). Associated malignancies were AML (9), ALL (2), MDS (2), HL (1), NHL (3). Median CD4 was 224 (55-833). Conditioning was MA (8) and RI (9). At 100 days there was no NRM, 13 pts were in CR, 4 pts had relapsed/progressive disease; and 8 pts achieved complete chimerism. The cumulative incidence of Grades (Gr) II-IV acute Graft vs Host Disease (GvHD) was 41 % (95%CI: 18 %, 64%). At 6 mo, OS was 82 % (95% confidence interval [CI]: 55%, 94%); 9 pts achieved complete chimerism. At 1 year, OS was 57 % (CI: 31%, 77 %); 8 deaths were from relapsed/progressive disease (5), acute GvHD (1), adult respiratory distress syndrome (1) and liver failure (1). Infections were reported in 11 pts (3 Gr 2, 8 Gr 3). Infectious HIV was detected by VOA in 2 of 3 pts who were mixed chimeras but 0 of 2 who were 100% donor. Median follow up of survivors is 24 mo (7 to 27). **Conclusions:** HIV pts with heme malignancies underwent MA or RI alloHCT without any100-day NRM and there were no infectious deaths at 1 year. AlloHCT should be considered the standard of care for HIV pts who meet usual eligibility criteria. Clinical trial information: NCT01410344.

7007 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Factors associated with allogeneic hematopoietic stem cell transplantation (HSCT) outcomes in patients (pts) with relapsed/refractory acute lymphoblastic leukemia (R/R ALL) treated with inotuzumab ozogamicin (InO) versus (v) conventional chemotherapy (C). *First Author: Partow Kebriaei, MD Anderson Cancer Center, Houston, TX*

Background: InO therapy in R/R ALL resulted in superior complete remission (CR)/CR with incomplete hematologic recovery (CRi) rates v C in the Phase 3 INO-VATE trial (NCT01564784; Kantarjian *NEJM* 2016). More InO v C pts proceeded to HSCT (41% [45/109] v 11% [12/109]; *P*<0.001). Factors associated with outcomes after HSCT are described. **Methods:** Full details have been published. Multivariate analyses (MVA) using Cox regression modeling were conducted to determine predictors of non-relapse mortality (NRM) and overall survival (OS). **Results:** As of 3/8/16, 108/326 pts underwent allogeneic HSCT (InO n=77; C n=31). Baseline characteristics were generally similar, except baseline platelet values were lower in InO v C pts. More InO v C pts achieved minimal residual disease negativity (MRD^{neg} [best status]; 71% v 26%; *P*<0.0001). Less InO v C pts received additional therapy before HSCT (14% v 55%, *P*<0.0001). NRM rates were higher in InO v C pts at 1 year (yr; 36% [95% CI 26–47] v 20% [8–36]) and 2 yrs (39% [27–51] v 31% [13–51]), but relapse rates were lower (1 yr, 23% [15–33] v 29% [13–48]; 2 yrs, 33% [22–44] v 46% [24–65]). No significant difference in post-HSCT survival was detected in InO v C pts; however, visual inspection of the curve suggested the survival probability varied before and after 15 months post-HSCT (1 yr, 44% [95% CI 33–55] v 65% [44–79]; 2 yr, 39% [28–50] v 34% [15–54]). Fatal veno-occlusive disease (VOD) was observed in 5 InO pts (all during the first 100 days from the date of HSCT) and no C pts. MVA showed that conditioning regimens without dual alkylators and thiotepa were associated (2-sided; *P*<0.05) with lower risk of NRM and post-HSCT survival, respectively. **Conclusions:** Compared with C, InO permitted more pts with R/R ALL to proceed to HSCT in CR/CRi with MRD^{neg} (best status). Despite increased NRM and fatal VOD, long-term survival was attainable in InO pts. In pts previously treated with InO, interventions to reduce NRM and improve OS after HSCT include avoiding dual alkylator conditioning regimens, especially those containing thiotepa. Funding: Pfizer Clinical trial information: NCT01564784.

7008 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Durable long-term survival of adult patients with relapsed B-ALL after CD19 CAR (19-28z) T-cell therapy. *First Author: Jae Hong Park, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: CD19-specific chimeric antigen receptor (CAR) T cells have demonstrated high initial responses in patients with relapsed B-ALL. However, clinical characteristics associated with the durability of response remain undefined. Herein, we report the results from analysis of our phase I clinical trial of 19-28z CAR T cells in adult patients with relapsed B-ALL (NCT01044069) with a focus to identify those patients who optimally benefit from 19-28z CAR T cell therapy with durable long-term survival and reduced toxicities. **Methods:** Adults with relapsed B-ALL were infused with autologous T cells expressing the 19-28z CAR following conditioning chemotherapy. Disease burden was assessed by bone marrow biopsy immediately prior to T cell infusion; patients with $<$ 5% blasts were classified as minimal residual disease (MRD) cohort vs. patients $\geq$5% blasts as morphologic disease cohort. Response assessment occurred at 4 weeks. Median follow-up duration was 18 months (range, 0.2-57.3). **Results:** 51 adults received 19-28z CAR T cells; 20 in the MRD and 31 in the morphologic cohort. Complete remission (CR) rates were comparable (95% and 77%, respectively). However, median event-free and overall survivals widely diverged among the 42 patients who achieved MRD-negative CR: not reached (NR) (95% confidence interval [CI]: 4.2-NR) vs. 6.3 months (95% CI, 4.8-9.0) (p = 0.0005), and NR (95% CI, 15.3-NR) vs. 17 months (95% CI, 8.5 – 36.2) (p = 0.0189), in the MRD and morphologic cohorts, respectively. Subsequent allogeneic HSCT in either cohort did not improve survival (p = 0.8). MRD cohort patients developed substantially less severe cytokine release syndrome (CRS) and neurotoxicity, both correlating with peak CAR T cell expansion (p = 0.0326 and p = 0.0001, respectively). **Conclusions:** Despite comparable initial CR rates regardless of pre-treatment disease burden, durability of 19-28z CAR T cell mediated remissions and survival in adult patients with relapsed B-ALL positively correlated to a low disease burden and do not appear to be enhanced by allogeneic transplant. Our findings strongly support the early incorporation of CD19 CAR therapy before morphologic relapse in B-ALL. Clinical trial information: NCT01044069.

7009 Poster Discussion Session; Displayed in Poster Session (Board #209), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

An antibody derived from a cured AML patient to identify a unique epitope on CD43 (CD43s) as a novel target for acute myeloid leukemia and myelodysplastic syndrome. *First Author: Mette D. Hazenberg, Academic Medical Center, Amsterdam, Netherlands*

Background: Immunotherapy for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) is hampered by the lack of tumor-specific targets. **Methods:** We took advantage of the tumor-immunotherapeutic effect of allogeneic hematopoietic stem cell transplantation (HSCT) and searched the B cell repertoire of a patient with a lasting and potent graft versus AML response for AML-specific antibodies. **Results:** We identified a donor-derived B cell clone that produced an IgG1 antibody, AT1413, that specifically interacted with AML cell lines, with the patient's autologous AML blasts, but not with lymphocytes or with cells from liver, colon, skin and other tissues. AT1413 recognized a unique, not previously described, sialylated epitope on CD43 (CD43s). CD43s is overexpressed on all types of AML and MDS, as illustrated by its reactivity with freshly isolated blasts of each of more than 60 randomly selected AML and MDS patients in our clinic, representing all WHO 2008 AML and MDS classes. AT1413 induced antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) of target cells in vitro. To investigate the effect of AT1413 *in vivo*we first generated mice populated with human effector cells (NK cells, CTL and myeloid cells) by injecting human hematopoietic stem cells into new born immunodeficient mice. After establishment of a human immune system in these mice we inoculated luciferase labeled AML cells via tail vein injection. Following engraftment of the tumor we dosed the mice biweekly with AT1413 or a control antibody. We observed strongly reduced numbers of AML cells in AT1413- but not in control antibody treated mice. Importantly, AT1413 treatment was tolerated well and did not affect numbers of non-malignant human myeloid cell in these mice. **Conclusions:** We have obtained an antibody from a cured AML patient which recognizes a unique sialylated epitope on CD43 (CD43s) that is selectively over-expressed on all WHO 2008 types of AML and MDS. This antibody was able to eliminate AML cells *in vivo* and therefore has high therapeutic potential.

7010 Poster Discussion Session; Displayed in Poster Session (Board #210), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

A phase I trial of ipilimumab (ipi) in patients (pts) with myelodysplastic syndromes (MDS) after hypomethylating agent (HMAs) failure. *First Author: Amer M Zeidan, Yale School of Medicine, New Haven, CT*

Background: Pts with HR-MDS after HMA failure have a poor overall survival (OS) of $<$ 6 months. Immune escape is associated with resistance to HMAs in MDS. We hypothesized that CTLA-4 blockade in these pts would be tolerable and lead to clinical responses. **Methods:** This investigator-initiated, CTEP-sponsored, multi-center phase 1b study enrolled pts after failure of HMAs. In dose-escalation, ipi monotherapy was given at 2 dose levels (DL): 3 and 10mg/kg. Four doses (every 3 weeks) were administered followed by a maintenance phase (4 doses every 3 months) for non-porgressors. Toxicities and responses were evaluated with CTCAE4 and IWG2006 criteria, respectively. OS was estimated using the Kaplan-Meier method. The impact on T-cells were studied by flow cytometry and TCR sequencing. **Results:** 29 pts from 7 centers were enrolled. Mean age (SD) was 67 (8) years. Most had IPSS high/int-2 (55%), 45% had int-1. Three of 6 pts in DL1 and 4 of 5 pts in DL2 experienced grade [G]2-4 immune-related adverse events [IRAEs] that were reversible with drug discontinuation or systemic steroids. The DL1 (3mg/kg) was expanded with no G2-4 IRAEs reported in the 18 additional pts. A total of 15 deaths occurred due to disease progression or other complications but none attributed to ipilimumab. In total, 52% received all 4 induction doses, and 24% received $\geq$1 maintenance dose. Best objective responses were 2 marrow complete responses (mCR, 7%). Prolonged stable disease (PSD) for $\geq$46 weeks occurred in 6 pts (21%) and for $\geq$54 weeks in 3 pts (10%). Five pts (17%) subsequently underwent allogeneic transplantation (alloSCT) without evidence of excessive toxicity. Median OS (censoring at alloSCT) was 294 days (95%CI, 240-671+) and 400 days (95%CI, 240-671+) for those who received maintenance (n = 7). Pts who achieved PSD and mCR had significantly increased expression of ICOS, a marker of T-cell activation. **Conclusions:** Immune checkpoint blockade with ipi is tolerable and can lead to PSD/mCR in a proportion of pts. However, ipi monotherapy efficacy is limited after HMA failure and combination-based approaches should be considered. Increased frequencies of ICOS expression might predict clinical benefit. Clinical trial information: NCT01757639.

7011 Poster Discussion Session; Displayed in Poster Session (Board #211), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Immune-related gene expression deficit of leukemia stem cells (LSC) in AML. *First Author: Kamal Chamoun, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: AML LSC are believed to be responsible for residual and resistant leukemic disease leading to relapse. Understanding differences between bulk AML and the LSC subpopulation may allow the identification of novel LSC targets, especially for the most adverse risk AML where few patients are cured. Targeting LSC may be needed to eradicate AML, and immune-based therapies provide an approach for eliminating LSC. The transcriptional landscape of immune-related genes in LSC is not well understood. **Methods:** Samples were collected at diagnosis from 12 patients with high-risk AML prior to therapy. Bulk (CD45-dim blasts) and LSC (Lin-CD34+CD38-CD123+) AML marrow cells were FACS-sorted and analyzed using whole genome RNA-sequencing. Transcriptomes were analyzed using AltAnalyze software to identify differentially expressed genes in bulk AML cells and in AML LSC populations. These genes were further assessed by gene enrichment analysis using data from Gene Ontology (GO) and the Cancer Genome Atlas Project (CGAP). **Results:** Sixty-eight genes were identified with greater than 3-fold differential expression between bulk AML and LSC. GO enrichment analysis demonstrated more than 10-fold enrichment of genes involved in the molecular functions, biologic processes, and cell components related to the antigen presentation pathway, with the comparative down-regulation occurring in LSC. Among the top differentially expressed gene clusters, both the MHC class II and interferon-gamma signaling/response pathway gene expression was blunted in LSC. Additional expression analysis revealed that 42% of a CGAP-curated list of 201 antigen-processing and -presentation genes had significantly decreased expression in the LSC subpopulation compared to bulk AML. **Conclusions:** LSC from primary AML patient samples are characterized by reduction in expression of MHC class II receptor and antigen presentation genes compared to bulk AML. These results suggest that impairment in the presentation and/or processing of tumor associated antigens by MHC class II on LSC, along with tonic sponging of immune response cells and diversion away from LSC by bulk AML, may contribute to LSC evasion of immune surveillance and response.

7012 Poster Discussion Session; Displayed in Poster Session (Board #212), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Five-year results of the ponatinib phase II PACE trial in heavily pretreated CP-CML patients (pts). *First Author: Hagop M. Kantarjian, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The tyrosine kinase inhibitor (TKI) ponatinib has potent activity against native and mutant BCR-ABL1 and is approved for use in pts with relapsed/intolerant CML or Ph+ ALL, or with BCR-ABL1/T315I. **Methods:** In the pivotal PACE study (NCT01207440), ponatinib (starting dose 45 mg/d) was assessed in pts with CML or Ph+ ALL resistant/intolerant to dasatinib or nilotinib, or with T315I. In Oct '13, dose reductions were implemented due to observed arterial occlusive events (AOEs). Efficacy and safety at 5 yrs (data as of 3 Oct '16) for CP-CML pts are reported. **Results:** Of 270 CP-CML pts in the safety population, 60% received ≥3 prior TKIs. At initiation of study closure, 99 pts were ongoing; among these pts, minimum follow-up was 52 months, and most (78%) had 15 mg/d as their last dose. In all CP-CML pts (n = 267, efficacy evaluable), cumulative response rates were: MCyR, 60%; CCyR, 54%; MMR, 40%; and $MR^{4.5}$, 24%. Among pts who achieved MCyR (n = 148) or MMR (n = 108), the Kaplan-Meier (KM) estimated probability of remaining in response at 5 yrs was 74% (95% CI, 62 – 83) and 61% (95% CI, 51 – 70), respectively. Regardless of dose reduction in Oct '13, maintenance of response was high (Table). KM estimated 5-yr rate for PFS/OS was 49%/77%. TEAEs in ≥45% of CP-CML pts were rash 47%, abdominal pain 46%, and thrombocytopenia 46%. Most newly occurring AEs were observed within the first year. The incidence of any AOEs/serious AOEs for CP-CML pts was 29%/23%. Among CP-CML pts with no prior AOEs who had a prospective dose reduction, 17% (11/63) had a first AOE occurring after Oct '13. **Conclusions:** Long-term (5-yr) results from PACE demonstrate that ponatinib continues to show clinical benefit, irrespective of dose reductions, with deep and lasting responses in heavily pretreated CP-CML pts. Safety results were consistent with the safety profile across the ponatinib clinical program. Clinical trial information: NCT01207440.

Maintenance of response following prospective dose reductions[a].

	MCyR		MMR	
	Pts in MCyR Oct '13 n	Maintained Response Oct '16[b] n	Pts in MMR Oct '13 n	Maintained Response Oct '16[b] n
Dose reductions as of Oct '13				
Total	69	66	52	47
45 or 30 to 15 mg/d	59	56	46	41
No dose reduction as of Oct '13				
Total	34	32	19	18
15 mg/d	25	25	17	17

[a]Excludes pts who lost response before Oct '13; [b]At last assessment up to Oct '16.

7013 Poster Discussion Session; Displayed in Poster Session (Board #213), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Frontline hyper-CVAD plus ponatinib for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Updated results of a phase II study. *First Author: Nicholas James Short, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The combination of chemotherapy plus a TKI is highly effective in Ph+ ALL. In this phase II study, we evaluated the safety and efficacy of HCVAD in combination with the third-generation pan-*BCR-ABL* inhibitor, ponatinib. **Methods:** Patients (pts) with newly diagnosed Ph+ ALL received 8 cycles of HCVAD alternating with high dose MTX/Ara-C every 21 days. Ponatinib was given at 45 mg daily for the first 14 days of cycle 1. Initially ponatinib 45 mg daily was given indefinitely beginning at cycle 2. Due to concern for vascular events, a protocol amendment was made in which, beginning in cycle 2, pts in CR received 30mg daily and pts in CMR received 15mg daily. Rituximab and IT chemotherapy were given with the first 4 courses. After 8 cycles of HCVAD, pts in CR received maintenance with ponatinib, vincristine and prednisone for 2 years followed by indefinite ponatinib. **Results:** 64 pts have been treated, 10 of whom had received prior treatment with another regimen (8 in CR, 2 not in CR). Median age was 48 years (range, 21-80) and median follow-up was 33 months (range, 2-62). Median cycles received was 6 (range, 2-8). 63 pts (98%) achieved CR after 1 cycle; 1 pt achieved CRp. CCyR was achieved in 98%, MMR in 97% and CMR in 77%. Median time to CMR was 10 weeks (range, 2-96). Median times to platelet and ANC recovery in cycle 1 were 22 and 18 days, respectively, and for subsequent cycles were 22 and 16 days, respectively. Grade ≥3 pancreatitis was observed in 12 pts (19%), thrombotic events in 4 (6%) and MI in 3 (5%). 8 pts have died, with 2 deaths attributed to ponatinib (both from MI). No grade ≥3 vascular events occurred after the protocol amendment. 38 pts continue to receive treatment (7 in consolidation, 14 in maintenance and 17 post-maintenance). 10 pts (16%) underwent allogeneic SCT in CR1. 7 pts have relapsed, 3 of whom were still receiving ponatinib. The 3-year continued remission and OS rates were 79% and 76%, respectively. In a landmark analysis at 4 months, CR duration and OS did not differ significantly in pts with or without allogeneic SCT. **Conclusions:** HCVAD plus ponatinib is highly effective in pts with newly diagnosed Ph+ ALL, resulting in high rates of CMR and promising long-term survival. Clinical trial information: NCT01424982.

7014 Poster Discussion Session; Displayed in Poster Session (Board #214), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Updated results of a phase I/II study of inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-hyper-CVD) as frontline therapy for older patients with acute lymphoblastic leukemia. *First Author: Nicholas James Short, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Inotuzumab ozogamicin (InO) is an anti-CD22 antibody-toxin conjugate that is effective in patients (pts) with relapsed/refractory ALL. Given the poor tolerance of elderly pts to intensive chemotherapy, we evaluated the safety and efficacy of low-intensity chemotherapy (mini-hyper-CVD) plus InO as frontline treatment for older pts with newly diagnosed ALL. **Methods:** Pts ≥60 years of age with newly diagnosed Ph-negative pre-B ALL received mini-hyper-CVD (no anthracycline, dose reductions of cyclophosphamide, dexamethasone, MTX and Ara-C). Pts received InO 1.3-1.8 mg/m2 on day 3 of cycle 1 and 0.8-1.3 mg/m2 on day 3 of cycles 2-4. Rituximab (if CD20+) and prophylactic IT chemotherapy were given for the first 4 cycles. Responding pts received POMP maintenance for up to 3 years. **Results:** 47 pts have been treated, 4 of whom were in CR at enrollment. Median age was 68 years (range, 60-81) and median CD22 expression was 97% (range, 72-100%). Among 43 pts evaluable for response, 41 (95%) achieved CR or CRp (CR, n = 36, CRp, n = 5). 1 pt achieved CRi and 1 did not respond. MRD negativity by 6-color flow cytometry was achieved in 31/41 pts (76%) after 1 cycle and in 44/46 pts (96%) overall. Median times to platelet and ANC recovery in cycle 1 were 23 and 16 days, respectively, and for subsequent cycles were 22 and 17 days, respectively. Prolonged thrombocytopenia (> 6 weeks) occurred in 37 pts (79%). 4 pts (9%) developed VOD, 1 after allogeneic stem cell transplant (ASCT) and 3 unrelated to ASCT. Only 1 pt developed severe VOD. Among 46 responders, 6 (13%) relapsed, 3 (7%) underwent ASCT in CR1, 27 (59%) remain on treatment or have completed maintenance, and 10 (22%) died in CR/CRp. With a median follow-up of 24 months, the 3-year continued remission and OS rates were 72% and 54%, respectively. Compared to a historical cohort of older pts treated with hyper-CVAD ± rituximab (n = 79), mini-hyper-CVD + InO resulted in significantly higher 3-year OS (54% vs 31%; P = 0.007). **Conclusions:** Mini-hyper-CVD plus InO is safe and effective in elderly pts with newly diagnosed ALL and appears to improve outcomes compared to hyper-CVAD in this population. Clinical trial information: NCT01371630.

7015 Poster Discussion Session; Displayed in Poster Session (Board #215), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2 (mIDH2). *First Author: Amir Tahmasb Fathi, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

Background: Enasidenib (AG-221), an oral mIDH2 inhibitor, promotes myeloid differentiation of leukemic blasts. Enasidenib treatment (Tx) can result in IDH-inhibitor-associated differentiation syndrome (IDH-DS), with manifestations akin to retinoic acid syndrome seen during acute promyelocytic leukemia Tx. **Methods:** A phase 1 dose-escalation/expansion study (N = 239) (NCT01915498) included 109 pts with relapsed/refractory AML who received enasidenib 100 mg /day. An independent Differentiation Syndrome Review Committee (DSRC) was formed to review potential IDH-DS cases. The DSRC identified and agreed on signs and symptoms possibly characteristic of IDH-DS, including fever, lung infiltrates, pleural or pericardial effusions, rapid weight gain, edema, and azotemia. Of the 109 pts, the DSRC identified and retrospectively reviewed 27 cases (8 investigator reported IDH-DS cases and 19 cases suggestive of IDH-DS) to determine consistency with IDH-DS. **Results:** The DSRC found 13 of the 27 cases to be consistent with IDH-DS (11.9% of 109 pts). Median time to onset was 30 days (range 7-116). Manifestations of IDH-DS in > 2 pts were dyspnea (n = 10), pyrexia (9), lung infiltrates (8), pleural effusion (5), and kidney injury (3). IDH-DS was effectively managed with systemic corticosteroids in 12/13 cases. Leukocytosis accompanied 4 cases and hydroxyurea was used for cytoreduction. Enasidenib was interrupted for 9 pts (median 7 days) but dose reductions or discontinuation were not required. Six of 13 pts had clinical responses (2 complete remission [CR], 2 CR with incomplete hematologic recovery, 1 partial remission, 1 morphologic leukemia-free state), 6 had stable disease and 1 had progressive disease. **Conclusions:** Systemic corticosteroids, close hemodynamic management, and hydroxyurea (in the presence of leukocytosis) are effective management strategies, should be administered promptly when IDH-DS is suspected, and continued until improvement. Enasidenib interruption can be considered if initial intervention is unsuccessful. IDH-DS represents a novel clinical finding in m*IDH2* AML treated with enasidenib, and is likely due to its suggested mechanism of action, differentiation. Clinical trial information: NCT01915498.

7016 Poster Discussion Session; Displayed in Poster Session (Board #216), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Effect of cytarabine/anthracycline/crenolanib induction on minimal residual disease (MRD) in newly diagnosed FLT3 mutant AML. *First Author: Richard M. Stone, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Baseline characteristics such as age >60, WBC>100,000/μL and *FLT3/NPM1/DNMT3A*+ve are known to be associated with a poor prognosis in AML. Ivey et al. (NEJM 2016) reported that *FLT3-ITD+ve* patients (pts) who were MRD+ve after 2 cycles of induction chemotherapy were more likely to relapse as compared to those who became MRD-ve (92% vs 35%). Eradication of *FLT3+ve*clones may lead to reduced relapse rates. Crenolanib is a type I FLT3 TKI, which inhibits both FLT3-ITD and TKD mutations. We here report that a single induction cycle of cytarabine/anthracycline/crenolanib leads to MRD negativity by multiparameter flow cytometry (MPF), and low rate of early relapse in pts with newly diagnosed *FLT3+ve*AML. **Methods:** This abstract includes 29 consecutively treated, newly diagnosed, *FLT3+ve* AML pts, who achieved CR1 after one course of cytarabine/anthracycline/crenolanib. Pts received 7+3 induction with cytarabine 100 mg/m^2/d for 7d and either daunorubicin (<60 y: 90 mg/m^2; ≥60 y: 60 mg/m^2) or idarubicin 12 mg/m^2 for 3d. Crenolanib (100 mg TID) was started on day 9 until 72 h prior to next chemotherapy. **Results:** 29 pts (15M, 14F), median age 55y (10pts ≥60y) are included. MRD at time of count recovery was assessed by MPF in 25/29 pts. 20/25 (80%) became MRD–ve. With a median follow up of 7mth, 4/25 pts have relapsed (2/5 MRD+ve, 2/20 MRD-ve).Age ≥60 was a risk factor for MRD+ve and relapse. All 4 pts with WBC>100K as well as 5 pts with *FLT3/NPM1/DNMT3A+ve* AML became MRD-ve after one induction cycle and none have relapsed. **Conclusions:** These data suggest, in the context of an ongoing trial (NCT02283177), crenolanib in combination with standard induction is associated with a high rate of achieving an MRD negative state by MPF and a low rate of relapse in previously untreated adults with mutant *FLT3*. Longer follow-up and comparison of MRD data with similar pts treated with standard chemo alone will be necessary to reach more definitive conclusions. Clinical trial information: NCT02283177.

Sub-group	MRD-ve	Relapse free
Total	20/25 (80%)	21/25 (84%)
MRD-ve at CR1	20	18/20 (90%)
MRD+ve at CR1	5	3/5 (60%)
<60y	14/15 (93%)	14/15 (93%)
≥60y	6/10 (60%)	7/10 (70%)
WBC >100,000/μL	4/4 (100%)	4/4 (100%)
FLT3/NPM1/DNMT3A+ve	5/5 (100%)	5/5 (100%)

7017 Poster Discussion Session; Displayed in Poster Session (Board #217), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Outcomes with lower intensity therapy in TP53-mutated AML. *First Author: Tapan M. Kadia, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: *TP53* mutations confer an adverse prognosis in patients (pts) with AML treated with standard chemotherapy. A recent study reported high response rates using a 10-day regimen of decitabine (DAC10) in pts with *TP53*-mutated (*TP53*-MUT) AML. The question remains whether this benefit is unique to DAC10 or whether the same benefit among *TP53*-MUT AML applies to other low intensity therapy (Rx). **Methods:** We reviewed our own experience of pts treated with low intensity Rx from 2012 - 2016. Mutation testing was performed using a whole-exome sequencing panel. We reviewed the clinico-pathologic characteristics of these pts, and compared their outcomes based on the presence/absence of a *TP53*mutation and by the type of Rx they received. **Results:** There were 131 pts in our cohort of which 33 (25%) had *TP53*-MUT. Pt characteristics are outlined in Table 1A. All pts were treated with low intensity Rx and were divided into the following groups: DAC10 [n=34, 26%]; 5-day decitabine, or 7-day azacytidine (DAC5) [n=39, 30%]; or cladribine+low dose araC (CLAD/LDAC) [n=58, 44%]. Response rates and OS by Rx and *TP53*-MUT status are summarized in Table 1B. While there was no significant difference in response rates or OS by *TP53*-MUT status within any of the treatment approaches, there was a trend for inferior response rates and OS among pts with *TP53*-MUT who received either DAC-5 or CLAD/LDAC ; this was not seen in pts receiving DAC10. **Conclusions:** The presence of a *TP53*-MUT was associated with a nonsignificant trend towards inferior outcomes among pts receiving DAC5 or CLAD/LDAC, but not among those receiving DAC10. Comparing across groups, the CLAD/LDAC combination was associated with the longest OS, and DAC10 was associated with superior outcomes compared to DAC5, in *TP53*-MUT cohort.

Charac. Median (range) or N, [%]	*TP53* – Mut	*TP53* – WT
N	33	98
Age	75 (62-90)	72 (61-91)
WBC	3.2 (0.5-26.9)	3 (0.2-77.8)
Platelet	28 (4-321)	36 (2-772)
BM Blasts	39 (3-90)	41 (8-88)
Complex karyotype	25 [76]	10 [10]
Diploid, -Y	4 [12]	42 [43]
-5/5q- and/or -7/7q-	23 [70]	24 [24]
Misc, Other Cyto	8 [30]	32 [33]

	N	TP53	CR	CRp	CR/CRp (%)	Median OS	1yr-OS %
DAC5/AZA	9	MUT	1	1	22	2.1	10
	25	WT	10	1	44	5.5	27
DAC 10	13	MUT	4	1	38	7.3	18
	26	WT	7	1	31	7.9	29
CLAD/LDAC	11	MUT	4	0	36	9	42
	47	WT	31	2	70	16.4	71

7018 Poster Discussion Session; Displayed in Poster Session (Board #218), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Achievement of a negative minimal residual disease state after hypomethylating agent therapy in older patients with AML to reduce risk of relapse. *First Author: Prajwal Boddu, MD Anderson Cancer Center, Houston, TX*

Background: Persistence of minimal residual disease (MRD) post therapy is a powerful predictor of outcome in patients with AML treated with traditional cytarabine and anthracycline based regimens. The clinical relevance of MRD in the context of hypomethylating agents has not been evaluated extensively. **Methods:** Among 194 patients with AML treated with single agent azacytidine, decitabine, or gaudecitabine, 116 (median age 76, range 60 - 92) had MRD analysis performed on bone marrow specimens obtained at time of assessment of response or thereafter; among them 69 (59%) achieved either morphologic complete remission (CR) or CR with incomplete recovery of platelets (CRp) or counts (CRi), and 61 (53%) had evaluable MRD data; MRD was assessed using an 8-color flow panel, with a detection sensitivity of 0.01%. **Results:** Median cycles to achieving response was 2 (range, 1-6). Sixty one patients had evaluable MRD data at the time of response, of whom 19 (28%) became MRD negative (-). This was associated with a reduced cumulative risk of relapse (p = 0.012) but did not translate to an improved relapse-free survival (RFS; p = 0.17) or overall survival (OS; p = 0.79) due to high frequency of non-relapse deaths (attributable to comorbidities and infections) in the MRD- group. Patients who achieved a MRD- state at the time of achieving response had a higher mortality [5/8 (62%)] when compared with those who achieved a MRD- state in subsequent cycles [1/13 (7.6%); p = 0.01], resulting in an inferior OS (6.2 months (mo) vs 20 mo, p = 0.012). Similarly, achieving negative MRD at CR and at any time up to 3 months post response was not associated with improved RFS or OS despite a lower cumulative risk of relapse (p = 0.045). There was no impact of MRD, on OS, whether the MRD- state was achieved after 1st, 3rd or 6thcycle of therapy. Association between depth of MRD response at time of remission and RFS was borderline significant (p = 0.08). On multivariate analysis, response (CR vs CRi/CRp), but not a negative MRD, was predictive for RFS or OS. **Conclusions:** In this cohort of older AML patients treated with hypomethylating agents, achieving a MRD- state was associated with a reduced risk of relapse but not improved RFS or OS.

7019 Poster Discussion Session; Displayed in Poster Session (Board #219), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

A Bayesian randomized phase II study of guadecitabine (SGI-110) based regimens comparing guadecitabine 5 days (SGI5), 10 days (SGI10), 5 days + idarubicin (SGI5 + Ida), 5 days + cladribine (SGI5 + Clad), in untreated patients ≥ 70 years with acute myeloid leukemia (AML). *First Author: Kiran Naqvi, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Guadecitabine is a next generation hypomethylating dinucleotide of decitabine and deoxyguanosine resistant to degradation by cytidine deaminase. This allows prolonged exposure of leukemia cells to its active metabolite, decitabine. We aimed to compare the efficacy and safety profile of guadecitabine in untreated ≥ 70 years AML patients. **Methods:** Untreated patients ≥ 70 years with AML were randomized in a phase 2 Bayesian design in one of the 4 arms: guadecitabine 60mg/m^2/daily x 5 (SGI5), guadecitabine 60mg/m^2/daily x 10 (SGI10), SGI5 + Ida (6mg/m^2/daily x 2), or SGI5 + Clad (3mg/m^2/daily x 5). The Bayesian design evaluated response and toxicities simultaneously. Primary objective was complete remission (CR) rate and remission duration. Survival was estimated using the Kaplan-Meier method. **Results:** Between June 2014 and Nov 2016, we treated 34 patients: 8 in SGI5; 9 in SGI10; 8 in SGI5 + Ida and 9 in SGI5 + Clad. Median age was 75 years. 38% had complex karyotype. Median follow-up was 8.3 months. Overall response rate (ORR= CR + CRi) was 53%, shown in the table below. Median remission duration was 7.4 months. 4 week mortality was 3%. Median survival is 13.1 months. A trend for superior survival was observed with SGI5 + Ida (median survival not reached; p=0.22). Common G3/4 toxicity included febrile neutropenia (48%), thrombocytopenia (26%), leukopenia (22%) and anemia (11%). **Conclusions:** Guadecitabine is clinically active and safe as single agent and in combination in elderly patients with untreated AML. A separate previously reported multicenter study showed no difference between SGI5 vs SGI10 in 103 treatment naïve elderly AML patients (Kantarjian et al. Blood 2015 126:458). CR and ORR were lower with SGI5 + Clad. Based on these findings, the study continues now comparing SGI5 vs SGI5 + Ida.

Response no. (%)	SGI5 (n=8)	SGI 10 (n=9)	SGI5+Clad (n=9)	SGI5+Ida (n=8)	Total (n=34)
CR	1 (13)	5 (56)	0	6 (75)	12 (35)
CRi	2 (25)	1 (11)	1 (11)	2 (25)	6 (18)
PR	0	0	1 (11)	0	1 (3)
Early death (4 weeks)	0	1 (11)	0	0	1 (3)
CR+CRi	3 (38)	6 (67)	1 (11)	8 (100)	18 (53)

7020 Poster Discussion Session; Displayed in Poster Session (Board #220), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Updated results from phase II study of guadecitabine for patients with higher risk myelodysplastic syndromes or chronic myelomonocytic leukemia. *First Author: Guillermo Montalban-Bravo, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Improving the current response and survival outcomes of patients with higher risk MDS and CMML is fundamental. Guadecitabine is a next generation hypomethylating agent with increased length of exposure compared to decitabine and clinical activity in patients with MDS. **Methods:** Single arm phase 2 clinical trial of guadecitabine at a dose of 60mg/m^2 sc daily for 5 days (days 1-5) every 28 days for patients with newly diagnosed MDS or CMML classified as Intermediate-2 or High risk by IPSS. Primary endpoint is complete response (CR). Responses were evaluated following the revised 2006 International Working Group criteria. Sequencing data was obtained at the time of pre-treatment evaluation by the use of a 28-gene next generation sequencing platform. Study included stopping rules for response and toxicity. Overall survival (OS) was censored at the time of transplant. **Results:** A total of 53 patients have been enrolled: 50 (94%) are evaluable for toxicity and 44 (83%) for response. Median age is 67 years (49-87). A total of 43 (86%) patients have MDS and 7 (14%) have CMML. A total of 21 (42%) have complex karyotype. Sequencing data was available in 48 (96%) patients with *TP53* mutations being the most frequently detected in 36% patients. After a median of 6 treatment cycles (1-20), the ORR is 71% including 32% CR. Median best response occurred by 3 cycles (1-6). Seven (21%) out of 33 evaluable patients achieved a complete cytogenetic response. Ten (20%) subjects proceed to allogeneic stem cell transplantation. Median follow up was 6.3 months (0-23). Median OS is 14.1 months (CI 13.3-14.9 months) and median EFS is 8.4 months (CI 5.6-11.2 months). Forty-five (90%) patients experienced at least one AE during therapy. Most common grade 1-2 AEs included fatigue (66%), nausea (38%) and dyspnea (26%). Dose reductions due to cytopenias were required in 17 (34%) patients. Early 8-week mortality occurred in 3 (6%) patients. **Conclusions:** Guadecitabine is well-tolerated and active in patients with higher-risk MDS and CMML even in the presence of adverse biological features such as high frequency of complex karyotype, therapy related disease and *TP53* mutations. Clinical trial information: NCT02131597.

7021 Poster Session (Board #221), Mon, 8:00 AM-11:30 AM

Creating a synthetic control arm from previous clinical trials: Application to establishing early end points as indicators of overall survival in acute myeloid leukemia (AML). *First Author: Donald A. Berry, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Clinical trials of experimental drugs require controls. Concurrently randomized controls are the gold standard for judging drug effect. Historical controls are not ideal but are much more efficient and economical. Historical controls derived from a single clinical trial have the biases of that trial. Using many trials with comparable end points and eligibility minimizes such bias. Medidata's archive contains >3000 trials with clinical data rights for deidentified aggregated analyses. We used this resource to develop a synthetic control arm (SCA) for a particular phase I/II single-arm trial in AML. We demonstrate the utility of this approach by addressing a different but equally important issue: establishing early end points as predictors of long term clinical outcomes. **Methods:** We built an SCA from 7 relapsed/refractory AML trials completed in last 5 yrs. They had similar eligibility criteria as a particular phase I/II trial for an investigational agent. We selected subjects for the SCA who had baseline covariates matching the subjects in the tri.al. Data cleaning and standardization ensured consistency of data fields. The primary outcomes were CR (complete remission) and CRi (CR without hematologic recovery) at 56 days, and overall survival (OS) subsequent to 56 days. Non-CR/non-CRi deaths before 56 days were set to OS=0. We used a landmark analysis to correlate CR and CRi with OS, calculating the hazard ratio (HR) of OS of CR and CRi vs its comparison group. **Results:** The SCA included 340 subjects (median age 63 yrs, 55% male, 77% White Non-Hispanic, 28% ECOG 0). Results are in this table. **Conclusions:** The Medidata trial archive is a resource for creating SCAs. The example SCA we created identified well-defined subjects for whom a CR or CRi is associated with longer OS. Investigations of SCAs for other drugs could aid in addressing the types of subjects and drug categories for which CR or CR/CRi predict longer OS. Such information can help build more efficient and more informative adaptive clinical trials.

	N	Median OS (wks)	Com-parison	HR	p value
CR	35	64	CRi	0.22	<0.001
CRi	51	23	Other	0.44	<0.001
CR/CRi	86	30	Other	0.28	<0.001
Other	254	11	–	–	–

7022 Poster Session (Board #222), Mon, 8:00 AM-11:30 AM

Molecular genetic testing patterns for patients with newly diagnosed acute myeloid leukemia (AML) enrolled in the CONNECT MDS/AML disease registry. *First Author: Daniel Aaron Pollyea, University of Colorado Comprehensive Cancer Center, Aurora, CO*

Background: Recurrent mutations in AML-associated genes have prognostic value and may help guide treatment decisions. Molecular genetic testing patterns for AML in clinical practice are largely unknown. Previously the CONNECT MDS/AML Disease Registry (George et al. ASH 2016. Abstract 3548) showed suboptimal adherence to WHO 2008 recommendations for AML in a cohort of newly diagnosed (ND) AML patients (pts) in clinical practice. Here we report a detailed analysis of patterns of molecular genetic testing in pts with ND AML in community and academic settings. **Methods:** The CONNECT MDS/AML Disease Registry (NCT01688011) is a US prospective, observational cohort study of pts with ND AML (≥55 years) or MDS. Enrollment is ongoing. All clinical decisions are made by study clinicians. The current analysis evaluated the percentage of pts with AML with molecular genetic testing recommended by NCCN guidelines (*NPM1*, *FLT3-ITD*, *CEBPA*, *IDH1*, *IDH2*, *DNMT3A*, and *KIT*). Chi-square tests evaluated effects of several variables on likelihood of molecular genetic testing. **Results:** Between 12 Dec 2013, and 8 Dec 2016 (data cutoff), 259 AML pts were enrolled at 86 sites. Molecular genetic testing was reported in 67% (173/259) of pts. Likelihood of testing varied, respectively, for academic vs community sites (76% [70/92] vs 62% [103/167], P= .018), normal vs abnormal karyotype (77% [79/103] vs 59% [79/133], P= .006), age < 65 vs ≥65 (83% [65/78] vs 60% [108/181], P= .0003), and Medicare vs other insurance (61% [83/137] vs 74% [90/122], P= .025). In pts with molecular genetic testing (n = 173), the mutations tested varied substantially. All of the NCCN-recommended molecular genetic tests were reported in 9% (15/173) of pts, including 8% (6/79) of those with normal karyotype. Of the 7 NCCN-recommended tests, *NPM1* (77%) and *FLT3-ITD* (76%) were most often reported and *DNMT3A* least often (16%). **Conclusions:** Early data from the CONNECT MDS/AML Disease Registry reveal that despite molecular testing reported in 67% of ND AML pts, a majority do not receive guideline-recommended testing. This prospective registry is uniquely positioned to capture changes in testing patterns as guidelines are established.

7023 Poster Session (Board #223), Mon, 8:00 AM-11:30 AM

Genomic landscape of adult mixed phenotype acute leukemia (MPAL). *First Author: Kiyomi Morita, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MPAL is a rare subgroup of acute leukemia characterized by both myeloid and lymphoid phenotypes. Genetic basis of MPAL is not well understood. **Methods:** We studied 31 patients (pts) with MPAL (median age 53) that met 2008 WHO criteria. Bone marrow samples were studied by targeted capture sequencing of 295 genes (median 393x), RNA sequencing, and Infinium methylation EPIC array (Illumina). Mutational landscape was compared to 194 AML, 71 B-ALL, and 6 T-ALL cases. Promoter methylation pattern was compared to the data from 194 AML (TCGA), 505 B-ALL and 101 T-ALL cases (Nordlund et al. Genome Biology. 2013). **Results:** Eighteen (58%) pts had myeloid-T and 13 (42%) had myeloid-B phenotype. Four pts had t(9;22), 1 had 11q23 rarrangement, and 8 had complex karyotype. MPAL had similar number of mutations with AML but had higher number of mutations than B-ALL or T-ALL. Both AML-type and ALL-type mutations were detected in MPAL, supporting the mixed phenotypic features. However, *NPM1*, *CEBPA* and *GATA2* mutations were specific to AML and were not found in MPAL. Myeloid-T and myeloid-B showed distinct patterns of mutations, in which *DNMT3A*, *IDH2, NOTCH1, IL7R,* and *FBXW7* mutations were enriched in myeloid-T whereas *RUNX1* mutations were enriched in myeloid-B. Myeloid-T and myeloid-B also showed distinct patterns of promoter methylation. Overall, myeloid-T had more hypermethylated CpG loci than myeloid-B. Genes that have essential role in T-cell receptor (TCR) pathway (*CD3D*, *CD7*, *CD247*, *LCK*, *PRKCQ, CCR9, and TCL1A*) were differentially methylated and differentially expressed between myeloid-T and myeloid-B. RNA sequencing revealed several known translocations such as, *NSD1-NUP98*, and *KMT2A-MLLT4,* in addition to the novel fusion proteins such as *FOXP1-DNAJC15*, *RUNX1-NAP1L1*, and *BCL2-TM9SF3*. Unbiased hierarchical clustering of MPAL, AML, B-ALL and T-ALL by promoter methylation revealed that myeloid-T had consistent similarity with T-ALL, while myeloid-B showed random similarity with either B-ALL or AML. **Conclusions:** MPAL is genetically heterogeneous and myeloid-T and myeloid-B shows distinct patterns of mutations, methylation and gene expressions. Therapy for MPAL may need to be tailored based on the genetic profiles.

7024 Poster Session (Board #224), Mon, 8:00 AM-11:30 AM

Baseline and early post-treatment clinical and laboratory factors associated with severe neurotoxicity following 19-28z CAR T cells in adult patients with relapsed B-ALL. *First Author: Jae Hong Park, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: CD19-specific chimeric antigen receptor (CAR) modified T cells produce high anti-tumor activity in relapsed or refractory (R/R) ALL, but can be associated with cytokine release syndrome (CRS) and neurotoxicity (NTX). Herein, we report baseline and post-treatment clinical and laboratory factors associated with severe NTX (≥Grade 3) in our phase I clinical trial of CD19-specific 19-28z CAR T cells for adult patients (pts) with R/R B-ALL (NCT01044069). **Methods:** 51 adult pts with R/R B-ALL were treated with 19-28z CAR T cells following conditioning chemotherapy at MSKCC. In order to identify clinical and serum biomarkers associated with severe NTX (sNTX), we examined demographic, treatment, and clinical blood parameters as well as in vivo CAR T expansion and serum cytokines, and performed univariate and multivariate analysis. **Results:** In this cohort of ALL pts, 20, 8, 2, 18 and 3 pts experienced Gr 0, 1, 2, 3, and 4 NTX, respectively. No pt developed grade 5 NTX. Disease burden (≥50% blasts) at the time of T cell infusion ($p = 0.0045$) and post-treatment ≥Gr3 CRS ($p = 0.0010$) were significantly associated with sNTX, but we found no association with age, weight, T cell dose, choice of conditioning chemotherapy (Flu/Cy s. Cy), and prior lines of treatment. Among the clinical and blood parameters, fever, low PLT, high ferritin and MCHC as well as elevated GM-CSF, IFNγ, IL-15, IL-5, IL-10, IL-2 at day 3 of T cell infusion at day 3 of T cell infusion were significantly associated with sNTX (all $p < 0.01$). While some of these cytokines were also elevated in severe CRS cases, IL-5 and IL-2 at day 3 were unique to sNTX. Furthermore, in vivo peak CAR T expansion at day 7 ($p = 0.0001$) significantly correlated with sNTX ($p < 0.01$). Lastly, multivariate analysis revealed baseline PLT < 60 or MCHC > 33.2% and morphologic disease (> 5% blasts) has 95% sensitivity and 70% specificity of identifying sNTX pts. **Conclusions:** These data provide a characterization of early clinical and serum biomarkers of sNTX in adult pts receiving 19-28z CAR T cells and should help identify appropriate pts for early intervention strategy to mitigate NTX. Clinical trial information: NCT01044069.

7025 Poster Session (Board #225), Mon, 8:00 AM-11:30 AM

Inotuzumab ozogamicin (IO) combined with mini-hyper-CVD as salvage therapy for patients (pts) with R/R acute lymphoblastic leukemia (ALL). *First Author: Rita Assi, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Outcome of pts with R/R ALL is poor. IO, a CD22 monoclonal antibody bound to a toxin, calicheamicin, has single-agent activity in R/R ALL with response rate of 80% and median survival of 7.7 months. Adding IO to low-intensity chemotherapy might further improve clinical outcomes. **Methods:** Pts ≥18 years with R/R ALL were eligible. Chemotherapy was of lower intensity than standard hyper-CVAD and referred to as mini-hyper-CVD (cyclophosphamide and dexamethasone at 50% dose reduction (DR), no anthracycline, methotrexate at 75% DR, cytarabine at 0.5 g/m^2 x 4 doses). Rituximab (if CD20+ blasts) and intrathecal chemotherapy were given for first 4 courses. IO was given on day 3 of each of the first 4 courses at a dose of 1.8 mg/m2 for cycle 1 then 1.3 mg/m2 for subsequent cycles. After the occurrence of veno-occlusive disease (VOD), IO was modified to 1.3 mg/m2 for cycle 1 followed by 1.0 mg/m2 for subsequent cycles. **Results:** Sixty pts with a median age of 35 years (range 18-87) were treated. Overall, 47 pts (80%) responded, 32 of them (54%) achieving complete response. The overall minimal residual disease negativity rate among responders was 82%. Grade 3-4 toxicities included prolonged thrombocytopenia (79%), infections during induction and consolidations (52%, and 73% respectively), and hyperbilirubinemia (13%). VOD of any grade occurred in 9 patients (15%). At a median follow-up of 19 months, the median relapse-free survival (RFS) and overall survival (OS) were 9 and 11 months, respectively. The 2-year RFS and OS rates were 33% and 38%. The 2-year OS rates for patients treated in salvage (S)1, S2, and S3 and beyond were 53%, 0%, and 34%, respectively ($p = 0.005$). When compared to IO monotherapy in a similar pts population, a significant improvement in OS was observed (11 and 6 months, respectively; $p = 0.003$). **Conclusions:** The combination of IO with low-intensity mini-hyper-CVD chemotherapy is effective in pts with R/R ALL. Results are encouraging and appear superior to those obtained with IO alone, particularly in pts treated in S1. The risk of VOD should be considered carefully for transplant candidates and pts with previous liver damage. Lower dose of weekly schedules of IO are being explored Clinical trial information: NCT01371630.

7026 Poster Session (Board #226), Mon, 8:00 AM-11:30 AM

Phase IB/II study of nivolumab with azacytidine (AZA) in patients (pts) with relapsed AML. *First Author: Naval Guastad Daver, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Blocking PD-1/PD-L1 pathways enhances anti-leukemia responses in murine AML (Zhang et al, Blood 2009). PD-1 positive CD8 T-cells are increased in bone marrow (BM) of pts with AML (Daver et al, ASH 2016). AZA up-regulates PD-1 in AML (Yang et al., Leukemia 2013). **Methods:** Pts were eligible if they had AML and failed prior therapy, had adequate performance status (ECOG ≤ 2), and organ function. AZA 75mg/m^{2}Days 1-7 with nivolumab 3mg/kg on Day 1 and 14 was established as the recommended phase II dose. Courses were repeated every 4-5 weeks indefinitely. Responses were evaluated at the end of 3 courses. **Results:** 53 pts with med age 68 years (range, 44 – 90), secondary AML (43%), poor risk cytogenetics (43%), med prior regimens 2 (range, 1-7) have been enrolled. Common mutations included *DNMT3A* (n = 11), *TP53* (n = 11), *TET2* (N = 8), *CEBPA* (n = 8), *ASXL1* (n = 8). All 53 pts are evaluable for response: 11 (21%) achieved CR/CRi and 7 (14%) had hematologic improvement (HI) for an overall response rate of 35%. Additionally, 14 (26%) had ≥50% BM blast reduction, 3 (6%) had stable disease > 6 months, and 12 (23%) had progression. The CR/CRi have been durable with 9 of 11 (82%) pts with CR/CRi alive at 1 year, after censoring for SCT. Med survival for the 53 evaluable pts was 5.7 months (range, 0.9 – 16.2) and in the 27 salvage 1 pts was 9.3 months (range, 1.6 – 16.2). These compare favorably to historical survival with AZA-based salvage protocols at MDACC. Grade 3/4 and Grade 2 immune toxicities were observed in 7 (14%) and 6 (12%) pts, respectively. These responded rapidly to steroids and 12 of 13 pts were successfully rechallenged with nivolumab. Multicolor flow-cytometry data were available on pretherapy, end of cycle 1, and end of cycle 2 BM aspirates in 9 CR/CRi and 22 non-responders. Pts who achieved CR/CRi had higher pre-therapy total CD3 ($P = 0.02$) and higher CD8$^+$ T-cells ($P = 0.07$) infiltrate in the BM. Responders demonstrated progressive increase in BM CD8$^+$ and CD4$^+$ infiltrate. Both responders and non-responders had increase in CTLA4$^+$ CD8$^+$ cells on therapy. **Conclusions:** Full dose AZA and nivolumab are tolerable and may produce durable responses in relapsed AML. Up-regulation of CTLA4 may be a mechanism of resistance to PD1 based therapies in AML. Clinical trial information: NCT02397720.

7027 Poster Session (Board #227), Mon, 8:00 AM-11:30 AM

Dose escalation results of a phase 1b study of the MDM2 inhibitor AMG 232 with or without trametinib in patients (Pts) with relapsed/refractory (r/r) acute myeloid leukemia (AML). *First Author: Harry Paul Erba, University of Alabama at Birmingham, Birmingham, AL*

Background: The ubiquitin ligase MDM2 inhibits the tumor suppressor p53. In preclinical AML models, MDM2 inhibitors have antitumor activity as monotherapy that is synergistic when combined with MEK inhibitors. This open-label phase 1b study assessed the maximum tolerated dose (MTD), pharmacokinetics (PK), and preliminary antitumor activity of the investigational oral, selective MDM2 inhibitor AMG 232 as monotherapy or combined with the MEK kinase inhibitor trametinib in pts with r/r AML. **Methods:** Pts with r/r AML received AMG 232 for 7 days every 2 weeks (7 days on/7 days off) at 60, 120, 240, 480, and 960 mg PO QD as monotherapy (Arm 1) or combined with trametinib 2 mg PO QD (Arm 2). Primary endpoints were the incidence of adverse events (AEs), dose-limiting toxicities (DLTs), and PK. Additional endpoints included best response (revised IWG) and serum MIC-1 level (increased MIC-1 suggests p53 activation). p53 target gene (*P21*, *BAX*, and *PUMA*) expression in bone marrow was assessed by microarray. **Results:** In total, 35 pts (Arm 1, n = 26; Arm 2, n = 9; median age, 68 y; range, 26–86) were treated. Arm 1 enrolled AMG 232 at 60 mg (n = 4), 90 mg (n = 4), 180 mg (n = 5), 240 mg (n = 3), and 360 (n = 10). Twenty-two (85%) pts in Arm 1 had treatment-related AEs; the most common were nausea (n = 14), diarrhea (n = 14), and vomiting (n = 6). No DLTs occurred; one pt is still on treatment. The MTD was determined as 360 mg based on tolerance of gastrointestinal toxicity. Arm 2 enrollment is ongoing at a fixed AMG 232 dose of 60 mg plus trametinib (n = 9). AMG 232 plasma exposure increased with dose escalation; PK was unaffected by trametinib. Trametinib PK was as expected. Increases from baseline (BL) to day 10 in serum MIC-1 were dose dependent. Evidence of increased *P21*, *BAX*, and *PUMA* expression (BL to day 7 or 8) was seen (n = 3). One pt (Arm 2) had complete remission (CR); three pts (Arm 1) achieved CRi/MLFS. Median response duration was 66 days [range, 21–377+]). **Conclusions:** AMG 232 monotherapy was tolerable in pts with r/r AML at doses up to 360 mg on a 7 days on/7 days off schedule with expected PK, on-target biological effects, and early evidence of antileukemia activity. Clinical trial information: NCT02016729.

7028 Poster Session (Board #228), Mon, 8:00 AM-11:30 AM

Efficacy of anti-CD19 chimeric antigen receptor modified T(CAR-T) cell therapy in Chinese patients with relapsed/refractory acute lymphocytic leukemia in a multicenter trial. *First Author: Lei Xiao, Innovative Cellular Therapeutics Co., LTD., Shanghai, China*

Background: r/r B-ALL was reported as the most-threatening disease because of the low disease free survival even treatment with allogeneic hematopoietic stem cell transplantation. For overcoming conventional therapies limitation, autologous CD19CAR-T was performed in our clinical trials to induce remission in patients with r/r disease. 30 patients (from 7 clinical centers, in China) as volunteers with r/r B-ALL were treated by autologous CD19 CAR-T. **Methods:** 5 juveniles and 25 adults with r/r ALL received autologous CD19 targeted CAR-T, the doses between 1.03×10^6 CAR-T cells/kg and 10.09×10^6CAR-T cells/kg. These 30 cases(from 7 clinical centers, in China) were treated with CAR-T cells from May. 8 2015 to January. 4 2017 (Table1). Patients were monitored for a response. Highly standardized CAR T cell preparation protocol and manageable CRS in most were kept for no significant difference in 7 clinical centers. **Results:** After treated with CAR-T, a total of 30 cases (5 juveniles and 25 adults coming from 7 clinical centers, in China) with r/r B-ALL were all detected the CAR-T cells proliferated in the blood and bone marrow. The results showed that complete remission (CR) is 26/30(86.67%) between day7-14 after CD19 CART cell infusion, and 25/30(83.33%) cases arrived at MRD negative. There is about 1/3 of the total cases receiving a repeat infusions following initial ones since these patients have no safety concerns. Additionaly, the severe Cytokine release syndrome (CRS) was 8/30(26.67%) of cases and 24/30(80%) of cases was seen CRS. The anti-IL6R agent tocilizumab and Methylprednisolone were effective confrontation Severe CRS. **Conclusions:** This is the first multicentre report to our knowledge of successful treatment of r/r ALL with anti-CD19 CAR T cells in China. Even r/r B-ALL with high-burden leukemia patients also was effective and associated with a high remission rate after infused autologous CD19 CAR-T).(NCT 02813837).

7029 Poster Session (Board #229), Mon, 8:00 AM-11:30 AM

Sorafenib plus 5-azacytidine (AZA) in older untreated *FLT3*-ITD mutated AML. *First Author: Maro Ohanian, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Sorafenib plus 5-azacytidine (AZA) is observed to be safe and effective in relapsed / refractory *FLT3*-ITD mutated acute myeloid leukemia (AML) patients (pts). **Hypothesis:** Combining sorafenib with AZA is safe and effective in older untreated *FLT3*-ITD mutated AML pts. **Methods:** Eligibility included: untreated *FLT3*-ITD mutated AML (≥10% mutation burden), age ≥60 yrs, adequate organ function, and ECOG performance status ≤ 2. The regimen was: AZA 75 mg/m^{2}daily x 7 days and sorafenib 400 mg twice daily for 28 days. **Results:** 26 pts with untreated AML [median age 73 (61-86)] were enrolled: 16 (62%) pts had normal karyotype, 2 (8%) complex karyotype, 4 (15%) other miscellaneous abnormalities, and 4 (15%) with insufficient metaphases. Prior to the initiation of treatment, *FLT3*-ITD was detected in all pts with a median allelic ratio of 0.3735 (0.009-0.885). The overall response rate (ORR) in 25 evaluable pts was (76%) [7 (28%) with CR, 10 (40%) CRi/CRp, and 2 (8%) PR]. Pts underwent a median of 3 (1-35) treatment cycles. The median number of cycles to response was 2 (1-4), and the median time to achieve response, 1.77 months (mos) (0.689-4.271 mos). The median duration of CR/CRp/CRi is 14.5 mos (1.18—28.74). Three (18%) responding pts (CR, CRp, CRi) have proceeded to allogeneic stem cell transplant. With a median follow-up of 6.8 mos (0.2-18.8), 6 pts are alive, 3 in remission (CR/CRP/CRi). The median overall survival (OS) for the entire group is 8.3 mos; 9.2 mos in 17 responders. Evaluable pts treated with AZA + sorafenib (n = 25) were compared to a matched cohort of historical FLT3-ITD mutated pts > 60 yrs, but treated with hypomethylator-based (HMA) therapy without sorafenib (n = 20); the respective ORR (CR, CRp, CRi, PR) (76% vs. 70%, p = 0.653) and median OS (8.3 and 9.4 mos, p = 0.69) were similar. The remission duration for the responding pts treated with AZA+sorafenib was significantly longer (14.5 mos) than those on other HMA regimens without sorafenib (3.8 mos) (p = 0.01). Adverse events possibly attributable to the regimen included: grade (Gr) 1/2 nausea (n = 3), Gr 1/2 diarrhea (n = 2), Gr 1 dyspnea (n = 1), and Gr 1 breast pain (n = 1). **Conclusions:** The combination of AZA and Sorafenib is both well tolerated and effective in older untreated *FLT3*-ITD mutated AML. Clinical trial information: NCT02196857;NCT01254890.

7030 Poster Session (Board #230), Mon, 8:00 AM-11:30 AM

Clinical observations of AML expressing mutant RUNX1 and pre-clinical studies of RUNX1-targeted novel therapy of AML. *First Author: Courtney Denton Dinardo, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Runt-related transcription factor 1 (*RUNX1*) is critically involved in normal and malignant hematopoiesis. Somatic mutations in *RUNX1* occur in ~10% of AML, especially in older patients with history of radiation or antecedent hematologic disorder. Presence of mRUNX1 is reported to confer relative resistance to therapy and poorer prognosis in AML, and there are no mRUNX1-targeted or specific therapies available. **Methods:** We retrospectively analyzed outcomes of 94 *mRUNX1* and 444 wild-type *RUNX1* AML patients treated at our institution from 9/2013 to 12/2016. We also determined the pre-clinical efficacy of a targeted therapy against cultured and primary AML cells expressing mRUNX1. **Results:** 67% of mRUNX1 patients were > 65 years of age. Co-occurring mutations with mRUNX1 were *ASXL1* (33%), *N/KRAS* (20%), *FLT3* (20%), *IDH2* (18%), *IDH1* (13%) and *TET2* (10%). In patients > 65 years treated with hypomethylating agent-based therapy, the presence or absence of *mRUNX1* did not impact response rate (42% vs 46% CR/CRp, p = 0.67), median event-free survival (3.4 vs 4.7 mo, p = 0.82) or overall survival (11.5 vs 9.3 mo, p = 0.97). In mRUNX1 expressing AML OCI-AML5 and MonoMac1 cells, knockdown of RUNX1 by shRNA repressed its targets, e.g., MYC and PU.1, inhibited growth and induced apoptosis. Ex vivo knockdown of RUNX1 abrogated in vivo leukemia initiation by OCI-AML5 cells. After engraftment, inducible shRNA-mediated in vivo knockdown of RUNX1 restored survival of immune-depleted NSG mice engrafted with OCI-AML5 cells. RUNX1 transcription is driven by a super enhancer occupied by the bromodomain extraterminal protein (BETP), BRD4. Accordingly, BRD4 knockdown by shRNA or treatment with the BRD4-inhibitor OTX015 depleted RUNX1 and its targets, and induced apoptosis of AML cells. Treatment of OCI-AML5 cell-engrafted NSG mice with OTX015 (50 mg/Kg/day X 5, for 3 wks) reduced AML burden and improved survival ($p < 0.01$). Co-treatment with the BETi and BCL2 inhibitor venetoclax or CDK4/6 antagonist palbociclib or decitabine synergistically induced apoptosis of OCI-AML5 and primary AML blasts. **Conclusions:** These findings highlight a novel, promising, BETP antagonist-based therapy of AML expressing mtRUNX1.

7031 Poster Session (Board #231), Mon, 8:00 AM-11:30 AM

Outcomes in AML patients age ≥70: A very large single institution experience. *First Author: Jeffrey E. Lancet, Moffitt Cancer Center, Tampa, FL*

Background: AML in older adults is associated with poor outcomes. The Moffitt Cancer Center AML Database was used to evaluate a very large cohort of patients (pts) age ≥ 70 with untreated AML to identify key prognostic variables affecting outcome. **Methods:** Overall survival (OS): Kaplan-Meier method and was compared across groups using the log-rank test. Association between OS and predictors: Cox regression model. Impact of participation of initial clinical trial on OS: Propensity score with stratified log-rank test. A predictive model for 12 month OS was developed using multiple logistic regression with backward elimination method. **Results:** Nine hundred eighty (980) pts were identified. M/F(%): 66/34. Median age at diagnosis: 75.7 years (range 70 – 95.7 years). De novo/secondary (%): 43/57. Fifty two % of pts had prior hematologic disease (AHD). Baseline karyotype at AML diagnosis: adverse in 31% and non-adverse in 58%. Baseline ECOG PS: 0-1 in 79%; ≥2 in 19%. Median OS was 7.1 months (95% CI 6.4 – 7.9) for the entire cohort. In the univariable model, factors associated with inferior survival included: secondary AML (sAML) status, poor-risk karyotype, ECOG ≥2, non HMA therapy (including clinical trials), Charlson Comorbidity Index ≥3, older age, increased WBC, decreased platelets (plts), and decreased hemoglobin (hgb). Independent negative predictors for OS in the multivariate model included sAML, poor-risk karyotype, ECOG ≥2, non-HMA initial therapy, older age, increased WBC, decreased plts, and decreased hgb. Propensity score matching revealed no significant difference in OS amongst pts receiving initial treatment on a clinical trial (median 7.8 months, 95% CI 6.4 – 10.4) vs not (median 7.0 months, 95% CI 6 –7.9). A model to predict OS at 12 month was developed in a subset of 446 pts. Independent predictive variables included karyotype, ECOG PS, AML type (de novo vs sAML), age, and WBC, with AUC of 0.78, indicating strong discriminatory capacity. **Conclusions:** In this largest reported cohort of AML pts age ≥ 70, prognostic modeling identifies differences in longer-term survival with conventional therapies, discriminating the highest risk subsets. Decision modeling to further assist choice of optimal therapies for these pts is in progress.

7032 Poster Session (Board #232), Mon, 8:00 AM-11:30 AM

Exposure-adjusted adverse events (AEs) comparing blinatumomab to standard of care (SOC) chemotherapy in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) from a randomized phase III study. *First Author: Anthony Selwyn Stein, Department of Hematology and Hematopietic Cell Transplantation, City of Hope, Duarte, CA*

Background: Blinatumomab (blin), a bispecific T-cell engaging antibody construct, has shown improved overall survival vs SOC in pts with r/r ALL in a randomized phase 3 study (*Haematologica* 2016;101:S129). To better evaluate safety, we compared AEs of blin vs SOC after adjusting for varying treatment exposure times. **Methods:** Adults $\geq$ 18 yrs with r/r ALL (refractory, 1st relapse $<$ 1 yr, $\geq$ 2 relapses or relapse after transplant) were randomized to receive blin or SOC (1 of 4 predefined regimens). Blin was dosed by continuous infusion (4 wks on/2 wks off) for up to 5 cycles (9 μg/d on d1−7 in cycle 1, then 28 μg/d); up to 4 maintenance cycles (4 wks on/8 wks off) were allowed for $\leq$ 12 mo. Exposure-adjusted (exp-adj) event rates were calculated as no. of events*100/total exposure time (Table). **Results:** Median (range) no. of cycles were 1 (1−4) for SOC and 2 (1−9) for blin. The highest exp-adj rates (per 100 pt-yrs) were for pyrexia (507 SOC vs 376 blin), anemia (987 vs 229), thrombocytopenia (750 vs 126) and neutropenia (351 vs 121), all lower in blin. Febrile neutropenia (365 vs 93) and infections (1216 vs 436) were also both lower in blin ($p < 0.0001$). Exp-adj rates for neurologic events were 743 SOC vs 472 blin, with median time (range) to onset of 7 (1−43) d and 7 (1−190) d, respectively, and gr $\geq$ 3 cytokine release syndrome (CRS) rates were 0 SOC vs 10 blin. The most frequent AEs in both cycles 1 and 2 were pyrexia, nausea and anemia in both arms; CRS events decreased in the blin arm between cycles 1 and 2 (14% vs 2%). Most fatal AEs were related to infection in both arms. **Conclusions:** Here blin showed an AE profile consistent with that previously reported for r/r ALL, including similar rates of manageable CRS and neurologic events. Exp-adj AE rates were generally higher in SOC vs blin, including for cytopenias and infections. Clinical trial information: NCT02013167.

	SOC N=109 pts		Blinatumomab N=267 pts	
	14.8		89	
Total exposure, yrs	No. of events	Exp-Adj event rate[a]	No. of events	Exp-Adj event rate[a]
All AEs	2037	13764	4108	4616
Gr 3	456	3081	707	794
Gr 4	195	1318	197	221
Fatal	19	128	51	57
Neurologic events	110	743	420	472
CRS	0	0	56	63
All serious AEs	95	642	311	349

[a] Per 100 pt-yrs

7033 Poster Session (Board #233), Mon, 8:00 AM-11:30 AM

Updated results of frontline ofatumumab-hyper-CVAD in adults with CD20+ acute lymphoblastic leukemia. *First Author: Abhishek Maiti, The University of Texas Health Science Center at Houston, Department of Internal Medicine, Houston, TX*

Background: Chemoimmunotherapy is an effective frontline therapy for acute lymphoblastic leukemia (ALL). Ofatumumab (O) binds to a proximal small-loop epitope on CD20 and is more potent *in vitro* than rituximab. Here we report interim results of its combination with hyper-CVAD (HCVAD) in adult patients (pts) with CD20+ ALL. **Methods:** Since 7/2011, we have enrolled 63 pts with Ph-negative CD20+ ALL (59 newly diagnosed, 4 previously treated). For the intensive phase, pts received 4 cycles (cy) of HCVAD (odd cy 1, 3, 5, 7) alternating with 4 cy of methotrexate-cytarabine (MTX-Ara-C, even cy 2, 4, 6, 8), and ofatumumab during cy 1-4. For maintenance, pts received POMP for ~30 months (mos), and intensification with MTX/PEGylated asparaginase on mos 6 and 18, and O-HCVAD on mos 7 and 19. Intrathecal MTX-Ara-C was used for CNS prophylaxis. Bulky mediastinal disease was irradiated when indicated. **Results:** Median age was 41 years (range: 18-71) and median WBC count was 4.6 x10^9/L (range: 0.6-201 x10^9/L). 22 pts (35%) had diploid cytogenetics and 8/35 pts (23%) had TP53 mutation. CD20 expression was $>$ 20% in 38 pts (60%), 10-20% in 6 pts (10%) and 1-10% in 16 pts (25%). Median follow-up was 20 mos (range: 1-58) and median number of cy was 8 (range: 1-8). 3 pts (5%) were in CR at the time of enrollment. Of 60 pts evaluable for response, 58 pts (97%) achieved CR; 1 pt achieved CRp and 1 pt died during cy 1 from sepsis. Flow cytometric minimal residual disease (MRD) was negative in 57/62 pts (92%) overall, and in 36/57 pts (57%) at CR. Median time to negative MRD was 0.7 mos. Median time to platelet and neutrophil recovery in cy 1 was 21 and 18 days, respectively. The most common grade 3/4 non-hematological toxicities were infections during induction (49%) and consolidation (72%), elevated transaminases (35%), and hyperbilirubinemia (21%). 5 pts (7%) experienced a grade 3/4 transfusion reaction. 8 pts (13%) received stem cell transplantation in CR1. 10 pts (16%) have relapsed (8 morphological, 2 MRD only). Overall survival and 2-year CR duration rates were 80% and 81%, respectively. Survival outcomes were independent of percentage of CD20 expression. **Conclusions:** O-HCVAD is safe, effective and results in durable responses in pts with CD20+ ALL. Clinical trial information: NCT01363128.

7034 Poster Session (Board #234), Mon, 8:00 AM-11:30 AM

Correlation between mutation clearance and clinical response in elderly patients with acute myeloid leukemia (AML) treated with azacitidine and pracinostat. *First Author: Koichi Takahashi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In a phase II study in 50 elderly patients (pts) with AML who were not eligible for intensive chemotherapy, treatment with pracinostat + azacitidine (AZA) was well tolerated, led to 42% complete remission (CR) rate and a median overall survival (OS) of 19.1 months (Blood 2016: 128;100). Here we investigate the impact of somatic mutations and their clearance on disease response and patient outcomes. **Methods:** 88 samples from 41 study pts were sequenced. All 41 pts were analyzed pre-treatment, and a median of 3 longitudinal samples were analyzed from 19 pts between Cycle 2 and 9. Mutations were assayed by SureSelect targeted capture exon sequencing (Agilent) of 295 genes that are recurrently mutated in hematologic malignancies. Longitudinal mutation clearance was analyzed by plotting variant allele frequency (VAF). **Results:** At baseline, 96 mutations in 28 genes were detected in 38 pts, with the most frequent being in *SRSF2* (27%), *DNMT3A* (20%), *IDH2* (17%), *RUNX1* (17%), and *TET2*(17%). Mutations associated with CR rate and OS are indicated in the Table. A CR was achieved in 10/19 pts that had longitudinal sequencing analysis and at the time of CR, 9 (90%) had persistently detectable mutations in their bone marrow. In 7 of them, continued exposure to pracinostat + AZA lowered the VAF or cleared residual mutations. In 2 pts, relapsed samples showed re-expansion of the founder clone. **Conclusions:** Mutations in *NPM1*, and DNA methylation pathway were associated with a better response to pracinostat + AZA, while *TP53* mutation was associated with a poor response. Persistent mutation at the time of CR suggests residual preleukemic clonal hematopoiesis in this elderly population. Benefit of prolonged exposure to pracinostat + AZA was also confirmed at molecular level where continued decline of mutation VAF was seen after achieving CR. Clinical trial information: NCT01912274.

	CR rate (%)		
Gene; n (%)	Mutated	Wild-type	p value
NPM1; 6 (15)	83	30	0.025
DNA methylation pathway*; 15 (37)	60	22	0.027
CEBPA; 3 (7)	100	33	0.052
TET2; 5 (12)	80	32	0.066
RAD21; 3 (7)	100	33	0.052
TP53; 5 (12)	0	46	0.065
	OS (months)		
CEBPA; 3 (7)	Not reached	14.8	0.061
NF1; 3 (7)	3.0	19	0.005
RUNX1; 6 (15)	7.9	18.1	0.078

* *DNTM3A, IDH1, IDH2*, or *TET2*

7035 Poster Session (Board #235), Mon, 8:00 AM-11:30 AM

Overall survival (OS) with CPX-351 versus 7+3 in older adults with newly diagnosed, therapy-related acute myeloid leukemia (tAML): Subgroup analysis of a phase III study. *First Author: Jeffrey E. Lancet, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: tAML may occur as a late complication of cytotoxic therapy and is associated with a poor prognosis. CPX-351 is a liposomal formulation that delivers a synergistic 5:1 molar ratio of cytarabine (C) and daunorubicin (D). In a randomized, open-label, controlled phase III trial in patients (pts) aged 60-75 years with newly diagnosed, secondary AML (tAML or after MDS), CPX-351 significantly improved OS versus 7+3. The current analysis of this phase III study evaluated outcomes in the subgroup of pts with tAML. **Methods:** Pts were randomized 1:1 to induction with 1-2 cycles of CPX-351 (100 u/m^2 [C 100 mg/m^2 + D 44 mg/m^2] on Days 1, 3, and 5 [2nd induction: Days 1 and 3]) or 7+3 (C 100 mg/m^2/day x 7 days [2nd induction: x 5 days] + D 60 mg/m^{2}on Days 1, 2, and 3 [2nd induction: Days 1 and 2]). Pts with complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 cycles of consolidation therapy. The study was not powered for this subgroup analysis. **Results:** 304 pts were enrolled and received study treatment, including 62 (20%) pts with tAML; demographics of tAML pts were similar between study arms. Pts with tAML had typically received prior non-anthracycline chemotherapy alone (25%), radiation alone (25%), or non-anthracycline chemotherapy + radiation (32%). CPX-351 was associated with an OS benefit versus 7+3 in older tAML pts and numerically longer event-free survival (EFS) and remission duration (Table). A greater proportion of tAML pts achieved CR+CRi (47% vs 36%, respectively) and proceeded to stem cell transplantation (37% vs 27%) with CPX-351. The safety profile of CPX-351 was comparable to that of 7+3. **Conclusions:** CPX-351 is associated with improved outcomes in older pts with newly diagnosed tAML. Outcomes in the tAML subgroup mirrored the overall study population, indicating CPX-351 may represent a new therapeutic option for this difficult to treat population. Clinical trial information: NCT01696084.

	CPX-351 (n = 30)	7+3 (n = 32)	HR (95% CI)
Median OS	12.17 mo	6.64 mo	0.49 (0.27, 0.88)
Median EFS	2.50 mo	1.64 mo	0.66 (0.38, 1.17)
Remission duration	10.87 mo	6.11 mo	0.50 (0.17, 1.50)

7036 Poster Session (Board #236), Mon, 8:00 AM-11:30 AM

Efficacy by consolidation administration site: Subgroup analysis of a phase III study of CPX-351 versus 7+3 in older adults with newly diagnosed, high-risk acute myeloid leukemia (AML). *First Author: Jonathan E. Kolitz, Hofstra Northwell School of Medicine, Hempstead, NY*

Background: The CPX-351 liposomal formulation delivers a synergistic 5:1 molar ratio of cytarabine (C) and daunorubicin (D) preferentially to leukemia cells. CPX-351 has demonstrated significantly improved overall survival (OS) versus 7+3 in a randomized, open-label, phase III study in patients (pts) aged 60-75 years with newly diagnosed, high-risk AML. In contrast to 7+3, which includes C continuous infusion, CPX-351 is administered as a 90-minute infusion and has the potential to be given in the outpatient setting. The current analysis of the phase III trial assessed the setting of consolidation therapy. **Methods:** Pts were randomized 1:1 to 1-2 induction cycles of CPX-351 or 7+3; pts with complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 consolidation cycles (CPX-351: 65 u/m^2 [C 65 mg/m^2 + D 28.6 mg/m^2] on Days 1 and 3; 7+3: C 100 mg/m^2/day x 5 days + D 60 mg/m^2 on Days 1 and 2). Site of administration was not protocol defined. **Results:** Few pts received induction as outpatient therapy (CPX-351 n = 3/153 and 7+3 n = 1/151 in each cycle). 49/153 CPX-351 pts and 32/151 7+3 pts received consolidation, with a substantial proportion of pts receiving CPX-351 as outpatients (consolidation 1: 51%; consolidation 2: 61%). CPX-351 consolidation was associated with substantial improvement in median OS versus 7+3 irrespective of inpatient/outpatient status (Table). Median OS was not diminished with CPX-351 administration in the outpatient versus inpatient setting (consolidation 1: 25.43 and 14.72, respectively; consolidation 2: 26.32 and not reached). **Conclusions:** Some pts can successfully receive CPX-351 consolidation as outpatients without diminished efficacy, potentially reducing hospitalizations associated with treatment administration. Clinical trial information: NCT01696084.

	Inpatient		Outpatient	
	CPX-351	7+3	CPX-351	7+3
Consolidation 1, n/N (%)	24/49 (49)	30/32 (94)	25/49 (51)	2/32 (6)
Median OS, mo	14.72	9.26	25.43	6.87
HR (95% CI)	0.55 (0.25, 1.21)		0.10 (0.01, 1.11)	
Consolidation 2, n/N (%)	9/23 (39)	12/12 (100)	14/23 (61)	0/12 (0)
Median OS, mo	Not reached	14.31	26.32	–
HR (95% CI)	0.45 (0.09, 2.36)		–	

7037 Poster Session (Board #237), Mon, 8:00 AM-11:30 AM

Idarubicin and cytarabine with clofarabine or fludarabine in adults with newly diagnosed acute myeloid leukemia: Updated results of a randomized phase II study. *First Author: Ghayas C. Issa, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The purine nucleoside analogues fludarabine and clofarabine are effective agents in the treatment of acute myeloid leukemia (AML). This study evaluated the efficacy and safety of combining idarubicin and cytarabine with either clofarabine (CIA) or fludarabine (FIA) in adults with newly diagnosed AML. **Methods:** Using a Bayesian adaptive design, patients (pts) deemed suitable for intensive chemotherapy were randomized to receive CIA (n = 106) or FIA (n = 76). All pts received idarubicin 10 mg/m^2 IV daily on Days 1-3 and cytarabine 1 g/m^2 IV daily on Days 1-5. Clofarabine and fludarabine were given at 15 mg/m^2 and 30 mg/m^2, respectively, IV daily on Days 1-5. Pts with FLT3 mutations could receive sorafenib. Up to 6 cycles of consolidation were allowed for responding pts. **Results:** Baseline characteristics were similar comparing CIA to FIA with a median age of 53 years (range, 20-66) vs 49 years (range, 18-66) respectively and ELN risk intermediate-2/adverse of 57% and 58% respectively. With a median follow-up of 27 months (range, 1-58), the CIA and FIA arms had a similar CR/CRp rate (80% and 82%, respectively). MRD negativity rate by multiparameter flow cytometry at the time of CR/CRp was higher comparing CIA to FIA (80% vs. 65%, respectively, P = 0.07). The median EFS were 13 months and 12 months, respectively (P = 0.91), and the median OS were 24 months and not reached, respectively (P = 0.23). There were more adverse events (all grades) associated with CIA, particularly AST/ALT elevation (29% vs 4%), hyperbilirubinemia (26% vs 9%) and rash (31% vs 9%). Early mortality was similar in the 2 arms (60-day mortality: 4% for CIA vs 1% for FIA; P = 0.32). Comparing the 2 arms to a historical cohort of pts treated with IA showed similar response rates, EFS and OS excluding pts with FLT3 mutations from this analysis. However, in pts < 50 years of age, FIA was associated with improved survival compared with IA (2-year EFS rate: 58% vs 30%, P = 0.05; 2-year OS rate: 72% vs 36%; P = 0.009). **Conclusions:** CIA and FIA have similar efficacy in younger pts with newly diagnosed AML. FIA is associated with a better toxicity profile and may improve survival compared to IA in pts < 50 years of age. Clinical trial information: NCT01289457.

7038 Poster Session (Board #238), Mon, 8:00 AM-11:30 AM

Prognostic significance of alterations of pathways regulating autophagy in acute myeloid leukemia. *First Author: Giovanni Marconi, Istituto Seragnoli, DIMES, University of Bologna, Bologna, Italy*

Background: Nowadays, science is debating if autophagy in cancer can lead to therapy resistance or it can favor apoptosis. Autophagy pathways are involved pro-apoptotic mechanism, or they can improve stresses survival eliminating damaged mitochondria and proteins. Levels and activity of pro-apoptotic and anti-apoptotic proteins (eg. bcl-2 and p53), high levels of cAMP, and a pink/park complex could play as fulcrum on this lever. Our study aims to define the role of autophagy in AML. **Methods:** We analyzed 148 consecutive non M3 AML with Affymetrix SNP array. We screened all patients for TP53, FLT3, NMP1 mutations. Patients was treated with intensive induction chemotherapy regimens. Survival data were collected prospectively, with a median follow-up of 18 months. **Results:** Autophagy alteration (gene group 1: *ULK1 CHR11; ULK1 CHR17; BECN1; ATG14; AMBRA1; UVRAG; ATG9A; ATG9B; PIK3C3; PIK3R4*) was related to lower Complete Remission rate (CR%) after induction in univariate ($p < .001$) and multivariable regression model with age, karyotype, secondary AML, TP53 mutation ($p = .014$); autophagy alteration shown to confer worst Overal Survival (OS) ($p < .001$) and was significantly associated with complex karyotype and TP53 mutation ($p < .001$). We detected significant differences in term of survival independently both in gain and loss in group 1 genes ($p < .001$). Alterations in genes in cAMP pathway (group 2: *SESN1; PRKAA1 CHR 3; PRKAB1: PRKAA1 CHR 1: PRKAG1 CHR11; PRKAG1 CHR 7; PRKAG3; PRKAB1*) and in genes that could be related to a switch from a physiological role of autophagy to a resiliency mechanism (group 3: *CCND1; BCL2; PINK1; PARK2; TP53; MDM1; MDM4*) showed to confer worst OS ($p < .001$ in both groups); Alteration in group 2 and group 3 were related to lower CR% after induction ($p < .001$ in both groups). Whole Exome Sequencing on 56 patients in our set did not found any significant mutation in genes we analyzed with the exception of TP53. **Conclusions:** Alterations in autophagy regulator genes are associated with poor prognosis and therapy resistance. A loss in autophagy could block apoptosis, a gain could confer cell resiliency. Acknowledgements: *ELN, AIL, AIRC, Progetto Regione-Università 2010-12,FP7 NGS-PTL, HARMONY*

7039 Poster Session (Board #239), Mon, 8:00 AM-11:30 AM

Response and survival rates with frontline hypomethylating agent (HMAs) in favorable risk AML. *First Author: Michael Richard Grunwald, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC*

Background: HMAs are an accepted frontline therapy for AML patients (pts) who are unfit for intensive induction therapy (IIT), particularly pts with unfavorable cytogenetics and/or p53 mutations. However, little is known about the response of favorable risk AML to HMAs. We previously reported that NPM1 mutated and/or CD34- AML status were predictors of response to HMAs. Here, we evaluated responses to frontline HMAs in AML. **Methods:** A total of 117 patients with *de novo* AML diagnosed between 7/2013 and 9/2016 were evaluated based on pt and disease related variables, overall response rate (ORR = CR + CR with incomplete count recovery + hematologic remission (ANC > 1000/μL, Hgb > 10g/dL, Plts > 100,000/μL, & no circulating blasts)), and overall survival (OS). Categorical variables were compared using Fisher's exact test. Kaplan Meier methods estimated survival outcomes, and log rank tests compared survival between groups. Multivariable analyses were performed using Cox proportional hazards models. **Results:** 51 pts, considered unfit for IIT, received frontline HMAs. ORR and OS were highest in the ELN favorable risk AML pts (n = 13; ORR = 92%, p = .009; median OS = 17.5 months, p = .022). Among 41 NPM1 mutated pts, 15 received HMAs; and 26 received intensive induction. ORRs were 73% and 84%, respectively (p = .434). No difference was found in OS distributions between the HMA and IIT groups in univariate and multivariate (adjusted for age and FLT3 status) models (p = .329 and .241, respectively). Interestingly, ORR was 100% among 9 HMA-treated pts with NPM1 mutated, CD34-, FLT3/ITD-, cytogenetically normal AML. **Conclusions:** HMA therapy is highly effective frontline treatment in favorable risk AML pts considered unfit for IIT. Survival results with HMAs in NPM1 mutated AML are comparable to those of fitter pts treated with IIT. In selected favorable risk pts considered unfit for standard induction, HMAs can be a successful bridge to potentially curative therapy, including more intensive therapy or transplant. Cytogenetically normal AML with an isolated NPM1 mutation and CD34- status appears to be exceptionally responsive to frontline treatment with HMAs. Prospective validation of these findings is necessary.

7040 Poster Session (Board #240), Mon, 8:00 AM-11:30 AM

CyFi: A phase I study exploring the role of cMET pathway inhibition with ficlatuzumab (Fi) combined with high-dose cytarabine (Cy) in patients with high risk relapsed or refractory acute myeloid leukemia (AML). *First Author: Victoria Wang, University of California, San Francisco, San Francisco, CA*

Background: Pts with AML who are refractory to induction therapy or relapse within 1 year have poor outcomes. Elevated serum HGF level is an adverse prognostic factor in AML (Verstovsek, et al. 2001; Kim, et al. 2005). Preclinical models have shown that myeloid blasts produce HGF in an autocrine fashion and pharmacologic blockade of the HGF/c-Met axis sensitizes blasts to cell death (Kentsis, et al. 2012). **Methods:** We initiated a phase I study to assess the safety and tolerability of Fi combined with Cy in patients with AML who are refractory to 7+3 or have relapsed within 1 year of induction. Fi is given in escalated dosing of 10, 15, or 20 mg/Kg for 4 doses every 2 weeks, starting on day 0, and Cy at a fixed dose of 2g/m2 on days 2-7, using a 3x3 design. PBMCs, BM and serum are collected at defined time points to assess HGF levels and activation of the c-Met pathway. **Results:** Dose escalation is complete and there were no protocol-defined DLTs identified in 9 evaluable pts. All pts treated to date were refractory to induction. Four had de novo AML; 2 had undifferentiated leukemia; 2 prior MDS; 1 prior MPN. Most frequent grade 3/4 TEAEs were febrile neutropenia (56%), LFT abnormalities (11%), and electrolyte disturbance (11%). There was 1 death (11%) from sepsis and multi-organ failure on day 23, following ANC recovery. Of the 7 evaluable pts, 3 achieved a CR (43%), all in the 2nddose cohort. Two of the 3 CRs are long lasting 11 and 12 months following AlloHCT. All patients had detectable circulating HGF levels at baseline compared to control subjects without AML. HGF levels increased following exposure to Fi by an average of 193%. Baseline HGF levels or change from baseline were not associated with treatment response. **Conclusions:** Ficlatuzumab can be safely combined with HiDAC in this high-risk AML population and produce durable clinical responses. Circulating HGF levels were detectable at baseline and uniformly increased with treatment suggestive of a feedback response or immune complex stabilization. Dose expansion is ongoing. Clinical trial information: NCT02109627.

7041 Poster Session (Board #241), Mon, 8:00 AM-11:30 AM

Emotion and Symptom-focused Engagement (EASE): A randomized pilot trial of an integrated psychosocial and palliative care intervention for individuals with acute leukemia (AL). *First Author: Gary Rodin, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Individuals diagnosed with AL may experience severe physical and psychological distress due to the illness and its treatment, the threat of relapse and treatment failure, and a high risk of mortality. To alleviate psychological and physical distress in this population, we developed a novel, 8-week, manualized intervention called EASE. This includes: 1) EASE-psy-a tailored psychotherapeutic component to reduce psychological distress; and 2) EASE-phys-symptom screening, with moderate to severe physical symptoms triggering early palliative care. **Methods:** To assess the feasibility and preliminary efficacy of EASE, patients were recruited within 2 weeks of admission to a comprehensive cancer center and randomized to receive either EASE or usual care (UC). Physical and psychological symptoms were assessed at baseline, 4, 8 (primary endpoint), and 12 weeks. Intervention patients received 6-10 psychotherapy sessions over 8 weeks, weekly assessment of physical symptoms, and consultation and follow-up by palliative care, when needed. One-way ANOVA was performed to assess mean change scores over time between groups. **Results:** Forty-two patients were randomized to EASE (n = 22) or UC (n = 20). Predefined feasibility outcomes were all met: $>$ 86% (19/22) of EASE participants (goal $>$ 64%) completed $>$ 50% of proposed EASE-psy sessions; 64% (14/22) completed symptom screenings (goal $>$ 50%); and 100% of those with moderate to severe symptoms had $>$ 1 meeting with the EASE-phys team (goal 100%). There were statistically significant findings favoring EASE vs. UC for satisfaction with care at 8 and 12 weeks (Δ: -3.12 vs 7.39, $p < 0.04$; -6.1910 vs 0.0125 $p < 0.03$). There were trends favoring EASE vs. UC for traumatic stress symptoms, depressive symptoms, quality of life, attachment security, and number, severity, and distress related to physical symptoms at 4, 8, and 12 weeks. **Conclusions:** Although not powered for statistical significance, this randomized pilot trial of EASE for AL showed promising reductions in psychological and physical distress and supports the feasibility and need for a larger randomized controlled trial. Clinical trial information: NCT02353559.

7042 Poster Session (Board #242), Mon, 8:00 AM-11:30 AM

Unsupervised hierarchical clustering of surface antigen expression to identify normal karyotype AML patients with distinct disease characteristics and poor outcome. *First Author: Madlen Jentzsch, Department of Hematology and Oncology, University of Leipzig, Leipzig, Germany*

Background: Surface antigen expression evaluation is part of the standard work-up at acute myeloid leukemia (AML) diagnosis. The biological & prognostic implications of surface antigen expression patterns in normal karyotype (NK) AML patients (pts) remain unknown. **Methods:** The diagnostic antigen expression patterns of mononuclear cells in bone marrow (BM) of 111 NK-AML pts were assessed using a standard flow cytometric panel. At diagnosis common AML gene mutations (mut) & expression levels were analyzed. Pts received stem cell transplantation (SCT, 98% allogeneic, 2% autologous; median age 63 years [y, range 26-74y]) after induction therapy at our institution. Median follow up was 3.3y. With R's gplot package unsupervised hierarchical clustering of surface antigens was performed & revealed 4 distinct clusters. **Results:** Pts in cluster 1 (n = 36) had higher expression of immature, in cluster 2 (n = 31) of thrombocytic/T-cell/erythroid, in cluster 3 (n = 24) of monocytic & in cluster 4 (n = 20) of myeloid surface antigens. All 4 clusters associated with distinct clinical & molecular features. At diagnosis, compared to all others, pts in cluster 1 had a higher CD34+/CD38- cell burden ($P<$ .001), higher blood blasts ($P<$ .03) & BM blasts ($P<$ .06) by trend. They had less *NPM1* mut ($P<$ .001) & *DNMT3A* mut ($P=$ .02), were more likely to be *EVI1* positive ($P=$ .03) & had higher *EZH2* ($P=$ .02), *RUNX1* ($P=$ .009), *BAALC* ($P<$ .001), *ERG* ($P=$ .02) & *MN1* ($P<$ .001) expression. Compared to all others, pts in cluster 1 had a higher cumulative incidence of relapse (CIR, $P=$ .002, at 1y 41% vs 15%) & shorter event-free survival (EFS, $P=$ .02, at 1y 50% vs 69%). In multivariate analysis, cluster 1 pts had a significantly higher CIR (Hazard Ratio [HR] 5.4, $P=$ .01) after adjustment for *FLT3*-ITD & shorter EFS (HR 2.1, $P=$ .02) after adjustment for *FLT3*-ITD, age & disease status at SCT. **Conclusions:** Pts in cluster 1 had high expression of immature surface antigens (eg CD34, CD117, CD13), genes involved in stem cell renewal & worse outcome. Our data indicate a relationship between easily accessible surface antigen expression patterns at diagnosis, molecular disease features & aggressiveness of the NK-AML phenotype.

7043 Poster Session (Board #243), Mon, 8:00 AM-11:30 AM

A phase 1b dose escalation study to evaluate safety, tolerability and pharmacokinetics of oral monotherapy with KX2-391 in elderly subjects with acute myeloid leukemia who are refractory to or have declined standard induction therapy. *First Author: Margaret T. Kasner, Thomas Jefferson University, Philadelphia, PA*

Background: Treatment of elderly AML patients is complicated by poor tolerance to standard therapies and multi-drug resistance. It is imperative to explore novel agents which are tolerable and target alternative pathways. KX2-391 is an oral non-ATP-competitive inhibitor of Src kinase and tubulin polymerase. We conducted a phase I open-label safety and activity study in elderly subjects with AML who were refractory to or declined standard induction chemotherapy. Five dose levels were tested from 40 to 160 mg daily. **Methods:** 24 subjects were recruited from 3 institutions with an average age of 74 years (range 63-86). The majority had previously received HMAs. 1 subject was treated at 40 mg, 2 at 80 mg, 8 at 120 mg, 12 at 140 mg, and 1 at 160 mg. Of the 24 subjects enrolled, 7 (29%) were on treatment for 12 days or less; 9 (38%) from 15 to 29 days, 5 (21%) from 33 to 58 days and 3 (13%) from 77 to 165 days. One subject treated at 120 mg for 165 days had a reduction in splenomegaly from 16 cm to 4 cm BLCM, and survived 373 days. A second subject was treated at 120 mg for 154 days until disease progression. One subject was dosed at 160 mg for 12 days and remained treatment-free for about 18 months. **Results:** DLTs occurred in 8 subjects at: 120mg (AST/ALT, elevated bilirubin); 140 mg (Mucositis, Allergic Reaction, 2 elevated LFTs, acute kidney injury) and 160 mg (Mucositis). The most common ($\geq$ 25%) treatment-related adverse events were nausea/vomiting; diarrhea; anorexia; fatigue/weakness; increase ALT/AST; hypokalemia; hypotension; febrile neutropenia; dyspnoea; abdominal pain; constipation; dizziness. The RPTD for KX2-391 is 120 mg given once daily. KX2-391 bone marrow concentrations are similar to the target IC50 of 142 ng/mL. **Conclusions:** This is the first study conducted to determine whether KX01 can be safely given to this high risk, frail AML patient population. The data from this study support proceeding with further studies including alternative dosing phase 1 studies (higher dose, shorter course followed by drug-free intervals) and phase 2 studies to assess efficacy. Clinical trial information: NCT01397799.

7044 Poster Session (Board #244), Mon, 8:00 AM-11:30 AM

The effect of donor source on outcomes after second allogeneic hematopoietic cell transplantation for relapsed leukemia. *First Author: Eric Huselton, Washington University in St. Louis, St. Louis, MO*

Background: There is no standard treatment for patients with leukemia who relapse after allogeneic stem cell transplant (HCT). A second HCT (HCT2) may be the only possibly curable option; however, this is performed in few patients. We hypothesized that patient and transplant characteristics, such as donor source will affect outcomes. **Methods:** We retrospectively evaluated adult patients who received a HCT2 for relapsed leukemia or MDS at a single institution between 2000-2016. 85 patients underwent a HCT2 with an unmanipulated graft from a matched related (MRD, n = 21), matched unrelated (MUD, n = 40), or haploidentical (haplo, n = 24) donor, preceded by either a reduced intensity (RIC) or myeloablative conditioning (MAC) regimen. **Results:** The median age at HCT2 was 50 yrs and the median time between transplants was 448 days. Patients had relapsed AML (n = 62), ALL (n = 12), and MDS (n = 10). The median length of follow up for survivors was 22.3 months (range 3.9-131) with 20 patients alive in June 2016. 65 patients died; 32 from relapse, 21 from infection, 7 from GvHD, and 5 from organ failure. 1-year OS from HCT2 was 38.6%. For patients with MRD, MUD, haplo donors, 1 year OS was 52.3%, 33.3%, and 34.6% (p = 0.72). 1-year DFS in the entire cohort, MRD, MUD, and haplo groups was 26.4%, 14.3%, 34.8%, and 25.3% (p = 0.45). 1-year TRM was 36.2% and not different across these groups (p = 0.80). Univariate analyses of OS, DFS, and TRM based on patient, disease, and transplant characteristics showed an association with RIC and worse OS and DFS (HR 2.0, 95% CI 1.2-3.3; and HR 1.9, 1.2-3.1). Having $>$ 1 year between transplants was associated with lower TRM (HR 0.38, 0.19-0.77). Traditional risk factors like age, presence of active disease at HCT2, shorter time between transplants, and using the same donor from the first HCT were not otherwise significantly associated with OS, DFS, or TRM. **Conclusions:** Outcomes after HCT2 did not differ based on donor source. MAC is associated with better OS relative to RIC (1yr OS 51% vs 23%, $p < 0.01$), DFS (1yr DFS 37% vs 12%, $p < 0.01$), with similar TRM (1yr TRM 30% vs 47%, p = 0.12). Based on these data, serious consideration is necessary before using RIC regimens for HCT2 in patients with relapsed leukemia.

7045 Poster Session (Board #245), Mon, 8:00 AM-11:30 AM

Allogeneic stem cell transplant (AHCT) in the eighth decade: Age is just a number. *First Author: Ravi Kishore Narra, Medical College of Wisconsin, Milwaukee, WI*

Background: Allogeneic hematopoietic cell transplant (AHCT) is a curative treatment for hematological malignancies but older adults ($>$ 70 years) have been historically excluded due to age-related comorbidities and concern for increased non-relapse mortality (NRM). Reduced intensity conditioning (RIC) regimens, and improvements in supportive measures have broadened AHCT to older adults. Limited data exist regarding AHCT in their eighth decade ($>$ 70). **Methods:** We evaluated 24 consecutive pts aged $>$ 70 years receiving AHCT for various hematological malignancies between 2012 and 2016 at the Medical College of Wisconsin. **Results:** Median age was 72 (range, 70-76), and 62% were male. Disease indications included 11 AML, 6 CMML, 1 MDS, 1 NHL, 1 MM with only 11 patients (46%) in CR at transplant. 15 patients (62%) had normal karyotype, while other 9 had complex karyotype (n = 4), trisomy 11 (n = 1), trisomy 8 (n = 1). 6 patients (26%) had low-risk DRI score, 9 (39%) intermediate and 8 (35%) had high-risk score. Median HCT-CI score was 1.5 (range, 0-5) and 79% patients had a score of $\leq$2. Donors were related in 50% cases (3 haploidentical, 7 matched siblings and 2 syngeneic). Conditioning was RIC in 23 pts and all peripheral blood grafts. Median follow up was 14.2 months (range, 1.5-42.3). At day 28, 92% had neutrophil engraftment and 87% platelet engraftment. 2 patients had primary graft failure. 4 patients had acute GVHD, 4 had chronic GVHD,1 had both. Median CD3 chimerism was 99% (range, 74-100), CD33 was 100% (range, 78-100). Median of hospital-free days in the first 100 days was 80 and 160 days in the first 6 months after AHCT. 4 pts (17%) underwent AHCT entirely in outpatient setting. 6 patients relapsed at a median of 145 days (range 40-195). Survival at 2 years was 67% with relapse-free survival of 56% and NRM of 14%. Causes of death included sepsis (n = 1), fungal pneumonia (n = 1), cardiac (1), IPS (1), relapse (3). **Conclusions:** This experience with septuagenarians undergoing AHCT demonstrated an excellent 2 yr survival of 67% and that they can receive AHCT in the outpatient setting with a median hospital-free period of 80 days within the first 100 days. In carefully selected patients NRM with AHCT is manageable. Age alone should not determine eligibility for AHCT.

7046 Poster Session (Board #246), Mon, 8:00 AM-11:30 AM

Better survival with fludarabine and timed sequential busulfan regimen in older patients with AML/MDS. *First Author: Uday R. Popat, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We previously reported 6% 100 day NRM with a MA fludarabine (Flu) and busulfan (Bu) in older patients with a median age of 60 years. MA dose of Bu in this timed sequential (TS) regimen was administered over a longer period of time. To assess its impact on survival, we compared the outcomes of older patients treated with the TS Bu (TS cohort) or the RIC Flu/Bu regimen, which is used as standard (ST) for older patients at our center (ST cohort). **Methods:** Patients in the TS cohort received IV Bu 80 mg/m^2/d on day -13 and -12 and Flu 40 mg/m^2/d followed by IV Bu on day -6 to -3, dose adjusted to achieve a total Bu course AUC of 20,000 μmol-min based on PK studies. Patients in the ST cohort received Flu 40 mg/m^{2}day followed by IV Bu daily for 4 days (day -6 to -3) dosed to achieve AUC of 16,000 μmol-min. Patients with AML or MDS were eligible for the study if they had adequate organ function, had matched related or unrelated donor and were treated between Jan 2012 and Sept 2016. **Results:** 162 patients, 50 with MDS and 112 with AML, were included in this study. Patient characteristics including age, sex, disease status, cytogenetic risk group, donor type, graft source CMV status and comorbidity were well balanced and without any significant difference in the two cohorts. Median age was 66 and 65 years in ST and TS cohorts, respectively. Overall survival (OS) and progression free survival (PFS) were significantly better in the TS cohort (see Table). This was due to a reduction in the disease progression without any increase in the non-relapse mortality (NRM). After adjusting for other covariates, the multivariate analysis for PFS confirmed longer PFS with TS Bu regimen (HR: 0.36; P=0.003). The benefit was mainly seen in patients with a comorbidity score $\leq$ 3. **Conclusions:** The myeloablative timed sequential Bu regimen improves survival and appears promising in older patients with AML/MDS. Clinical trial information: NCT01572662.

	Standard Cohort		TS Cohort		TS vs STD		
	N=78		N=84		HR	95% CI	P
2 y OS	31%	(20-42)	51%	(39-62)	0.6	0.3-0.9	0.01
2 y PFS	24%	(15-34)	45%	(33-55)	0.6	0.4-0.8	0.004
2y Progression	59%	(48-71)	34%	(25-46)	0.5	0.3-0.8	0.003
D100 NRM	3%	(1-10)	5%	(2-12)	1.9	0.3-10	0.5
1 y NRM	12%	(6-22)	15%	(9-25)	1.3	0.6-3.1	0.5
2 yr NRM	15%	(9-26)	21%	(14-33)	1.4	0.7-3	0.3
Median Follow up in months	27		24				

7047 Poster Session (Board #247), Mon, 8:00 AM-11:30 AM

Timing of initiation of defibrotide (DF) post-diagnosis of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after hematopoietic stem cell transplantation (HSCT): Final data from an expanded-access protocol. *First Author: Stephan A. Grupp, Pediatric Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: VOD/SOS is an unpredictable, potentially life-threatening complication of HSCT. VOD/SOS with multi-organ dysfunction (MOD) may be associated with $>$ 80% mortality. DF is approved to treat hepatic VOD/SOS with renal/pulmonary dysfunction post-HSCT in the US and to treat severe hepatic VOD/SOS post-HSCT in the European Union. **Methods:** In an expanded-access study, VOD/SOS patients (pts) with or without renal/pulmonary MOD after HSCT or chemotherapy received DF 25 mg/kg/d (6.25 mg/kg q6h) for a recommended $\geq$21 days. For these exploratory analyses, D*ay +100* survival rates in HSCT pts were examined *post hoc* by time from diagnosis to start of DF for (1) all pts before/after days 1, 2, 3, 4, 7, and 14, using Fisher's exact test and (2) pts starting DF on a particular day: 0, 1, 2, 3, 4, 5, 6, 7, 8–14, and $\geq$15, by Cochran-Armitage test for trend across days. Causes of treatment delay were not assessed. **Results:** In the final dataset, timing of initiation was available for 1000 HSCT pts (512 with MOD) who received $\geq$1 dose of DF. In 31.0% of pts, DF was started the day of diagnosis; in 92.9%, by Day 7. In the analysis of initiation before/after days 1, 2, 3, 4, 7, and 14 post-diagnosis, earlier initiation was associated with significantly higher Day +100 survival rates for all days ($P \leq .001$), except Day 14 (2.6% of pts started DF after Day 14). The trend test for particular initiation days also showed a significant trend over time for higher Day +100 survival with earlier DF initiation post-diagnosis ($P < .001$). Adverse events (AEs) and serious AEs occurred in 70.8% and 53.4% of pts. Other than VOD/SOS and MOD, the most common AE was hypotension (11.7%) and most common serious AE was respiratory failure (7.3%). **Conclusions:** In this exploratory analysis of final study data, earlier DF initiation post-VOD/SOS diagnosis improved Day +100 survival, confirmed by the Cochran-Armitage test ($P < .001$). No specific day provides a clinically meaningful cutoff for better Day +100 survival, suggesting that later intervention retains value if treatment must be delayed. *Support:* Jazz Pharmaceuticals. Clinical trial information: NCT00628498.

7048 Poster Session (Board #248), Mon, 8:00 AM-11:30 AM

Allogeneic transplant leads to markedly improved survival in older patients with AML. *First Author: Curtis Andrew Lachowiez, Oregon Health & Science University, Portland, OR*

Background: AML is a disease of the elderly, and outcomes with standard treatment are dismal. Allogeneic transplant is the only curative therapy for most patients with AML. Recent work has shown age is not a factor in transplant outcomes, and should not be a limiting factor for transplant. The treatment pathway for older patients with AML should take into account their disease risk, comorbidities, and treatments with a proven survival advantage. We investigated our institutional experience to help guide the establishment of optimal pathways for patients. **Methods:** We conducted a retrospective analysis of 118 patients over age 65 with AML treated at our institution between 2010-2015. Patients receiving therapy (n = 90) were categorized into two groups: intensive induction therapy (7+3 based) or induction therapy with a hypomethylating agent. The groups were well matched in regard to comorbidities. **Results:** In poor risk patients, complete remission (CR) was achieved in 42% (n = 30/71). Select patients up to age 75 proceeded to allogeneic transplant if they achieved CR. Survival in CR1 was higher in the transplant (n = 22, median 719 days, 95% CI: 366-1071 days), than in the non-transplant group (n = 8, median 257 days, 95% CI: 92-421 days, p-value $<$ .001). In analyzing all risk groups, overall survival was superior in transplant (median 1188 days) versus non-transplant recipients (median 185 days) (see 1, 2, and 3 year survival in table). No difference in median survival occurred based on age at induction (older than 70: n = 9, younger than 70: n = 16, p-value = 0.316). There was no difference in median survival based on chemotherapy regimen without transplant: intensive induction (n = 24, survival 250 days, p-value 0.179) compared to hypomethylating agents (n = 22, survival 139 days). **Conclusions:** We confirm that transplant can be safely performed in patients over 70 years of age, and highlight the survival advantage of transplant to chemotherapy alone. Additionally, our data found no survival benefit of hypomethylating agents in elderly patients with poor risk AML.

Overall Survival (all risk groups)	Transplant	No transplant
1 year	76% (23/30)	23% (14/60)
2 year	40% (12/30)	6% (4/60)
3 year	20% (6/30	5% (3/60)

7049 Poster Session (Board #249), Mon, 8:00 AM-11:30 AM

Ten-year survival after randomized comparison of imatinib (IM) 400 mg vs. IM 800 mg vs. IM + IFN vs. IM + Ara C vs. IM after IFN in chronic myeloid leukemia (CML). *First Author: Ruediger Hehlmann, Medizinische Fakultaet Mannheim Universitaet Heidelberg, Mannheim, Germany*

Background: It is unclear whether IM 400 mg is the optimum choice for the successful treatment of CML. Treatment optimization was therefore attempted. **Methods:** From July 2002 to March 2012, 1551 newly diagnosed patients in chronic phase (CP) were randomized into a 5-arm study to analyze 2 IM doses and 3 combinations. 1536 patients were evaluable, 400 for IM 400 mg, 420 for IM 800 mg, 430 for IM + Interferon (IFN), 158 for IM + Ara C and 128 for IM after IFN. Recruitment to the latter two arms was stopped after a pilot phase. **Results:** 10-year overall survival (OS) of all patients was 82%, 10-year progression free survival (PFS) 80%. 10-year OS was 80% with IM 400 mg, 79% with IM 800 mg, 84% with IM + IFN, 84% with IM + Ara C and 79% with IM after IFN. The differences were not significant. 10-year PFS was 80% with IM 400mg, 77% with IM 800mg, 83% with IM + IFN, 82% with IM + Ara C and 75% with IM after IFN. The differences were not significant either. Survival with any treatment was not significantly different from IM 400mg at any risk level by any risk score (Euro Sokal, EUTOS, ELTS). 87 patients progressed to blast crisis (BC). The 10-year cumulative incidence of BC was 5.8% (95% CI: 4.7%; 7.1%) equally distributed across treatment arms. Most BC occurred in the first 2 years. Median survival after BC was 7.9 months across treatment arms. 275 patients have died, 23 after stem cell transplantation in first CP. Two thirds of deaths were unrelated to CML. Incidence of death due to CML by competing risk analysis with death unrelated to CML as competing risk was not different between the 5-treatment arms. 10-year relative survival probability was 92% when compared to matched general population data. Patients reaching the cytogenetic or molecular response landmarks according to European LeukemiaNet criteria ($<$ 10% BCR-ABL IS at 3 months, $<$ 1% BCR-ABL IS or complete cytogenetic remission at 6 months, $<$ 0.1% BCR-ABL IS (MMR) at 12 months) had a significantly better survival than those not reaching the landmarks regardless of therapy. **Conclusions:** In conclusion, outcome of CML is currently more determined by prognostic markers than by choice of therapy. IM400 mg remains an excellent choice for initial therapy of CP-CML. Clinical trial information: NCT00055874.

7050 Poster Session (Board #250), Mon, 8:00 AM-11:30 AM

Impact of early landmark responses with ponatinib on 4-yr outcomes in CP-CML patients (pts) in PACE, a pivotal phase II trial. *First Author: Martin Mueller, Universitätsmedizin Mannheim, Mannheim, Germany*

Background: Ponatinib is approved for pts with refractory CML or Ph+ ALL for whom no other TKI therapy is indicated, or for patients with T315I. Previously (Mueller ASCO '16), we reported the positive association of early landmark responses with ponatinib on survival at 3 yrs in heavily pretreated pts with CP-CML in PACE (NCT01207440). Here, we provide an update with survival outcomes at 4 yrs. **Methods:** The association of molecular (assessed in a central lab) and cytogenetic responses (CyR) at 3, 6 and 12 mo with 4-yr post-landmark PFS and OS was evaluated in CP-CML pts (n = 267). *P* values: calculated using log-rank test. Data cutoff: 3 Oct '16. **Results:** At baseline, median time from diagnosis: 7 (range, 0.5–27) yrs; median age: 60 (18–94) yrs; median %Ph+: 100% (3–100), ≤10% Ph+: 19 pts (7%); 61% of pts had ≥3 prior TKIs. Among evaluable pts at 3, 6 and 12 mo, MCyR/CCyR was achieved in 48%/39%, 62%/52% and 71%/56% and MMR in 14%, 29% and 39% of pts, respectively. Greater reductions in BCR-ABL1 levels (Table) and CyR at most landmark time points were associated with improved 4-yr post-landmark PFS and OS. Deeper responses at all landmark time points were associated with achievement of $MR^{4.5}$ over time. **Conclusions:** As with the 3-yr landmark analysis, CyR and deep reductions in BCR-ABL1 transcripts at early time points correlated with improved 4-yr post-landmark survival in this refractory population. These data continue to demonstrate the prognostic value of early cytogenetic and molecular responses with ponatinib in heavily pretreated pts with CP-CML. Clinical trial information: NCT01207440.

Estimated PFS and OS at 4 yrs past landmark by BCR-ABL1 level.

Landmark time	Response	n	PFS	*p–value	n	OS	*p–value
3 mo	BCR-ABL1						
	≤ 0.1%	32	97%	–	33	97%	–
	> 0.1–1%	47	57%	.32	48	85%	.54
	> 1%–10%	51	56%	.0050	55	80%	.10
	> 10%	82	51%	.0003	94	78%	.12
				overall: 0.0011			*overall: 0.27*
6 mo	BCR-ABL1						
	≤ 0.1%	57	83%	–	61	93%	–
	> 0.1–1%	42	53%	.011	44	83%	.021
	> 1%–10%	30	59%	.0004	32	90%	.18
	> 10%	57	50%	< .0001	74	78%	.0017
				overall: 0.0001			*overall: 0.0099*
12 mo	BCR-ABL1						
	≤ 0.1%	61	81%	–	63	97%	–
	> 0.1–1%	25	59%	.0086	27	85%	.014
	> 1%–10%	19	66%	.0092	22	95%	.058
	> 10%	41	52%	< .0001	50	80%	.0001
				overall: 0.0011			*overall: 0.0014*

*Calculated across the entire post-landmark timespan and unadjusted for multiple comparisons

7051 Poster Session (Board #251), Mon, 8:00 AM-11:30 AM

Impact of dose reductions on 5-year efficacy in newly diagnosed patients with chronic myeloid leukemia in chronic phase (CML-CP) from DASISION. *First Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Dasatinib (DAS) dose modifications generally mitigate adverse events (AEs) without affecting efficacy for responding patients (pts). A 2-year retrospective analysis of DASISION showed that rates of cytogenetic and molecular responses remained higher for pts given DAS vs imatinib (IM), even when daily doses were modified (Jabbour ASH 2011). Efficacy was not compromised due to dose reductions to manage DAS-related AEs. Here, we report results from a 5-year analysis evaluating the impact of dose reductions on efficacy in pts from DASISION. **Methods:** In DASISION (NCT00481247), pts with treatment-naïve CML-CP were randomized to receive either DAS (100 mg once/day; N = 259) or IM (400 mg once/day; N = 260). Up to 2 dose reductions were permitted for AEs (DAS: 80 mg, then 50 mg; IM: 300 mg, then 200 mg). Efficacy in all pts was evaluated retrospectively by 5 years. **Results:** Molecular response rates remained higher for DAS than IM, independent of dose reductions, and were comparable in pts with and without dose modifications in each arm (table). Overall, 95 (37%) DAS- and 44 (17%) IM-treated pts had dose reductions at any time due to AEs. Median average daily dose was 83 mg DAS and 328 mg IM for pts with reductions for any cause and 82 mg DAS for pts with reductions due to pleural effusion. The most common AEs resulting in dose reduction were hematological toxicity for IM (9%) and pleural effusion for DAS (12%). **Conclusions:** A 5-year retrospective analysis of DASISION showed molecular responses remained higher for DAS vs IM when daily doses were modified due to AEs. Dose reductions for any cause, including pleural effusion, did not affect efficacy (MMR rates were not reduced). In this analysis, for pts who experienced AEs, DAS dose reductions to 80 mg or 50 mg were safe and effective treatment options. Clinical trial information: NCT00481247.

Molecular responses by 5 years, % (95% confidence interval).

Dose reductions		DAS	IM
Any AE		n = 95	n = 44
	MMR	75 (65, 83)	64 (48, 78)
	MR^4	50 (39, 60)	46 (30, 61)
Pleural effusion		n = 30	n = 0
	MMR	83 (65, 94)	-
	MR^4	57 (37, 75)	-
None		n = 164	n = 216
	MMR	77 (70, 83)	64 (57, 70)
	MR^4	56 (48, 64)	44 (37, 50)

MMR, major molecular response; MR^4, 4-log reduction in *BCR-ABL1* transcripts.

7052 Poster Session (Board #252), Mon, 8:00 AM-11:30 AM

Tyrosine kinase inhibitor (TKI) therapy discontinuation in patients with CML in chronic phase: A US clinical practice perspective. *First Author: Ellen K. Ritchie, Weill Cornell Medical College, New York, NY*

Background: This study assessed TKI discontinuation practice in the US before the publication of new practice guidelines in November 2016 including recommendations on TKI discontinuation for patients (pts) with CML in chronic phase (CML-CP). **Methods:** From 10/12/2016 to 11/9/2016, 300 US oncologists/hematologists completed a survey on the reasons for TKI discontinuation in pts with CML-CP, their perspective on adequate response pts should achieve before considering TKI discontinuation (minimum response to TKI, response duration, and TKI therapy duration), and post-discontinuation CML monitoring. **Results:** One third of participating physicians reported having attempted TKI discontinuation (102 of 300); 66 did so outside of a clinical trial. Physicians who reported TKI discontinuation were more likely to practice in academic centers; were more experienced clinicians ($>$ 10 years in practice); and followed a larger number of CML pts vs those who did not. Among the 66 physicians, the majority would consider TKI discontinuation for medical reasons (76% adverse events, 47% pregnancy planning), with fewer for economic reasons (35%); 12% reported they would consider it for all of their pts who achieve an adequate response. There was no consensus on the minimum response achieved (56% consider a decrease in BCR-ABL of $\geq$4.5 log, 21% 3 log, and 11% 1 log), the minimum response duration (29% 3 yrs, 24% 2 yrs, and 20% 1 yr), and the minimum TKI therapy duration (44% 3yrs, 20% 2 yrs, 19% 1 yr) before TKI discontinuation. There was no consensus on the frequency of CML monitoring post-discontinuation with $<$ 10% of physicians considering monthly molecular monitoring in the first year. **Conclusions:** TKI discontinuation in pts with CML-CP responding to TKI was attempted outside of clinical trials without clear guidelines. Conditions under which TKI therapy was discontinued differed from new recommended practice guidelines, which may have resulted in discontinuation where deep response may not be achieved and disease not adequately monitored. The recommended practice guidelines need to be communicated to physicians as TKI discontinuation is likely to be conducted in a broader population.

7053 Poster Session (Board #253), Mon, 8:00 AM-11:30 AM

Clinical relevance of mutations in patients with myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms with normal karyotype. *First Author: Guillermo Montalban-Bravo, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Clinical outcomes of patients with myelodysplastic syndromes (MDS) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are heterogeneous. Specific mutations and mutation patterns are known to define prognostic groups in normal karyotype acute myeloid leukemia. Whether this is the case in MDS and MDS/MPN remains unknown. **Methods:** We evaluated 325 previously untreated patients with MDS or MDS/MPN with normal karyotype evaluated from 2012 to 2016. Next generation sequencing (NGS) on whole bone marrow DNA analyzing a panel of 28 or 53 genes was performed at the time of diagnosis. **Results:** A total of 225 (69%) patients had MDS and 100 (31%) had MDS/MPN including 77 (24%) patients with chronic myelomonocytic leukemia (CMML). Median age was 69 years (31-92). Among patients with MDS, 189 (84%) had lower-risk and 36 (16%) had higher-risk based on IPSS. NGS data was obtained by 53-gene panel in 93 (29%) patients and by 28-gene panel in 232 (71%). A total of 202 (62%) patients had detectable mutations. Median number of mutations was 1 (range 0-6). Detected mutations are detailed in Table 1. A total of 111 (34%) patients, 70 with MDS and 41 with MDS/MPN, received therapy with hypomethylating agents. Median follow up was 12 months (0-167). By univariate analysis, *NRAS* (HR 3.28, CI 1.25-8.62, p=0.016) and *TP53* (HR 4.9, CI 1.44-16.67, p=0.011) predicted for shorter overall survival (OS) among MDS patients. After multivariate analysis including IPSS-R, only *TP53* retained its impact in OS (HR 5.25, CI 1.44-19.13, p=0.012). Among MDS/MPN patients, no mutation was found to significantly impact OS. **Conclusions:** With the exception of *TP53* mutations, no other identified mutation seemed to independently define prognosis of patients with MDS or MDS/MPN with normal karyotype. In view of the high proportion of lower-risk patients, longer follow up is required to better define prognostic impact of mutations in this population.

Gene	Frequency (%)
TET2	31
ASXL1	22
RUNX1	10
DNMT3A	9
NRAS	9
IDH2	7
JAK2	5
KRAS	5
TP53	4
IDH1	4
EZH2	3
GATA2	2
KIT	2
NPM1	2
GNAS	1
NOTCH1	1
GNAQ	1
WT1	1
BRAF	$<$1
MLL	$<$1
MPL	$<$1
ABL1	$<$1
EGFR	$<$1
FLT3	$<$1
IKZF2	$<$1
PTPN11	$<$1

7054 Poster Session (Board #254), Mon, 8:00 AM-11:30 AM

Prevalence and complications associated with off-label use of lenalidomide in older patients with myelodysplastic syndromes (MDS). *First Author: Andrew Mark Brunner, Massachusetts General Hospital, Boston, MA*

Background: Lenalidomide (LEN) is approved for patients with lower-risk MDS with del5q who are transfusion-dependent (TD). We aimed to assess the prevalence and complications associated with LEN use in non-TD older patients with MDS. **Methods:** Using the SEER-Medicare database we identified Medicare enrollees diagnosed with MDS from 2007-2011. Medicare part D claims were analyzed for evidence of LEN use. CPT, HCPCS, and ICD-9 codes were used to characterize TD MDS (claims for $\geq$ 2 RBC transfusions within 8 weeks prior to LEN), complications, and baseline risk per SEER-Medicare MDS Risk Score (SMMRS; Uno, *Leuk Res* 2014). Incident complications during LEN were noted if there were no prior claims for the same within a 1-yr look-back window. **Results:** Among 469 patients initiating LEN (median age 78 years), 77% received it first-line, and 23% after a hypomethylating agent. Among all, 19% had del5q, 37% had non-del5q MDS, and 44% no histology specified (MDS NOS). SMMRS risk was evenly distributed between low (36%), intermediate (30%), and high (34%). Only 42% of patients were TD at the time of first LEN prescription, and 26% had not been transfused within six months prior to LEN. Non-TD patients receiving LEN were more likely to have lower-risk disease (p = .004), and less likely to have pre-treatment thrombocytopenia (p = .005) or neutropenia (p = .003); they did not differ significantly in age (p = .85), documentation of del5q (p = .51), comorbidity (p = .65) or treatment center volume (p = .80). Median days on LEN for the non-TD was 121. Incident complications post-LEN among the non-TD are shown. **Conclusions:** These data suggest there is widespread off-label use of LEN in older patients with MDS, as many receive the drug who are not TD. Moreover, off-label exposure to LEN in these patients is associated with a sizable risk of incident complications, which is difficult to justify given they are already living free of transfusion dependence.

New complication during LEN among non-TD	Prevalence (%)
Dyspnea	24.4
Thrombocytopenia	21.9
Pancytopenia	20.0
Fatigue	18.2
Neutropenia	18.2
Neuropathy	17.8
Diarrhea	17.8
Arthralgia	13.3
Rash	13.0
Dizziness	13.0
Cough	13.0
Back Pain	10.7
Constipation	10.4
VTE	10.0

7055 Poster Session (Board #255), Mon, 8:00 AM-11:30 AM

Implementation of a screening program for identification of unrecognized inherited marrow failure syndromes. *First Author: Curtis Andrew Lachowiez, Oregon Health & Science University, Portland, OR*

Background: Inherited marrow failure syndromes (IMFS) are considered diseases of childhood, but testing adults with atypical presentations of diseases associated with IMFS is critical for establishing an optimal treatment protocol. The most common IMFS, Fanconi Anemia and Telomere Biology Diseases, are associated with MDS and aplastic anemia (AA), head and neck cancers, skin, and cervical cancer. Such patients can have profound toxicity with standard chemotherapy regimens. **Methods:** We implemented a screening protocol in patients at highest risk of an undiagnosed IMFS (MDS under age 60, AA patients under age 65, and head and neck cancers under age 60) with chromosome breakage analysis and telomere length testing. **Results:** Our protocol diagnosed nine patients (estimated ~10% of patients $<$ age 60 with these diseases) with IMFS. The features of these patients are described in the table. Only three (33%) patients had the classic physical characteristics of IMFS. Three patients were over age 50 when diagnosed with an inherited disorder. Most importantly, in all patients the treatment approach was modified significantly, including minimizing conditioning for BMT, utilizing danazol as first line treatment for AA, as well as aggressive cancer and endocrinopathy screening. Outcomes with modified treatment have been favorable, and occult malignancies were detected through screening in two patients. **Conclusions:** Inherited marrow failure syndromes are uncommon yet under recognized disorders that significantly impact treatment decisions in addition to implementation of surveillance programs for both the affected individual and their relatives alike. Through this approach of thoughtful screening of patients presenting to our institution with marrow failure we identified an unrecognized IMFS in an estimated 10% of patients.

Age	Hematological Findings	Additional Findings	Diagnosis
28	MDS	No	FA
22	AA	Café au lait spots, Cervical cancer	FA
37	MDS	No	FA
30	MDS	Nail dystrophy, skin changes	Dyskeratosis Congenita
43	AA	No	Telomere Disease
44	MDS	No	Telomere Disease
59	MDS	Cirrhosis	Telomere Disease
52	AA	Nail dystrophy, skin changes	Dyskeratosis Congenita
57	MDS	No	Telomere Disease

7056 Poster Session (Board #256), Mon, 8:00 AM-11:30 AM

Relationship of bone marrow blast (BMBL) response to overall survival (OS) in a multicenter study of rigosertib (Rigo) in patients (pts) with myelodysplastic syndrome (MDS) with excess blasts progressing on or after treatment with a hypomethylating agent (HMA). *First Author: Aref Al-Kali, Mayo Clinic, Rochester, MN*

Background: No therapies are approved for MDS after HMA failure. 04-24 was a single-arm study to evaluate best BMBL response as a potential surrogate for OS in higher-risk (HR) MDS pts who progressed on or after an HMA. Rigo is a Ras-mimetic that inhibits the RAS-RAF-MEK pathway, which is frequently activated in HR MDS (Athuluri-Divakar *Cell* 2016; Gil-Bazo *Cancer Biol Ther* 2016). **Methods:** Eligible MDS pts had 5-30% BMBL confirmed within 6 wks pre-study and progression per International Working Group (IWG) 2006 criteria on or after HMAs within 2 yrs. Rigo 1800 mg/24 hrs was continuously infused over 72 hrs q 2 wks × 8 cycles, then q 4 wks until progression or unacceptable toxicity. Primary endpoint was relationship of best BMBL IWG response to OS by Kaplan Meier method. **Results:** 64 pts were treated (median 5 cycles, range 1-32+), with 61% male, median age 73 (range 47-87), median prior HMA duration 10.8 mos (range 1.2-70.2). Revised International Prognostic Scoring System scores were low 2%, intermediate 11%, high 27%, very high 53%, and unknown 8%. ≥Grade 3 adverse events in ≥10% of pts were anemia 19%, thrombocytopenia 19%, and febrile neutropenia 16%. At the analysis time 40 pts (63%) had died. Best BMBL IWG response was marrow complete response (mCR) 14 pts (22%), stable disease (SD) 30 (47%), progressive disease (PD) 15 (23%), and failure (early death/withdrawal) 5 (8%); 2 mCR pts had transplant. Median OS was 7.0 mos (95% confidence interval 4.8-10.8). Landmark median OS (from day of best BMBL response) was mCR not reached; SD 6.3 mos; PD 3.3 mos. Median OS of mCR+SD was 8.5 mos, with log-rank p = 0.011 (mCR+SD OS to PD OS). **Conclusions:** BMBL response is a predictor of survival for MDS pts receiving Rigo after HMA failure, confirming findings in earlier Phase 1/2 studies (Silverman ASCO 2015 Abstr 7017). Based on earlier results identifying an MDS subset benefitting from Rigo (Garcia-Manero *Lancet Oncol* 2016; ASCO 2016 Abstr 165681), a randomized Phase 3 trial of Rigo vs physician's choice (INSPIRE) is ongoing to determine if Rigo improves survival after HMA failure within 9 cycles. Clinical trial information: NCTO 1928537.

7057 Poster Session (Board #257), Mon, 8:00 AM-11:30 AM

Hypomethylating agent (HMA) therapy use and survival in older patients with higher risk myelodysplastic syndromes (HR-MDS) in the United States (USA): A large population-based study. *First Author: Amer M Zeidan, Yale School of Medicine, New Haven, CT*

Background: The HMA azacitidine improved overall survival (OS) compared to conventional care in patients with HR-MDS in the landmark randomized clinical trial AZA-001 by a median of 9.5 months compared to conventional care regimens. However recent registry data from USA (Zeidan et al, 2016) and Spain (Bernal et al, 2015) did not show substantial population-level gains in OS. We used HMA market entry in the US (2004-06) as a natural experiment to assess the effect of HMA on OS. **Methods:** We conducted a retrospective cohort study using Surveillance, Epidemiology, and End Results-Medicare data.Individuals were included if they were 66 years or older in age, had refractory anemia with excess blasts (RAEB, considered to have HR-MDS), and were diagnosed in 2001-11.We performed 2-stage residual inclusion instrumental variable (IV) analysis, using diagnosis year as the IV. Residuals from the first stage model were added to the second stage regression to control for effects of unobserved factors between HMA treatment and OS. We also adjusted for demographic characteristics, comorbidity, disability status and transfusion receipt. **Results:** Among 2,581 patients with RAEB, the median OS from diagnosis was 9 months, and 35.8% received HMAs. In the first stage model, diagnosis year was a strong predictor of HMA (2001-06 vs. 2011, Odds Ratio = 0.004-0.56, P-value < .01). In IV analysis, patients who received HMAs showed no gain in OS (Hazard Ratio (HR) = 0.93, 95% Confidence Interval (CI) = 0.76-1.14), while there was a strongly protective effect of unobservable characteristics on OS (HR = 0.58, 95% CI = 0.47-0.73). **Conclusions:** In our US population-based analysis,HMA use was not associated with survival prolongation in older adults with HR-MDS. It is unclear if this is related to suboptimal use of HMAs (alternate schedules, doses, number of cycles), use of decitabine (which did not show survival benefit in randomized studies), or the unselected nature (compared to strict eligibility in clinical trials) of patients receiving HMAs at the community level. Better understanding of these issues is vital for optimal HMA patient selection and administration.

7058 Poster Session (Board #258), Mon, 8:00 AM-11:30 AM

Prognostic and therapeutic impact of cytogenetic abnormalities in patients with myelodysplastic/myeloproliferative neoplasms, unclassifiable. *First Author: Abhishek Avinash Mangaonkar, Mayo Clinic, Rochester, MN*

Background: The 2016 WHO classification includes myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN-U), as an MDS/MPN overlap syndrome not meeting criteria for well-defined entities such as CMML. No standard prognostication or treatment guidelines exist for such patients. **Methods:** We retrospectively identified MDS/MPN-U cases from 1990-2016 through our myeloid malignancies database. All bone marrow reports were reviewed to ensure compliance with 2016 WHO criteria. Clinical & cytogenetic parameters at diagnosis were assessed & compared with treatment outcomes. **Results:** Eighty nine patients met study criteria, with a median age of 69 years (range: 37-93); 58 (65%) males. Median follow-up was 22.2 months (range: 0-172), with 41 (46%) deaths & 13 (15%) leukemic transformations. Median OS was 24.8 months (range: 0-172). 43 (53%) patients had an abnormal karyotype, with common abnormalities being trisomy 8 (12%), complex karyotype (9%) & del (20q) (6%). Given the fewer types of abnormalities identified, the IPSS cytogenetic stratification was more effective than IPSS-R, with risk categorization including; 45 good (55%), 20 intermediate (25%) & 16 high risk (20%) respectively (8 unavailable). On univariate analysis, increased age (p = 0.05), decreased hemoglobin (p = 0.02), higher ANC (p = 0.03), circulating immature myeloid cells (p = 0.02), higher LDH (p = 0.009), absence of bone marrow ring sideroblasts (p = 0.001) & higher risk (intermediate & high) IPSS cytogenetic categories (p = 0.01) adversely impacted OS. In a multivariate model that included the aforementioned variables, higher risk IPSS cytogenetics retained a negative prognostic impact (p = 0.04). 28 patients received a median of 6 cycles (range: 1-21) of hypomethylating agent therapy (HMA), with an overall response rate of 18% (CR-3, PR-2). All responders had an abnormal karyotype (p = 0.01). However, HMA did not affect either OS or LFS. **Conclusions:** Intermediate & high risk IPSS cytogenetic categories independently & adversely impact survival in WHO defined MDS/MPN-U patients. HMA use did not impact OS; however, patients with abnormal karyotypes were more likely to respond.

7059 Poster Session (Board #259), Mon, 8:00 AM-11:30 AM

Axl blockade in vitro and in patients with high-risk MDS by the small molecule inhibitor BGB324. *First Author: Sonja Loges, Department of Oncology, Hematology, BMT with Section Pneumology and Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: The interplay with bone marrow stroma plays an important role in the pathobiology of MDS. Gas6 is secreted by mesenchymal bone marrow stroma cells and promotes survival and therapy resistance of AML cells expressing the Axl receptor. We hypothesized that inhibiting Axl by the small molecule inhibitor BGB324 might hold therapeutic potential in MDS. **Methods:** We investigated the inhibitory effect of BGB324 on primary bone marrow mononucleated cells (BMMNC) and mesenchymal stroma cells (MSC) from MDS patients in comparison to healthy donors. In the ongoing first-in-patient Phase 1a/b trial BGBC003 A standard 3 + 3 dose escalation study was performed to identify the maximum tolerated dose of BGB324 in patients with previously treated high risk MDS or AML. BGB324 was administered as an oral loading dose on days one and two followed by a reduced daily maintenance. Three dose levels were explored 400/100mg, 600/200mg and 900/300mg. **Results:** We found that BGB324 inhibited BMMNC from low- and high-risk MDS patients with an IC50 of 2.1 μM and 3.8 μM, respectively (n = 5). In comparison, BMNNC from healthy donors were resistant to BGB324 (IC50 9.4 μM, p < 0.05, n = 10). Axl expression was present in MSC isolated from the BM of MDS patients and BGB324 inhibited the proliferation of MSC from low- and high-risk MDS patients (IC50 2.5 μM and 2.7 μM, respectively; n = 7/5).To date, 3 patients with MDS were treated with 400 mg loading dose and 100 mg maintenance dose of BGB324. Therapy has been well-tolerated and the MTD has not yet been reached. The majority of adverse events reported have been Grade 1 and 2. The most common related adverse events are diarrhea and fatigue. One patient with MDS was treated for 80 weeks and experienced a PR. Evidence of target inhibition was demonstrated by almost complete inhibition of Axl phosphorylation accompanied by reduction in phosphoErk and phosphoAkt signalling at day 21 of treatment. **Conclusions:** BGB324 is well-tolerated and might represent a promising novel treatment approach in MDS. Safety and efficacy of BGB324 will be explored further in clinical trials. Clinical trial information: NCT02488408.

7060 Poster Session (Board #260), Mon, 8:00 AM-11:30 AM

Does supplemental interphase FISH analysis to standard chromosom analysis improve the detection of myelodysplastic syndrome? *First Author: Benjamin Joseph Lang, Baylor University Medical Center, Dallas, TX*

Background: Our objective was to evaluate whether the addition of interphase FISH analysis to standard chromosome analysis (CA) improves the detection of chromosomal abnormalities in patients with work up for myelodysplastic syndromes (MDS), acute myeloid leukemia, and myelodysplastic/myeloproliferative disorders and thereby increases diagnostic and prognostic information. We performed a retrospective data review of all MDS orders between January and September 2015 at our institution and evaluated concurrent tests for discrepancies between CA and FISH results. Our aim was to evaluate best practices with regard to diagnostic test utilization, specifically to assess the diagnostic and prognostic value of FISH in addition to CA for patients with potential and known MDS. **Methods:** Retrospective data review of concurrent test orders of CA and myelodysplastic FISH panel were reviewed. The myelodysplastic FISH panel consists of screening for monosomy 5/deletion 5q, monosomy 7/deletion 7q, CEP7, trisomy 8, and D20S108 (20q12). The results of CA and FISH results were analyzed using a chi-square test to evaluate statistical significance. **Results:** A total of 1121 samples were queried, of which 55 were excluded due to inability to perform CA and limited diagnostic value of accompanying standalone FISH data on the 4 markers tested in this study. Analysis of the eligible 1066 samples showed that the standalone CA had significantly higher sensitivity ($p < 0.0001$) in detecting abnormal cases (N = 247, 23.17%) as compared to standalone FISH analysis (N = 180, 16.89%). Overall, 173 (16.23%) cases were determined to be abnormal by both methods. CA correctly interpreted 1059 of 1066 cases (99.34%).Only 7 samples were interpreted as normal by CA but were found to be abnormal by FISH. This results in overall 0.66% (2.76% of the abnormal cases) of abnormalities that would have been missed by CA only. **Conclusions:** These findings suggest that FISH studies with 4 markers used in this study provide limited additional utility in cases with a complete CA.

7061 Poster Session (Board #261), Mon, 8:00 AM-11:30 AM

Phase I/II trial of glasdegib in patients with primary or secondary myelofibrosis. *First Author: Aaron Thomas Gerds, Leukemia Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland, OH*

Background: Glasdegib is a small molecule inhibitor of the Sonic Hedgehog pathway, and data from the single arm, lead-in cohort of a phase 1b/2 trial in myelofibrosis (MF) are shown. **Methods:** Patients (age ≥18 yrs) with primary/secondary MF previously-treated with ≥1 Janus Kinase inhibitor (JAKi) were enrolled and received glasdegib 100 mg QD orally in 28 day cycles. AEs and laboratory abnormalities were assessed. Key efficacy endpoints were proportion of patients with spleen volume reduction (SVR) ≥35% and ≥50% reduction in total symptom score (TSS) measured by the MPN Symptom Assessment Diary (MPN-SAD) at Week 24. **Results:** 21 patients were enrolled between Oct '14-Oct '15 in this ongoing study. Mean age was 69.3 yrs (range 58-83). Median duration of treatment was 85 days (22-343). 52% were refractory patients with inadequate response to prior JAKi. Baseline symptoms were mostly mild (1-4), except fatigue (>4). No patients achieved SVR ≥35%, 5 patients had some SVR (maximum 2.3-21.4% reduction from baseline), and no progressive disease prior to Day 71. At week 24, 1 patient had ≥50% reduction in TSS, but 3/21 and 4/21, respectively showed 30% and 20% TSS reduction. Of 14 patients with severe baseline symptoms (1 with ≥5, or ≥2 with ≥3), 1, 1, and 2 achieved 50%, 30%, and 20% TSS reduction, respectively at week 24. TSS, spleen-related, and constitutional symptom scores showed a trend of reduction over 24 weeks with spleen-related symptoms, inactivity, and fatigue showing greatest improvement (52%, 58%, and 36%, respectively). Dysgeusia (N=13), muscle spasms (N=12), alopecia (N=8), decreased appetite (N=7), fatigue (N=7), lipase increase (N=5), and weight decrease (N=5) occurred in ≥20% patients. None, except 1 episode of fatigue, were considered serious AEs. Glasdegib steady state PK was consistent with previous single agent data. **Conclusions:** Glasdegib has an acceptable toxicity profile in patients with primary/secondary MF previously treated with JAKi. Symptom responder definition for refractory patients may not be the same as for JAKi naïve patients. Patient reported symptom improvement may be a more sensitive indicator of treatment benefit vs SVR. Further study of glasdegib may be warranted. Clinical Trial Information: NCT02226172.

7062 Poster Session (Board #262), Mon, 8:00 AM-11:30 AM

Allogeneic hematopoietic cell transplantation for myelofibrosis (MF) in high risk patients. *First Author: Swapna Narayana, Froedtert Hospital and Medical College of Wisconsin, Milwaukee, WI*

Background: Although allogeneic transplantation(alloHCT) is the only curative treatment modality for MF, given the median age of MF, most patients are not candidates for alloHCT due to concerns for treatment-related mortality(TRM), age and comorbidities. **Methods:** We reviewed the outcomes of 24 recipients of matched related/unrelated donor alloHCT for MF at the Medical College of Wisconsin. All patients with JAK2 mutation(62%) and/or constitutional symptoms recieved Roxulitinib atleast 4 months prior to alloHCT with discontinuation of Ruxolitinib 48 hrs prior to the start of conditioning. Majority (91%) received conditioning with Fludarabine and Busulfan(Flu/Bu4, Flu/Bu3, Flu/Bu4). Only 2 patients received TBI based regimen; Flu/TBI(2-4Gy). Those with splenomegaly > 22cm received pre-transplant splenic radiation(n = 11; 49%). Survival outcomes were analyzed using Kaplan-Meier curves and compared between groups using log-rank test. **Results:** Median age was 57 years(range,40-67) with 29% > 60 years. A 46% had primary ET or PV that evolved to MF and 17% had MDS cytogenetics. Majority(74%) patients MF-3 grade. More than 80% recieved Ruxolitinib and 25% were treated with hypomethylating/cytotoxic chemotherapy. HCT-CI score was≥3 in 62%. Four patients had cirrhosis and portal hypertension(PHTN), and another 3 had PHTN without Cirrhosis.At median follow up of 36months, 3-year overall survival(OS) and relapse-free survival were(RFS) 70%. Marrow fibrosis improved post HCT with only 15% grade 3. One patient relapsed and died from AML 15 months post-HCT. TRM was 25% at 3 years; causes of death were sepsis(n = 3), alveolar hemorrhage(n = 1) and myocardial infarction(n = 1). Variables such as type of donor, DIPSS scoring, MF grade and age of the patient were not significantly associated with OS/RFS on univariate analysis. **Conclusions:** Despite advanced age and 62% with HCT CI≥3, we report excellent survival outcomes compared to other prior data. Careful patient selection, use of Ruxolitinib pre-HCT, splenic irradiation pre-HCT and Flu/Bu based conditioning regimen all contributed to the remarkable results in this series.

7063 Poster Session (Board #263), Mon, 8:00 AM-11:30 AM

Phase 2 study of ruxolitinib in combination with 5-azacitidine in patients with myelofibrosis. *First Author: Lucia Masarova, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Ruxolitinib (RUX) is effective in controlling symptoms and organomegaly in patients with myelofibrosis (MF). Combination with azacitidine (AZA) may further improve its efficacy. **Methods:** RUX 15 or 20 mg orally twice daily was given continuously since cycle 1. AZA 25 to 75 mg/m2 on days 1-5 of each 28-day cycle was added starting cycle 4. Responses were assessed per International Working Group for Myelofibrosis Research and Treatment 2013 criteria (IWG-MRT). **Results:** Among 44 pts enrolled between 03/2013 and 06/2016, 39 patients (89%) were evaluable for response. After median (med) follow-up of 20.4+ months (range, 0.5-37+); 24 pts (54%) are on study with a med overall survival of 39+ months. Med age was 66 years (range, 48-87), 36 pts (82%) had int-2/high IPSS score, 29 (66%) had spleen ≥5cm, and 24 (55%) were $JAK2^{V617F}$ positive. Twenty five pts (57%) were previously treated. Twenty eight (72%) pts had objective response regardless of previous therapy (Table). Med time to response was 1.0 months. 7 (25%) responses occurred after the addition of AZA with med time to response of 4.2 months. In total, 23 pts (79%) had palpable spleen reduction by > 50%, which occurred after AZA was added in 6 (28%) of them. $JAK2^{V617F}$ allele reduction was noted in 13 (87%) evaluable pts, including > 50% reduction in 3 pts (13%). A reduction in bone marrow fibrosis grade was observed in 12 (31%) responders, including ≥2 and 1 grade reduction in 2 and 9 pts, respectively. Grade 3/4 non-hematological and hematological toxicities occurred in 4 and 16 pts, respectively. The most common reasons for therapy discontinuation (n=17) were stem cell transplantation (n=6), lack of response (n=3) and progression to AML (n=2). **Conclusions:** Concomitant RUX with AZA was feasible with overall IWG-MRT response rate of 72%, including >50% spleen reduction in 79% of patients, which compares favorably to single RUX. Clinical trial information: NCT01787487.

IWG-MRT 2013	N (%)
Overall response	28 (72)
Partial remission (PR)	2 (7)
Clinical improvement (CI) spleen + total symptom score (TSS)	7 (25)
CI TSS + CI hemoglobin	2 (7)
CI spleen + complete cytogenetic remission (CCyR)	2 (7)
CI TSS + CCyR	1 (4)
CI spleen + TSS + molecular PR (JAK2)	2 (7)
CI TSS only	8 (28)
CI spleen only	4 (14)

7064 Poster Session (Board #264), Mon, 8:00 AM-11:30 AM

Ruxolitinib (RUX) in combination with azacytidine (AZA) in patients (pts) with myelodysplastic/myeloproliferative neoplasms (MDS/MPNs). *First Author: Rita Assi, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Clinical trials exclusively focusing on pts with MDS/MPNs are lacking. Combining RUX and AZA may target distinct manifestations of MDS/MPNs. **Methods:** Pts were treated with single-agent RUX 15 mg or 25 mg (based on platelets count) orally twice daily continuously in 28-day cycles for the first 3 cycles. AZA 25 mg/m^2 (day 1-5) was added on each cycle starting cycle 4 and could be increased to 75 mg/m^2 (maximum) or started earlier than cycle 4 and/or at higher dose in pts with proliferative features or high blasts. **Results:** 35 pts with med age 70 years (range, 43-79) were enrolled (MDS/MPN-U, n = 14; CMML, n = 17; atypical CM (aCML), n = 4), 28 (80%) were Int-2/High per MF DIPSS, 14 (41%) had splenomegaly > 5 cm, and 12 (34%) had EUMNET MF-2/MF-3 fibrosis. Common mutations on a 28-gene sequencing panel included JAK2 (29%), RAS (27%), ASXL1 (21%), TET2 (18%), and DNMT3A (12%). All 35 pts were evaluable for response per MDS/MPN IWG criteria and 17 (49%) responded. 6/17 (35%) IWG responses occurred after the addition of AZA (med time after AZA = 1.8 months). JAK2 mutated pts had a trend to higher responses vs those with non-mutated pts (8/10 vs 9/25, P = 0.19). Ten pts had > 5% pretreatment BM blasts and 7 achieved a reduction in blasts to < 5% (70%). A > 50% reduction in palpable spleen length reduction at 24 weeks was seen in 9/12 (75%) pts. New grade 3/4 anemia and thrombocytopenia occurred in 18 pts (51%) and 19 (54%) pts but were manageable with dose modifications. Only one pt discontinued therapy due to cytopenias. At a med follow-up of 17.4 mo (range, 1.2-36.8+), 14 (40%) pts died: pneumonia (n = 4), sepsis (n = 4), progression to AML (n = 4), and cardiac arrest (n = 1). The med survival for all pts was 16.6 mo (1.0 - 36.8). Compared to CMML and aCML, MDS/MPN-U pts had significantly better med survival (26.4+ vs 15.0+ vs 1.5+ mo, respectively; p = 0.01). **Conclusions:** The combination of RUX and AZA showed an IWG-response rate of 49% in pts with MDS/MPNs, and was well-tolerated. The benefit appears more profound in pts with MDS/MPN-U. This study is ongoing. (ClinicalTrials.gov Identifier: NCT01787487).

7065 Poster Session (Board #265), Mon, 8:00 AM-11:30 AM

Identification of effective therapy in Langerhans cell histiocytosis in the adult population. *First Author: Jennifer Ma, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Langerhans cell histiocytosis (LCH) is a rare disorder of histiocytic proliferation most commonly observed in children. LCH in adults is less characterized and a standard of care has not been established. Here we review clinical outcomes of adult LCH patients (pts) treated with various therapies at a large referral center. **Methods:** We identified 108 pts over 18 years of age with histologically confirmed LCH presenting to our center between 1990-2015. Clinical and treatment characteristics were examined and classified by single or multi-system involvement (SSI or MSI, respectively) and risk-organ involvement (ROI; liver, spleen, hematopoietic system and CNS). Overall survival (OS) and freedom from first progression (FFFP) were calculated by the Kaplan-Meier method. Univariate analysis was performed with the Cox proportional hazards model. **Results:** Median age at diagnosis was 44 years (range 18-89) with a median follow-up of 3.9 years (0.1-9.1). Median OS was 16.1 years and FFFP was 5.6 years, with 94 (87%) pts alive at last follow-up. Eighty-three (77%) had SSI and 13 (12%) had ROI. The most common sites of disease were bone (52 pts; 48%), lung (28; 26%), and skin (24; 22%). Only 11 pts (9%) experienced progression of disease (POD) after first treatment. Twenty-four (22%) received radiotherapy, 42 (39%) underwent excision, and 26 (24%) received systemic therapy at any point during treatment. The most common systemic agents were vinblastine, 6-mercaptopurine (6-MP), methotrexate (MTX), and cladribine. Eight received combination vinblastine, 6-MP, and MTX (VMM), 4 of which had MSI. Median progression-free survival (PFS) of VMM pts was 6 months, compared with 2.8 for all other systemic agents (p = 0.1). For OS, lack of ROI was the only significant variable upon univariate analysis (HR .22, 95%CI 0.06-0.75, p = 0.016). No variables were significant for PFS. **Conclusions:** Effective therapy for adult LCH has not been clearly identified. In our cohort of both low and high risk patients, the low POD rate observed is encouraging. VMM, a regimen previously studied in pediatric pts, is also effective in adults and may be considered the combination of choice for treatment of adult LCH. Further prospective study is warranted.

TPS7066 Poster Session (Board #266a), Mon, 8:00 AM-11:30 AM

CASCADE: A phase 3, randomized, double-blind study of vadastuximab talirine (33A) versus placebo in combination with azacitidine or decitabine in the treatment of older patients with newly diagnosed acute myeloid leukemia (AML). *First Author: Eunice S. Wang, Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY*

Background: AML is associated with poor survival rates in patients (pts) who are not eligible for intensive chemotherapy or allogeneic stem cell transplant (allo-SCT) due to advanced age, comorbidities, and/or disease risk factors. Non-intensive therapies, such as the hypomethylating agents (HMAs) azacitidine and decitabine, are frequently employed in this setting; however, response rates and survival remain suboptimal in this pt population. Vadastuximab talirine (33A) is a CD33-directed antibody conjugated to pyrrolobenzodiazepine (PBD) dimers. Upon binding, 33A is internalized and transported to the lysosomes where PBD is released via proteolytic cleavage of the linker, leading to DNA crosslinking and cell death. In preclinical studies, HMA priming followed by 33A exposure upregulated CD33 expression, increased DNA incorporation of the PBD dimer, and enhanced cytotoxicity. In a phase 1 study, 33A plus HMA was generally well tolerated without a significant pattern of off-target toxicity. Activity of the combination was markedly improved compared to historical data of HMA monotherapy, with a high MRD-negative remission rate and activity maintained in the highest risk subgroups (Fathi et al, ASH 2016). **Methods:** This phase 3, randomized, double-blind, placebo-controlled global study was designed to compare overall survival between pts treated with 33A plus HMA vs. pts treated with placebo plus HMA (NCT02785900). Secondary endpoints include composite complete remission rate (CR/CRi), event-free survival, and safety. Approximately 500 pts will be randomized in a 1:1 manner to one of the study arms. Investigators may select either HMA (azacitidine or decitabine). Eligible pts are adults with newly diagnosed, previously untreated, de novo or secondary AML, and have intermediate or adverse cytogenetic risk. Pts must not have AML associated with favorable risk karyotype or be a candidate for allo-SCT. Combination treatment may be repeated every 4 weeks until disease progression, leukemic recurrence, or unacceptable toxicity. Study enrollment began in June 2016.

TPS7067 Poster Session (Board #266b), Mon, 8:00 AM-11:30 AM

An open-label, randomized phase III study of gilteritinib versus salvage chemotherapy in relapsed or refractory FLT3 mutation-positive acute myeloid leukemia. *First Author: Alexander E. Perl, University of Pennsylvania, Philadelphia, PA*

Background: *FLT3* mutations occur in 30% of patients with acute myeloid leukemia (AML), most often as internal tandem duplications (FLT3-ITD) or point mutations at codon D835. FLT3-ITDs are associated with high relapse rates, short remission duration, and poor overall survival (OS); FLT3-D835 can confer resistance to other tyrosine kinase inhibitors (TKIs). Gilteritinib is a highly selective FLT3/AXL TKI with activity against both FLT3-ITD and FLT3-D835 mutations. A recent phase 1/2 study of gilteritinib (20–450 mg/d) in relapsed/refractory (R/R) AML showed favorable tolerability at doses ≤300 mg/d, and consistent, potent FLT3 inhibition at doses ≥80 mg/d. Patients with FLT3 mutation-positive (FLT3^{mut+}) AML receiving doses ≥80 mg/d had an ORR of 52% (CR/CRp/CRi = 41%, PR = 11%) and longer OS than historic experience in R/R AML with combination cytotoxic chemotherapy or other FLT3 TKIs as monotherapy. Given these results, we initiated a phase 3 trial of once-daily (QD) 120 mg gilteritinib. **Methods:** This randomized, open-label phase 3 study (NCT02421939) will enroll 369 adults with FLT3^{mut+} AML in first relapse or refractory to front-line therapy. Patients who have not previously received FLT3 inhibitors, except sorafenib and midostaurin, will be randomized 2:1 to either 120 mg gilteritinib QD or the investigator's pre-randomization specified salvage chemotherapy choice (LoDAC, Aza, MEC, FLAG-IDA), and stratified by prior chemotherapy response and salvage chemotherapy intensity. Gilteritinib or low-intensity chemotherapy cohorts will receive continuous 28-day treatment cycles until a discontinuation event occurs; the high-intensity chemotherapy cohort will receive ≤2 treatment cycles before response measurement. Primary objective is OS; key secondary objectives are event-free survival and CR rate. Other secondary objectives: leukemia-free survival, remission duration, composite CR rate, subsequent transplantation rate, patient-reported fatigue, and safety. A formal interim analysis is planned when ~50% of planned death events have occurred. Study enrollment began on Oct 23, 2015; as of Jan 20, 2017, 167 subjects have been randomized. Clinical trial information: NCT02421939.

TPS7068 Poster Session (Board #267a), Mon, 8:00 AM-11:30 AM

A phase II/III, multicenter, open-label, 3-arm study of gilteritinib, gilteritinib plus azacitidine, or azacitidine alone in the treatment of newly diagnosed FLT3 mutation-positive acute myeloid leukemia (AML) patients ineligible for intensive induction chemotherapy. *First Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Gilteritinib, a highly selective, potent FLT3/AXL inhibitor, showed antileukemic activity with favorable tolerability in a Phase 1/2 trial of FLT3 mutation-positive ($FLT3^{mut+}$) relapsed/refractory AML. In $FLT3^{mut+}$ AML cell lines, gilteritinib plus azacitidine (AZA) inhibited growth, and induced apoptosis and differentiation. This ongoing Phase 2/3 trial will examine the efficacy, safety, and tolerability of gilteritinib alone, gilteritinib plus AZA or AZA alone in newly diagnosed $FLT3^{mut+}$AML patients ineligible for intensive induction chemotherapy. **Methods:** This open-label, 3-arm, 2-stage randomized trial (NCT02752035) will enroll ~540 newly diagnosed adults with $FLT3^{mut+}$ (FLT3-ITD or -TKD) AML; those with APL, BCR-ABL^{+}, or active CNS leukemia will be excluded. Before initiation, the safety and tolerability of gilteritinib plus AZA will be assessed in a Safety Cohort to establish the appropriate gilteritinib dose for combination therapy. Subjects will then be randomized 1:1:1 to receive oral gilteritinib alone (120 mg daily; Days 1–28), AZA alone (75 mg/m^2 by subcutaneous injection or intravenous infusion on Days 1–7), or AZA (75 mg/m^2; Days 1–7) plus oral gilteritinib (daily on Days 1–28 at the dose determined from the Safety Cohort), and stratified by age (< 75 vs ≥ 75 years). Subjects will continue treatment until a discontinuation event occurs. The primary endpoint is overall survival of subjects receiving gilteritinib or gilteritinib plus AZA versus AZA alone; the key secondary endpoint is event-free survival. Additional secondary endpoints: complete remission rate, leukemia-free survival, remission duration, composite remission rate, tolerability, and fatigue. Dose changes and interruptions are allowed in all treatment arms. A formal interim futility analysis by an Independent Data Monitoring Committee is planned when ~50 subjects in each treatment arm have either discontinued therapy or completed 2 treatment cycles. Enrollment began on November 21, 2016; as of January 31, 2017, the Safety Cohort is ongoing. Clinical trial information: NCT02752035.

TPS7069 Poster Session (Board #267b), Mon, 8:00 AM-11:30 AM

Phase 3, randomized, double-blind, placebo-controlled study of venetoclax combined with azacitidine versus azacitidine in treatment-naïve patients with acute myeloid leukemia. *First Author: Jalaja Potluri, AbbVie Inc., Chicago, IL*

Background: Elderly acute myeloid leukemia (AML) is a biologically and clinically distinct disease with a diminished response to chemotherapy, low remission rates, and short disease-free and overall survival. Venetoclax (VEN) is a potent, selective small-molecular inhibitor of BCL-2. In preclinical models, venetoclax has been shown to kill AML cells as a single agent with demonstrated synergistic activity in combination with the DNA methyltransferase inhibitor azacitidine (AZA). Early clinical data from a phase 1b study (NCT02203773) showed that VEN plus AZA had an acceptable safety profile and promising efficacy in treatment-naïve elderly patients with AML. The current phase 3 study continues to evaluate the combination for this AML population. **Methods:** This phase 3, randomized, double-blind, placebo-controlled study (NCT02993523) is designed to assess VEN plus AZA compared with placebo plus AZA in treatment-naïve elderly and adult patients with AML who are not eligible for standard induction therapy due to age or comorbidities. Primary objectives of the study are to evaluate if VEN with AZA will improve overall survival (OS) and composite complete remission rate (CR +CRi) versus placebo with AZA. Secondary objectives include event-free survival, CR+CRi rate at the end of Cycle 1, and if combining VEN plus AZA reduces fatigue and improves global health status/quality of life based on patient reported outcomes versus placebo with AZA. Exploratory objectives are to evaluate biomarkers predictive of VEN activity including minimal residual disease negativity rate, and BCL-2 expression and outcome measures of overall survival and complete remission rate, as well as the impact of VEN on additional quality of life measures. Patients will be randomized 2:1 to VEN plus AZA (arm A) or placebo plus AZA (arm B). Patients on arm A will receive once daily 400 mg VEN orally on days 1–28 plus daily 75 mg/m^2 SC or IV AZA for 7 days in a 28-day cycle. Patients on arm B will receive once daily placebo orally on days 1–28 plus daily 75 mg/m^2 SC or IV AZA for 7 days on a 28-day cycle. Study recruitment began in February 2017, with target enrollment of 400 patients. Clinical trial information: NCT02993523.

TPS7070 Poster Session (Board #268a), Mon, 8:00 AM-11:30 AM

A phase I, first-in-human study of MGD006/S80880 (CD123 x CD3 DART) in AML/MDS. *First Author: Norbert Vey, Institut Paoli-Calmettes, Centre Régional de Lutte Contre le Cancer, Marseille, France*

Background: MGD006/S80880 is a novel CD123 x CD3 DART molecule designed to target CD123-positive cells for recognition and elimination by CD3-expressing T lymphocytes as effector cells. CD123, the alpha chain of the interleukin 3 receptor (IL-3Ra) is known to be highly expressed in $>$ 90% of AML patients and at least 50% of MDS patients. Based on these observations, targeting CD123 could be a promising strategy in the preferential ablation of AML and MDS cells. **Methods:** MGD006 is currently being evaluated in a Phase 1 dose-escalation and cohort expansion study in relapsed/refractory (R/R) AML or intermediate-2/high risk MDS. The objectives of the study are to determine the MTDS and safety profile, and describe the pharmacokinetics and preliminary activity of MGD006. Patients are dosed in 28-day cycles. All patients start with a lead-in continuous IV infusion of 30ng/kg/day for 3 days followed by 100ng/kg/day for 4 days. Subsequent weeks (2-4) are dosed in two different schedules. One arm receives MGD006 for 4 days on/3 days off and the second arm receives MGD006 for 7 days continuously at the maximal dose assigned to each cohort (up to 1000ng/kg/day). Beginning with the second cycle, all patients are administered MGD006 for 4 days on/3 days off at the maximal dose/cohort. Patients can continue on treatment until 2 cycles (8 weeks) after the attainment of a CR, maximum of 12 cycles of MGD006, DLT or treatment failure. Once the MTDS is identified, two cohorts of 24 patients each, one in AML and one in MDS, will be enrolled. Response is assessed by IWG or IPSS criteria for AML and MDS, respectively. Signs and symptoms of cytokine release syndrome (CRS), a common AE, are graded according to Lee criteria. The study continues to enroll patients with open sites in the US, France, Germany, Italy, and The Netherlands. ClinicalTrials.gov #NCT02152956. EudraCT #2015-003813-11.

TPS7071 Poster Session (Board #268b), Mon, 8:00 AM-11:30 AM

A biomarker-directed phase 2 trial of SY-1425, a selective retinoic acid receptor alpha agonist, in adult patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). *First Author: Rachel J. Cook, Oregon Health & Science University, Portland, OR*

Background: SY-1425 (tamibarotene) is an orally available, synthetic retinoid approved in Japan for the treatment of relapsed/refractory (R/R) APL. SY-1425 is a more potent and selective retinoic acid receptor alpha (RARα) agonist with improved pharmacologic properties compared to all-trans retinoic acid (ATRA) including increased half-life and lack of metabolism by CYP26A1 resulting in extended relative exposures. SY-1425 binding to RARα relieves pathogenic repression of myeloid differentiation. Super-enhancers associated with *RARA* and upregulation of *RARA* expression correlate with increased sensitivity to SY-1425 *in vitro* and predict for response to SY-1425 with induced differentiation and reduced proliferation in RARA-high PDX AML models, but not in RARA-low models. SY-1425 also induces the RARα target gene *DHRS3* in RARA-high AML cell lines. This study is designed to demonstrate pharmacodynamic (PD) and clinical effects of SY-1425 in non-APL AML and MDS patients (pts) positive for the *RARA* super-enhancer associated biomarker or exploratory *RARA* pathway biomarker, IRF8. **Methods:** This study is enrolling pts with R/R AML, R/R higher-risk MDS, newly-diagnosed AML $\geq$60 yrs unlikely to respond to or tolerate standard therapy, and transfusion dependent lower-risk MDS pts without del 5q who are unlikely to respond to or have failed ESAs. Pts must be biomarker positive based on centralized testing of tumor cells from blood. All pts receive SY-1425 at 6 mg/m^2/day PO with continuous twice daily dosing. Primary objectives are to characterize the activity of SY-1425 by ORR in AML and higher-risk MDS pts or transfusion independence in lower-risk MDS pts. Secondary objectives include event-free and relapse-free survival, duration of response, overall survival, hematologic improvement and safety. PD evaluation includes induction of *DHRS3* and expression of myeloid differentiation markers. Target enrollment is 80 pts. This trial opened in September 2016. Through a protocol amendment, SY-1425 treatment in combination with azacitidine will also be evaluated. ClinicalTrials.gov identifier: NCT02807558.

TPS7072 Poster Session (Board #269a), Mon, 8:00 AM-11:30 AM

A randomized, double-blind phase III study of ibrutinib versus placebo in combination with corticosteroids in patients with new onset chronic graft versus host disease. *First Author: David Bernard Miklos, Stanford University Medical Center, Stanford, CA*

Background: Chronic graft versus host disease (cGVHD) is a common complication of allogeneic stem cell transplantation, with pathophysiology involving alloreactive and dysregulated T and B cells and innate immune populations. Ibrutinib, a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is indicated by the US FDA for the treatment of patients (pts) with CLL/SLL. Ibrutinib recently received breakthrough therapy and orphan drug designation for the treatment of pts with cGVHD who did not respond to one or more lines of systemic therapy. Ibrutinib reduces severity of cGVHD in murine models and recently was shown to achieve an NIH-defined overall response rate of 67% in pts with steroid relapsed/refractory cGVHD (Miklos *Blood* 2016). **Methods:** The primary objective of this Phase 3, multicenter, international, randomized, controlled, double-blind study is to evaluate the 24-week response rate of ibrutinib versus placebo in combination with prednisone. Pts with newly diagnosed moderate or severe cGVHD, as per NIH Consensus Development Project Criteria (2014), will be randomized in a 1:1 ratio to receive either oral ibrutinib (arm A) or placebo (arm B) in combination with oral prednisone. Ibrutinib or placebo will be given until unacceptable toxicity, relapse of underlying disease, death, or the need for a new systemic treatment for progressive cGVHD. Eligible study pts (age ≥12 yrs) must require systemic treatment with corticosteroids and have no prior systemic treatment for cGVHD. The primary endpoint is response rate (complete or partial response) at 24 weeks, as per NIH Consensus Development Project Criteria, and must occur in the absence of both new therapy for cGVHD and relapse/return of the underlying disease that was the indication for transplant. Secondary endpoints will assess for additional clinical benefit including corticosteroid dose reduction, improvement of Lee cGVHD Symptom Scale scores, withdrawal of all immunosuppressants, and overall survival. This study is currently enrolling pts. Funding source: Pharmacyclics LLC, an AbbVie Company. Clinical trial information: NCT02959944.

TPS7073 Poster Session (Board #269b), Mon, 8:00 AM-11:30 AM

The OMNI patient registry: A prospective observational registry to assess vascular safety in patients with CML and Ph+ ALL treated with ponatinib. *First Author: Annette Stemhagen, United BioSource, LLC (UBC), Blue Bell, PA*

Background: Ponatinib is an oral TKI with potent activity against BCR-ABL1. The pivotal PACE study (NCT01207440) formed the basis for approval of ponatinib in the US for the treatment of patients with resistant/intolerant CML or Ph+ ALL, or those with the T315I mutation. Long-term follow-up of PACE showed a higher cumulative incidence of vascular occlusive events (VOEs) than reported at the time of approval — dose reductions were later implemented to mitigate VOEs. VOEs comprise arterial occlusive events (AOE) and venous thromboembolic events. The exposure-adjusted incidence of AOEs has not increased over time in PACE; in patients with a history of ischemic disease, the relative risk of serious AOEs was 2.6 in those with ≥2 vs 0 risk factors. The primary objective of this patient registry is to assess VOEs occurring during ponatinib use in routine clinical practice in the US. **Methods:** OMNI (NCT02455024) is a prospective observational registry of eligible patients (Table) with CML or Ph+ ALL for whom the decision to initiate treatment with ponatinib has already been made for the approved US indications. Patients voluntarily enroll into the registry, which is non-interventional with no protocol-mandated tests/procedures — all treatment decisions are made at the discretion of the health care practitioner in consultation with their patient. Study duration is anticipated as ~30 mo (~18-mo enrollment followed by 12 mo of data collection, which will occur every 3 mo). The primary analysis will be performed 12 mo after last patient enrolled and will estimate the incidence of VOEs by duration of ponatinib exposure. To understand differences between those with and without VOEs, exploratory analyses will be performed, considering factors such as patient demographics, risk factors for developing VOEs, dose and duration of ponatinib treatment, and concomitant medications. VOE outcomes also will be assessed. Enrollment will begin in 2017, with a target of ≥300 patients. Clinical trial information: NCT02455024.

Key inclusion criteria	CP-CML, AP-CML, BP-CML, or Ph+ ALL With/without anticoagulant and/or antiplatelet agents ≥18 yrs
Key exclusion criteria	Concomitant TKI therapy

TPS7074 Poster Session (Board #270a), Mon, 8:00 AM-11:30 AM

A randomized, open-label, phase II study of azacitidine (AZA) in combination with durvalumab in patients (pts) with previously untreated higher-risk myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) ineligible for hematopoietic stem cell transplantation (HSCT). *First Author: Lewis R. Silverman, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Hypomethylating agents (HMAs) induce hematologic response in ~ 50% of higher-risk MDS pts; however, there are few treatment options for nonresponding pts at increased risk of AML progression and death. While older AML pts ineligible for HSCT have similar overall survival (OS) with AZA and chemotherapy (13.3 vs 12.2 months) (Döhner et al. Haematologica 2015;100: P566), there is an opportunity to further improve responses and OS in these pts. Blockade of the programmed cell death-1 (PD-1)/PD-ligand 1 (PD-L1) pathway with immune checkpoint inhibitors is an emerging paradigm in anticancer therapy. PD-L1 is expressed on cells from AML and MDS pts; expression is upregulated on myeloblasts following HMA therapy (Yang et al. Leukemia 2014; 28:1280) and during MDS transformation to AML (Ogata et al. Leuk Res 2012; 36:1229). Durvalumab (MEDI-4736), a human anti-PD-L1 monoclonal antibody, is well tolerated and induces durable responses in pts with solid tumors (Lutzky et al. JCO 2014;32:3001). This randomized, open-label, phase 2 study evaluates efficacy and safety of subcutaneous (SC) AZA ± durvalumab in pts with higher-risk MDS and older pts with AML. **Methods:** Eligible MDS pts (< 20% blasts) aged ≥ 18 years, with IPSS intermediate- or high-risk MDS, and AML pts (≥ 20% blasts) aged ≥ 65 years, are randomized 1:1 to receive either AZA 75 mg/m^2 SC for 7/28 days or AZA 75 mg/m^2 SC for 7/28 days plus durvalumab 1500 mg IV on day 1 of 28-day cycles. Pts are stratified by cytogenetic risk: intermediate- vs poor-risk AML, and intermediate- vs poor-/very-poor-risk MDS. Primary endpoint is overall response rate per IWG 2006 criteria in MDS pts, and proportion of pts achieving complete response (CR) or CR with incomplete blood count recovery (CRi) per modified IWG 2003 criteria in AML pts. Other endpoints include safety, time to response, overall survival and PD-1/PD-L1 activity. Pts will be followed every 3 months until discontinuation. Target enrollment is 182 pts: 72 MDS pts and 110 AML pts. Enrollment began in June 2016 (ClinicalTrials.gov NCT02775903).

TPS7075 Poster Session (Board #270b), Mon, 8:00 AM-11:30 AM

H3B-8800-G0001-101: A first in human phase I study of a splicing modulator in patients with advanced myeloid malignancies. *First Author: David P. Steensma, Dana-Farber Cancer Institute, Boston, MA*

Background: Dysregulated mRNA splicing is important in tumorigenesis and in resistance to cancer therapy. Somatic heterozygous mutations in core spliceosome genes (e.g. *SF3B1, SRSF2, U2AF1*) have been reported at high frequencies in patients with myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and chronic myelomonocytic leukemia (CMML). These mutations confer a change of function resulting in aberrant mRNA splicing that, in preclinical models, results in defects in hematopoietic cell development and myelodysplasia. Recurrent mutations in the spliceosome of patients with malignancies suggests importance in disease pathogenesis. Cells bearing splicing mutations depend on wild-type spliceosome function, suggesting the spliceosome as a therapeutic target. In vitro data indicate preferential induction of apoptosis (measured by caspase 3/7 activation) in SF3B1-mutant cells following treatment with the SF3B1 modulator H3B-8800. H3B-8800 inhibits growth in human AML cell lines, including those with mutations in U2AF1, SRSF2 or SF3B1. Oral administration of H3B-8800 modulates splicing and induces antitumor activity in xenograft leukemia models expressing mutant core spliceosome components. **Methods:** This study explores the safety of H3B-8800 in patients with myeloid cancers. Dose escalation (Cohort A) follows a 3+3 design with a starting dose of 1 mg daily for 5 consecutive days every 14 days in a 28 day cycle. Cohort A is open to patients with MDS, AML or CMML, irrespective of spliceosome mutations. In parallel to dose escalation, up to 6 patients with mutations of interest may be enrolled at doses determined to be safe in Cohort A (Cohort B). After determining the recommended phase 2 dose, 4 expansion cohorts will enroll patients with: (1) International Prognostic Scoring System (IPSS) low/int-1 risk MDS with SF3B1 mutations, (2) IPSS low/intermediate risk-1 MDS with mutations in SRSF2, U2AF1, or ZRSR2, (3) high/intermediate risk-2 MDS or AML, and (4) CMML; 3 and 4 having mutations in SF3B1, SRSF2, U2AF1, or ZRSR2. The first cohort enrolled 3 patients and the trial is currently enrolling patients at the second dose level. Clinical trial information: NCT02841540.

7500 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

First-line treatment of iNHL or MCL patients with BR or R-CHOP/R-CVP: Results of the BRIGHT 5-year follow-up study. *First Author: Ian Flinn, Tennessee Onc, Nashville, TN*

Background: BRIGHT, a phase 3, open-label, noninferiority study comparing efficacy and safety of bendamustine plus rituximab (BR) vs rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or rituximab with cyclophosphamide, vincristine and prednisone (R-CVP) in treatment-naive patients (pts) with indolent non-Hodgkin lymphoma (iNHL) or mantle cell lymphoma (MCL), showed that the complete response rate for first-line BR was statistically noninferior to R-CHOP/R-CVP (*Blood* 2014). Pts were monitored for ≥5 years (yr) to assess the overall effect of BR or R-CHOP/R-CVP in a controlled clinical setting. This analysis reports the time-to-event variables of the 5-yr follow-up (FU) study. **Methods:** Pts with iNHL or MCL randomized to 6-8 cycles of BR or R-CHOP/R-CVP underwent complete assessments at end of treatment, then were monitored regularly. Progression-free survival (PFS), event-free survival (EFS), duration of response (DOR) and overall survival (OS) were compared using a stratified log-rank test. **Results:** Of 447 randomized pts, 224 received BR, 104 R-CHOP, and 119 R-CVP; 419 entered the FU. The median FU time was 65.0 and 64.1 months for BR and R-CHOP/R-CVP, respectively. The 5-yr PFS rate was 65.5% (95% CI 58.5-71.6) and 55.8% (48.4-62.5), and OS was 81.7% (75.7-86.3) and 85% (79.3-89.3) for BR and R-CHOP/R-CVP, respectively. The hazard ratio (95% CI) for PFS was 0.61 (0.45-0.85; *P*= .0025), EFS 0.63 (0.46-0.84; *P*= .0020), DOR 0.66 (0.47-0.92; *P*= .0134), and OS 1.15 (0.72-1.84; *P*= .5461) comparing BR vs R-CHOP/R-CVP. Similar results were found in iNHL [PFS 0.70 (0.49-1.01; *P*= .0582)] and MCL [PFS 0.40 (0.21-0.75; *P*= .0035)], with the strongest effect in MCL. Use of R maintenance was similar, 43% in BR and 45% in R-CHOP/R-CVP. B was included as second-line in 27 (36%) of the 75 pts requiring therapy who originally received R-CHOP/R-CVP. Comparable safety profiles with expected adverse events were observed in the FU study in BR vs R-CHOP/R-CVP. **Conclusions:** The long-term FU of the BRIGHT study has confirmed that PFS, EFS, and DOR were significantly better for BR, and OS was not statistically different between BR and R-CHOP/R-CVP. The safety profile was as previously reported. Clinical trial information: NCT00877006.

7501 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas: Nine-year updated results from the StiL NHL1 study. *First Author: Mathias J. Rummel, Department of Haematology and Oncology, Justus-Liebig Universität, Giessen, Germany*

Background: This multicenter, randomized, phase III study compared B-R and CHOP-R as first-line treatment in patients (pts) with indolent lymphomas or mantle cell lymphoma and was first published in The Lancet in 2013. The final analysis demonstrated a significantly prolonged progression-free survival (PFS) in the B-R group compared to the CHOP-R group, with a median PFS of 69.5 vs. 31.2 months, respectively. In the current analysis, we present updated results for overall survival (OS), time-to-next-treatment (TTNT), and secondary malignancies (sNPL) with a median follow-up of 113 months for patients with indolent lymphomas (excluding MCL). **Methods:** 447 pts with indolent lymphomas were randomized to receive B-R or CHOP-R for a maximum of 6 cycles. The primary endpoint was PFS; secondary endpoints included OS, TTNT, and sNPL. **Results:** Patient characteristics were well balanced between arms; median age was 64 years. The difference in OS between the two treatment arms was not statistically significant, with 60 deaths in the B-R group vs 68 deaths with CHOP-R (HR 0.82, 95% CI 0.58 – 1.15, p = 0.249). The estimated 10-year survival rates were 71% for B-R and 66% for CHOP-R. TTNT was significantly prolonged with B-R compared with CHOP-R (HR 0.52, 95% CI 0.38 – 0.69, p < 0.001). Median TTNT was not yet reached in the B-R group (95% CI 124.9 – n.y.r) vs. 56 months in the CHOP-R group (95% CI 39.1 – 82.0). Patients treated initially with B-R needed fewer second-line treatments due to disease progression compared to CHOP-R treated pts: 73 pts (34%) in the B-R group received salvage treatment compared with 106 pts (52%) in the CHOP-R group. For B-R pts, CHOP-R was used as second-line therapy 26 times (36%), whereas B-R was used for pts initially treated with CHOP-R 49 times (46%). 36 pts with sNPL were observed in the B-R group compared with 39 in the CHOP-R group, with 7 hematological malignancies in both groups to date. **Conclusions:** In pts with previously untreated indolent lymphomas, B-R demonstrates a PFS and TTNT benefit over CHOP-R. Clinical trial information: NCT00991211.

7502 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Phase IIIb randomized study of lenalidomide plus rituximab (R^2) followed by maintenance in relapsed/refractory NHL: Analysis of patients with double-refractory or early relapsed follicular lymphoma (FL). *First Author: David Jacob Andorsky, Rocky Mountain Cancer Centers/US Oncology Research, Boulder, CO*

Background: Chemoresistant patients with FL and those who progress within 2 y after initial diagnosis have poor outcomes (Casulo. *JCO.* 2015) and highlight an unmet need. **Methods:** MAGNIFY (NCT01996865) is a phase IIIb, multicenter, open-label study of relapsed/refractory (R/R) NHL patients, including grades 1-3b or transformed FL (tFL). Patients receive 12 cycles of lenalidomide plus rituximab (R^2); those with stable disease or better are randomized 1:1 to maintenance R^2 or rituximab alone. The primary endpoint is progression-free survival (PFS). This analysis focuses on FL: double-refractory (DR) patients are refractory to both rituximab (as monotherapy or combination) and an alkylating agent, and early relapse (ER) patients progressed or relapsed within 2 y of initial diagnosis. **Results:** As of July 19, 2016, the R/R FL population (N = 117) included 32 (27%) DR and 43 (37%) ER patients, median ages of 64 and 65 y, respectively, mostly grade 1-3a FL (94%; 91%) and 2 tFL (1 DR; 1 ER); 72% and 49% were stage IV at study entry. Patients had a median of 2 prior regimens (DR 3; ER 2). Of ER patients, 31 had first-line R-chemo vs 12 with R-mono/other. Response rates are in Table 1. Median time to response was 2.8 mo for DR and 2.7 mo for ER patients, with median duration not reached. 1-y PFS for FL patients was 66% (DR 66%; ER 45%); 1-y PFS for ER patients with first-line R-chemo was 50% vs 27% in others. Common grade ≥3 treatment-emergent AEs for DR and ER patients were neutropenia (53%; 33%), leukopenia (9%; 12%), and lymphopenia (9%; 5%). **Conclusions:** R^2 followed by maintenance showed favorable activity and tolerable safety profiles in FL patients who are double-refractory or had early relapse (< 2 years) after initial diagnosis. Enrollment in MAGNIFY is ongoing. Clinical trial information: NCT01996865.

Best response for evaluable patients in induction and maintenance.

Response status, n (%)	DR (n = 28)	ER (n = 33)	All FL (N = 91)
ORR	13 (46)	16 (48)	61 (67)
95% CI	28%-61%	31%-67%	56%-77%
CR/CRu	6 (21)	4 (12)	33 (36)
PR	7 (25)	12 (36)	28 (31)
SD	10 (36)	13 (39)	21 (23)
PD*	5 (18)	4 (12)	9 (10)

*Includes PD and/or death prior to response evaluation completion.

7503 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

A genetic risk-stratified, randomized phase 2 intergroup study of fludarabine/antibody combinations in symptomatic, untreated chronic lymphocytic leukemia (CLL): Results from Cancer and Leukemia Group B (CALGB) 10404 (Alliance). *First Author: Amy S. Ruppert, The Ohio State University, Columbus, OH*

Background: Prior to use of novel targeted agents for CLL, debate existed regarding the best chemoimmunotherapy regimen to build upon in patients (pts) with non-del(11q) disease. The role of lenalidomide (L) was also not defined. CALGB 10404 was a randomized phase 2 study addressing these questions. **Methods:** Pts with untreated CLL requiring therapy were randomized to treatment with fludarabine + rituximab (FR), FR + 6 monthly consolidative treatments of L (5 mg days 1-21/28 x 1 then 10 mg days 1-21/28 x 5) (FR+L), or FR + cyclophosphamide (FCR). Based on pretreatment central interphase cytogenetic screening, pts with del(11q22.3) in at least 20% of cells were excluded from the primary analysis, testing whether 2-year progression-free survival (PFS) rate was improved in non-del(11q) pts within each arm. A target accrual of 103 non-del(11q) pts per arm provided at least 84% power to detect an increase in 2-year PFS rate from 60% to 73%; the critical value was 69% using a single stage design and type I error rate of 4%. **Results:** A total of 342 non-del(11q) CLL pts were randomized to treatment with FR (n = 123), FR+L (n = 109), or FCR (n = 110). Baseline characteristics were similar across arms. Two-year PFS rates with exact 90% CIs were 64% (57-71%) (FR), 71% (63-78%) (FR+L), and 74% (66-80%) (FCR). Median PFS was significantly shorter with FR compared to FR+L (p = 0.03) and FCR (p < 0.01): 43 (95% CI: 33-50), 66 (95% CI: 45-not reached), and 78 (95% CI: 58-not reached) months respectively. Median overall survival (OS) has not been reached for any arm. OS at 1, 2, and 3 years was similar across arms, although there was a plateau in OS with no events beyond 41 months in the FR+L arm, different from FR/FCR where events continued to occur. The most common adverse events were cytopenias and infections. **Conclusions:** FR+L and FCR met the protocol defined primary endpoint. FR+L extended PFS relative to FR and a plateau in survival differentiated this arm from the FR/FCR arms. Future studies comparing FR+L to FCR or incorporating L into other novel treatment regimens are justified. Support: U10CA180821, U10CA180882, Celgene. Clinical trial information: NCT00602459.

7504 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Ublituximab and ibrutinib for previously treated genetically high-risk chronic lymphocytic leukemia: Results of the GENUINE phase 3 study. *First Author: Jeff Porter Sharman, Willamette Valley Cancer Institute and Research Center/US Oncology Research, Springfield, OR*

Background: Patients (pts) with high-risk chronic lymphocytic leukemia (CLL) defined by interruptions in TP53 (either by mutation or deletion) or loss of chromosome 11q experience inferior outcomes with ibrutinib (IB) monotherapy (O'Brien ASH 2016). Ublituximab (UTX) is a novel glycoengineered mAb with enhanced ADCC targeting a unique epitope on the CD20 antigen. GENUINE is the first randomized Ph 3 trial conducted assessing the addition of a novel agent to ibrutinib in high-risk rel/ref CLL, and evaluates IB monotherapy vs. UTX + IB. **Methods:** Eligible pts with rel/ref CLL and centrally confirmed del17p, del11q, and/or a TP53 mutation were randomized 1:1 to receive IB (420 mg QD) alone or with UTX (900 mg on D1, 8, 15 of Cycle 1, D1 of Cycle 2-6, and Q3 Cycles thereafter). There was no limit on number of prior therapies. Prior IB exposure was excluded. The primary endpoint was overall response rate (ORR) per iwCLL 2008 criteria, with secondary endpoints including CR rate, MRD negativity, PFS, time to response (TTR) and safety. **Results:** 126 pts were randomized at sites in the US and Israel, with 117 pts treated (59 on UTX + IB, 58 on IB alone). Median age 67, median 3 prior therapies (range 1-8), > 70% of were male. High-risk cytogenetics were relatively balanced with ~ 50% of pts having del17p. UTX+IB was well tolerated, with infusion reactions the most prevalent AE (44%, GR3/4 5%). Neutropenia was comparable with the combination (17%, Gr3/4 7% vs. 10%, Gr3/4 9%), and other AE's were similar or lower with UTX+IB vs. IB alone (all grades), including fatigue (17% vs. 31%), dizziness (12% vs. 21%), contusion (12% vs. 26%), anemia (10% vs. 16%), and myalgia (9% vs. 14%). At median follow-up of 12 mo, best ORR per independent central review was 80% for UTX + IB vs. 47% for IB alone ($p < 0.001$). While not powered for secondary endpoints, observed advantages were seen in PFS and radiographic CR rate in the UTX + IB arm. CR and MRD confirmation is ongoing. Median TTR for the combo was 1.97 mo vs. 3.8 mo for IB alone. Both arms have responses pending confirmatory assessments. **Conclusions:** The addition of UTX to IB demonstrated a superior response rate compared to IB alone without additional clinically significant toxicity. Clinical trial information: NCT02301156.

7505 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Richter's syndrome (RS) in patients with chronic lymphocytic leukemia (CLL) on novel agent therapy. *First Author: Matthew Steven Davids, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

Background: Novel agents (NA) targeting B cell receptor kinases and Bcl-2 have substantially improved outcomes in CLL; however, the development of RS in CLL patients (pts) on NAs has been observed, and has not been systematically evaluated. **Methods:** We retrospectively reviewed pts at 9 academic centers diagnosed with pathologically-confirmed RS from 2011-16. Informed consent was provided through IRB-approved protocols. Descriptive statistics were utilized and overall survival (OS) was calculated from RS diagnosis (dx) to death or last follow-up by Kaplan-Meier. **Results:** 71 pts who developed RS on NAs for CLL were identified. Median age at CLL dx was 55 yrs (range 21-82), median of 3 therapies (range 0-12) prior to the NA. 68% pts were fludarabine-refractory, and 5 pts (7%) had relapsed post alloHCT. Median time from CLL dx to initiation of NA was 68.5 mo. (range 1.1-246.2). FISH at NA initiation: del(17p) 30/61 (49%), del(11q) 15/61 (25%), trisomy 12 15/61 (25%). Complex karyotype was present in 40/53 (75%). 46/52 (88%) were *IGHV* unmutated, VH1-69 10/43 (23%), VH4-39 4/43 (9%). 59 (83%) pts were on a BTK inhibitor, 6 (8%) PI3K inhibitor, 6 (8%) venetoclax. RS histology: DLBCL (87%), plasmablastic (6%), Hodgkin (4%), 3% other. RS Ki-67%: >90 (23%), 75-90 (25%), 50-75% (25%), <50% (28%). Median time from start of NA to RS dx was 9.1 mo (range 0.9-48.2), with 65% developing RS within 12 mo. of starting NA. In 56 pts, 19 different regimens were used as initial RS therapy, including: R-EPOCH (36%), R-CHOP (20%), checkpoint blockade (9%), OFAR (7%), or a different NA (7%). Of the 48 pts evaluable for response, ORR was 42% (15% CR, 27% PR). In 29 evaluable pts receiving R-EPOCH/CHOP, ORR was 48% (21% CR). With a median follow-up of 10.6 mo., median OS was only 3.3 mo. (95%CI 2.2-6.0), though none of the 7 pts who achieved CR has died. **Conclusions:** We report to our knowledge the largest series of CLL pts developing RS on NAs. Pts often had high risk CLL, particularly complex cytogenetics, and RS frequently developed within the first year of NA therapy. Substantial variation exists in treatment, and outcomes are poor for those who do not achieve CR. Identification of molecular drivers of RS and development of novel treatment strategies are urgently needed.

7506 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Radiotherapy to bulky disease PET-negative after immunochemotherapy in elderly DLBCL patients: Results of a planned interim analysis of the first 187 patients with bulky disease treated in the OPTIMAL>60 study of the DSHNHL. *First Author: Michael Pfreundschuh, University Saarland Medical Schoolý, Homburg Saar, Germany*

Background: RT to bulky sites improves outcome of elderly DLBCL patients [Lancet Oncol 2008; 9: 105-116; J Clin Oncol 2014; 32:112-1118]. Whether RT can be spared in PET-negative pts. after R-CHOP was prospectively addressed in OPTIMAL >60. **Methods:** 61 to 80 y-old pts. were randomized in a 2x2 factorial design to 6xCHOP-14 or 6xCHLIP-14 (liposomal instead of conventional vincristine) plus 8 x rituximab 375 mg/m^2(R) q 2 wks. or 12xR (days -4,-1,1,4,14,28,42,56,91,126,175, 238). Pts. with bulk (>=7.5 cm) PET-positive after 6 cycles chemotherapy were assigned to RT (39.6 Gy), while PET-negative bulks were observed. **Results:** 187/505 (37%) had bulky disease and were compared to 117/306 (38%) RICOVER-60 pts. (38%) who had received 6xCHOP-14+8R. OPTIMAL>60 pts. were older (70 vs. 68 years) and had more IPI=3 (33% vs. 29%) and IPI=4,5 (34% vs. 23%) compared to RICOVER-60. PET was performed in 166/187 OPTIMAL>60 bulk pts. (reasons for no PET: early death: 5; excessive toxicity: 3; protocol violation: 1, non-compliance: 4, change of diagnosis: 6, others: 2). 80/166 (48%) bulks remained PET-positive after 6 cycles of chemotherapy and 62/80 (78%) were irradiated (reasons for no RT: progression: 8; medical reasons: 9; negative biopsy: 1), reducing RT from 67/117 (57%) in RICOVER-60 by 42% to 62/187 (33%) in OPTIMAL>60. Despite the unfavorable demographics, outcome of the 187 bulk pts. in OPTIMAL>60 was non-inferior to RICOVER-60, not even in the least intensive of the 4 OPTIMAL>60 treatment arms consisting of 47 pts. who received 6xCHOP-14+8R as in RICOVER-60. 2-year PFS and OS in OPTIMAL>60 was 79% and 88%, respectively, compared to 75% and 78% of the 117 RICOVER-60 pts. In a multivariable analysis adjusting for the IPI risk factors, the hazard ratio of the OPTIMAL>60 compared to the RICOVER-60 bulk pts. was 0.7 (95% CI: 03.; 1.5; p=0.345) for PFS and 0.5 (95% CI: 02.; 1.3; p=0.154) for OS. **Conclusions:** RT can be spared in bulky disease PET-negative after chemotherapy. This strategy results in a 42% reduction of RT without compromising the outcome of these patients. Supported by Amgen, Roche, Spectrum. Clinical trial information: NCT01478542.

7507 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Noninvasive detection of clinically relevant copy number alterations in diffuse large B-cell lymphoma. *First Author: Michael C. Jin, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Somatic copy number alterations (SCNAs) are common and clinically important genomic events in lymphomas. For example, *MYC* and *BCL2* amplifications are associated with adverse outcomes (Quesada, ASH 2016), while *PD-L1* (*CD274*) amplifications are associated with improved response to checkpoint inhibitors (Ansell, NEJM 2015). However, noninvasive detection of these events from circulating tumor DNA (ctDNA) remains difficult. Using CAPP-Seq, a targeted high-throughput sequencing platform, we developed a method to profile both focal and broad SCNAs from plasma. **Methods:** We profiled plasmas from a cohort of 75 pretreatment diffuse large B-cell lymphoma patients and 48 healthy controls. Focal SCNAs were evaluated at ultra-high depths (~10,000x), allowing for detection of lesions at ~1% ctDNA fraction. Thresholds were tuned to allow a false positive rate of 1%, which was empirically validated in an independent healthy cohort (n = 15), yielding a panel-wide false discovery rate of ~2.3% (0% in our genes of interest). Sequencing reads outside the targeted regions were separately pooled and analyzed to evaluate arm and chromosome level SCNAs. **Results:** We detected SCNAs in clinically relevant genes at the frequencies reported in literature, including amplifications in *MYC* (8.0%), *BCL2* (24.0%), and *BCL6* (14.7%) and deletions in *TP53* (13.3%) and *CDKN2A* (9.3%). Remarkably, 26.7% of the cohort demonstrated amplification of both *PD-L1* and *PD-L2* (*PDCD1LG2*). Furthermore, we discovered amplifications in *PD-L2*, but not *PD-L1*, in 13.3% of our patients. Interestingly, *PD-L1* amplifications were more common in patients with relapsed lymphoma than in those with treatment-naïve disease (43.5% vs 19.2%, p = 0.02). Most *PD-L1* amplifications were focal (65%) while the remainder typically involved > 80% of Chr9p. Corresponding tissue profiling data is in progress and will also be presented. **Conclusions:** Noninvasive sampling of lymphoma ctDNA enables detection of both focal and broad SCNAs, including amplifications of *MYC*, *BCL2*, and *PD-L1*. The ability to noninvasively profile copy number altered regions allows for biopsy-free discovery of clinically significant structural alterations in lymphoma patients.

7508 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Autologous (auto) versus matched sibling donor (MSD) or matched unrelated donor (MUD) allogeneic (allo) hematopoietic cell transplantation (HCT) in follicular lymphoma (FL) patients (pts) with early chemoimmunotherapy failure (ECF): A Center for International Blood and Marrow Transplant Research (CIBMTR) analysis. *First Author: James K. Godfrey, University of Chicago, Chicago, IL*

Background: Contrary to most FL, high-risk FL pts with ECF (i.e. relapse within 2 yrs of frontline chemoimmunotherapy) have a 5 yr OS of only 50%. (Casulo, JCO 2015). We used the CIBMTR database to compare autoHCT versus either MSD or MUD alloHCT as the first transplant approach in FL pts with ECF. **Methods:** Adult FL pts (age ≥18) undergoing autoHCT or alloHCT between 2002-2014 and receiving first line rituximab-based chemoimmunotherapies with evidence of ECF (defined as disease relapse or progression within 2 yrs of treatment initiation) were included. The primary endpoint was OS; secondary endpoints were progression-free survival (PFS), relapse and non-relapse mortality (NRM). **Results:** 440 pts had ECF (auto = 240, MSD = 105, MUD = 95) (Table 1). The 5 yr adjusted probabilities (AjP) of NRM were significantly lower with autoHCT (5%), versus MSD (17%) or MUD (33%) HCT ($p<0.0001$). 5 yr AjP of relapse were significantly lower with MSD (31%) or MUD HCT (23%), versus autoHCT (58%; $p<0.0001$). AjP of 5 yr PFS following auto, MSD and MUD HCT were 38%, 52% and 43% (p=.006) respectively. The AjP of 5 yr OS was significantly higher following autoHCT (70%) or MSD HCT (73%) versus MUD HCT (49%; p=0.004). **Conclusions:** AutoHCT for FL pts with ECF has low NRM and 5 yr OS rates (70%) that are provocatively higher than historical data (~50%). MSD HCT had the lowest relapse rate with similar survival. A prospective trial confirming the role of HCT in ECF FL is warranted.

	Auto (N=240)	MSD (N=105)	MUD (N=95)
Med age (range)	56 (23-79)	52 (29-68)	53 (21-74)
Med number of therapies before HCT (range)	2 (1-6)	3 (1-9)	3 (1-8)
Med time from diagnosis to HCT (range), months	24 (6-203)	23 (3-128)	27 (7-167)
AlloHCT conditioning intensity			
Myeloablative	-	35 (33)	27 (28)
Remission @HCT			
CR	86 (36)	25 (24)	19 (20)
PR	92 (38)	32 (30)	34 (36)
Refractory	55 (23)	46 (44)	40 (42)
Missing	7 (3)	2 (2)	2 (2)
Med follow-up (range), months	73 (3-142)	69 (3-152)	73 (12-121)

7509 Poster Discussion Session; Displayed in Poster Session (Board #271), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

CD19 CAR-T cells combined with ibrutinib to induce complete remission in CLL. *First Author: Saar Gill, University of Pennsylvania, Philadelphia, PA*

Background: Immunotherapy with anti-CD19 CART cells induces complete remission (CR) in the minority of patients with CLL, but where CRs occur they tend to be durable. Based on preclinical evidence of synergy, we combined anti-CD19 CAR T cells with ibrutinib to test the hypothesis that pre- and concurrent treatment would enhance the CR rate. **Methods:** This is a pilot trial of anti-CD19 CAR T cells in adults with CLL/SLL who were not in CR despite at least 6 months of ibrutinib. Pts must have failed at least 1 regimen before ibrutinib, unless they had del(17)(p13.1) or a *TP53* mutation. T cells were lentivirally transduced to express a CAR comprising CD3z, 4-1BB, and humanized anti-CD19 scFv (CTL119). Pts were lymphodepleted 1 week before infusion. Ibrutinib was continued throughout the trial. **Results:** Manufacturing was successful in all pts. Ten pts (9M, 1F; ages 47-77; 0-12 regimens prior to ibrutinib) have been infused. All had abnormalities of *TP53* or *ATM* and two pts had increasing *BTK* C481S clones. Median marrow CLL burden was 10% (range 10-50%). The median follow-up is 6 months (range 0.5-9). Cytokine release syndrome (CRS) developed in 9 pts; gr1 in 2, gr2 in 6 and gr3 in 1 pt. One pt developed gr4 tumor lysis syndrome. Treatment of CRS with the IL-6 receptor antagonist tocilizumab was not required. At 3 months, 8 evaluable pts had achieved an MRD-ve marrow CR (89%) by 9-color flow, and all remain in marrow CR at last F/U. There was modest residual splenomegaly in 3/5 patients, and adenopathy resolved in 4/6 subjects with progression in 1/6. MRD assessment by deep sequencing will be presented. **Conclusions:** We observed 89% MRD-ve marrow CR in pts with high-risk CLL using a well-tolerated combination of CART cells and ibrutinib. Longer follow-up will reveal the durability of these results and could support evaluation of a first-line combination approach in an attempt to obviate the need for chronic therapy. Clinical trial information: NCT02640209.

7510 Poster Discussion Session; Displayed in Poster Session (Board #272), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Long-term efficacy and safety with ibrutinib (ibr) in previously treated chronic lymphocytic leukemia (CLL): Up to four years follow-up of the RESONATE study. *First Author: John C. Byrd, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Ibr, a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is FDA-approved for all pts with CLL/SLL. We report updated safety and efficacy results with up to 4 y follow-up from the ph III RESONATE trial of ibr vs ofatumumab (ofa). **Methods:** Pts had ≥1 prior therapy. Pts received 420 mg ibr PO until PD or ofa up to 24 wks. At interim analysis (median 9 mo follow-up), the DMC declared superiority of ibr vs ofa for PFS and OS, and ibr access was recommended for all ofa pts. Long-term follow-up efficacy endpoints are per investigator assessment. Ofa pts were censored at crossover for OS. **Results:** 391 pts were randomized to receive ibr (n = 195) or ofa (n = 196). Median age was 67 y (40% ≥70 y); 57% had Rai stage III/IV. With median follow-up of 44 mo (53 mo max) for ibr arm, PFS was significantly longer for ibr vs ofa (median NR vs 8 mo, [HR 0.133; $P<0.0001$]; 3-y PFS 59% vs 3%) with significant benefit across subgroups. PFS with ibr for del11q subgroup trended to have the most favorable outcome; however, PFS was not statistically different for pts with del17p or del11q or without these FISH abnormalities. At analysis, with the majority of pts (68%) randomized to ofa crossing over to ibr, OS was longer for ibr vs ofa (median OS NR for either arm). The OS rate for ibr at 3 y was 74%. ORR for ibr was 91% with CR/CRi rates (now 9%) increasing over time. Baseline cytopenias improved with extended ibr therapy for hemoglobin (85%), platelet (95%), and absolute neutrophil counts (95%). AE profile of ibr was consistent with previous reports. Major hemorrhage, Gr ≥3 atrial fibrillation, and Gr ≥3 hypertension occurred in 6%, 6%, and 8% of pts, respectively, over a follow-up of up to 4 y. Incidence of most Gr ≥3 AEs decreased from y 1 vs y 2-3: neutropenia- 18% vs 8%; pneumonia- 11% vs 4%; atrial fibrillation- 4% vs 2%, respectively. Discontinuations were most frequently PD (27%) and AE (12%). At analysis, 90 ibr pts (46%) continue ibr on study. **Conclusions:** Long-term treatment with ibr in this international ph III RESONATE study is tolerable and continues to show sustained PFS and OS regardless of high-risk cytogenetics. Ph III results in relapsed del17p and del11q pts compare favorably to prior ph II reports. Clinical trial information: NCT01578707.

7511 Poster Discussion Session; Displayed in Poster Session (Board #273), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Tolerability and activity of chemo-free triplet combination of TGR-1202, ublituximab, and ibrutinib in patients with advanced CLL and NHL. *First Author: Loretta J. Nastoupil, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Novel targeted agents are emerging for B-cell malignancies, but few studies have safely combined these agents. Ublituximab (UTX) is a novel glyco-engineered mAb targeting a unique epitope on the CD20 antigen. TGR-1202 is a next generation, once daily PI3Kδ inhibitor, demonstrating a favorable safety profile compared to prior inhibitors, including in long-term follow up (Burris, 2016). This Ph 1 trial evaluates the safety/efficacy of the triplet combination of a novel anti-CD20 mAb + PI3Kδ + BTK inhibitor (ibrutinib) in pts with B-cell malignancies. **Methods:** Eligible pts had CLL or rel/ref NHL w/o limit to prior therapies, including those ref to prior PI3Kδ or BTK inhibitors. UTX dosed on D1, 8, 15 of C1; D1 of C2-6, and C9 & 12. TGR-1202 dose escalated (400/600/800mg QD), ibrutinib dosed at 420mg (CLL) or 560mg (NHL), both on C1D1. **Results:** 38 pts were enrolled: 20 CLL/SLL and 18 NHL, including 6 follicular (FL), 6 DLBCL, 4 mantle cell (MCL) and 2 marginal zone (MZL). Med age 65 yrs (range 32-85); 29 M/9 F; med prior tx = 3 (range 0-6). 2 pts were ref to prior PI3Kδ and 2 were prev treated with ibrutinib (1 ref/1 rel). MTD was not reached. Most common (> 20%) all causality AE's were fatigue (42%), diarrhea (39%), dizziness (34%), nausea (32%), neutropenia, pyrexia, rash, infusion reaction, insomnia (each at 29%), thrombocytopenia, cough (each at 26%), anemia (24%) and sinusitis (21%). GR 3/4 AE's were minimal, the only event > 10% was neutropenia (16%). ORR amongst 36 evaluable pts is shown in the table below. 53% of evaluable CLL pts had high-risk cytogenetics and 4/6 DLBCL pts were non-GCB. One CLL pt (17p/11q del) ref to both PI3Kδ and ibrutinib achieved a CR. Med time on study is 10 mos (range 1 – 27+ mos). Med DOR not reached (range 3 – 24+ mos). **Conclusions:** This is the first known triple combination of an anti-CD20 mAb + PI3Kδ + BTK inhibitor. The combination of UTX, TGR-1202, and ibrutinib has been well tolerated with activity observed across heavily pre-treated and high-risk B-cell malignancies. Expansion cohorts at the highest dose (800mg TGR-1202 + full dose ibrutinib) are underway. Future trials for the triplet are warranted. Clinical trial information: NCT02006485.

Subtype	N	CR	PR	ORR
CLL/SLL	19	3	16	100%
FL/MZL	7	2	4	86%
DLBCL	6	0	1	17%
MCL	4	1	3	100%

7512 Poster Discussion Session; Displayed in Poster Session (Board #274), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Clinical and biologic covariates of outcomes in ZUMA-1: A pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (r-NHL). *First Author: Frederick Lundry Locke, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: Outcomes in activated B cell subtype diffuse large B cell lymphoma (ABC-DLBCL) and r-NHL are poor (Sehn *Blood* 2015, Crump ASCO 2016). ZUMA-1 is the first, multicenter trial of anti-CD19 chimeric antigen receptor (CAR) T cells, axi-cel, in r-NHL. **Methods:** Dosing and eligibility were per Neelapu ASH 2016. The primary endpoint was objective response rate (ORR); secondary endpoints were duration of response (DOR), overall survival (OS), and safety. Cell of origin (COO) and CD19 status were assessed centrally using Lymphoma Subtyping Test NanoString (Wallden *JCO* 2015) and a validated immunohistochemistry assay, respectively. **Results:** As of Jan 27, 2017, 111 patients (pts) were enrolled; the manufacturing success rate was 99% with an average 17-d turnaround time; 101 pts (modified intent-to-treat [mITT] population) received axi-cel. In the mITT population, the ORR was 82% (complete response [CR], 54%). With 8.7 m median follow-up, 44% remain in response and 39% in CR. The median DOR was 8.1 m and not reached (NR) for pts with CR. Median OS was NR. Results for clinical and biologic covariates are listed in the table. In pts who received tocilizumab (n = 43) and/or steroids (n = 27) for cytokine release syndrome (CRS) and/or neurologic events (NE), ORR was 84% and 78%, respectively. Most common grade ≥3 adverse events (AEs) were neutropenia (66%), leukopenia (44%), anemia (43%), febrile neutropenia (31%), thrombocytopenia (24%), and encephalopathy (21%). Rates of grade ≥3 CRS and NE were 13% and 28%, respectively. There were 3 grade 5 AEs (Neelapu ASH 2016). **Conclusions:** Axi-cel induced an ORR of 82% in pts with r-NHL, response is ongoing in 44% of pts at 8.7 m. Similar clinical responses were observed in pts with r-ABC-DLBCL. AEs were manageable and the use of tocilizumab/steroids did not appear to impact ORR. Drs Locke and Neelapu contributed equally. Funding source: Kite Pharma and Leukemia & Lymphoma Society Therapy Acceleration Program Clinical trial information: NCT02348216.

Group (n = samples evaluable)	% Positive for Marker in Evaluable Samples	ORR/CR
mITT (n = 101)	N/A	82%/54%
GCB (n = 69)	71%	88%/57%
ABC (n = 69)	25%	76%/59%
CD19+ (n = 82)	90%	85%/57%
CD19- (n = 82)	10%	75%/50%

7513 Poster Discussion Session; Displayed in Poster Session (Board #275), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T-cell product JCAR017 (TRANSCEND NHL 001). *First Author: Jeremy S. Abramson, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: JCAR017 is a second-generation, CD19-directed, 4-1BB CAR T cell product comprising CD8 and CD4 CAR T cells in a 1:1 ratio. A multicenter phase 1 trial of JCAR017 in R/R B-cell NHL (NCT02631044) is underway. **Methods:** Patients with R/R DLBCL, PMBCL, FL grade 3B, or MCL and adequate organ function are eligible. There was no minimum ALC requirement for apheresis; no test expansion was required. Treatment includes lymphodepletion with fludarabine and cyclophosphamide, followed by JCAR017. Multiple dose levels (DLs)/administration schedules of JCAR017 are being evaluated. Study objectives include safety, PK, and antitumor response. **Results:** As of November 23, 2016, 28 patients have been treated and are evaluable for safety and efficacy. Nineteen were male, 9 female; 25 DLBCL, 2 MCL, and 1 FL grade 3B. Median age was 63 years (range 37-79), median number of prior therapies was 4 (range 1-8), 23 (82%) were refractory to their last chemotherapy, and 16 (57%) had prior transplant. No severe cytokine release syndrome (sCRS) was observed; 10 patients had grade 1-2 CRS (1 received tocilizumab). Five patients developed neurotoxicity, including 4 grade 3-4; all events resolved in the 4 patients who had adequate follow up. Median onset of CRS and neurotoxicity were 5 and 11 days, respectively. Four deaths after disease progression occurred, none related to JCAR017. In 20 patients treated at DL1 (5×10^7 cells), the RR was 80% with 60% achieving CR. One patient with secondary CNS involvement achieved CR without neurotoxicity. JCAR017 was detected at 3 and 6 months in responding patients, including some who relapsed; higher mean peak levels were detected in patients with durable response at 3 months. Data on patients treated at DL2 (1×10^8 cells), alternative dose schedules, tumor biopsy, and additional biomarkers will be presented. **Conclusions:** Treatment with JCAR017 results in high CR rate in patients with heavily pretreated R/R DLBCL. Relapses can occur despite persistence of JCAR017, suggesting tumor immune evasion mechanisms may contribute to relapse. Observed toxicities are manageable and occurred at rates lower than those reported for other CD19-directed CAR T cell products. Clinical trial information: NCT02631044.

7514 Poster Discussion Session; Displayed in Poster Session (Board #276), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

L-mind: MOR208 combined with lenalidomide (LEN) in patients with relapsed or refractory diffuse large b-cell lymphoma (R-R DLBCL)—A single-arm phase II study. *First Author: Kami J. Maddocks, Division of Hematology, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: The Fc-enhanced CD19 antibody MOR208 and the immunomodulatory drug LEN have demonstrated single agent activity in patients (pts) with R-R DLBCL. MOR208 and LEN have shown synergy in vitro and in vivo in preclinical lymphoma models. This ongoing phase II study assesses the safety and efficacy of MOR208 + LEN in pts with R-R DLBCL. **Methods:** Pts >18 years old with R-R DLBCL, ECOG 0–2, adequate organ function, having previously received ≥1 but not more than 3 prior therapies, including ≥1 CD20-targeting regimen and who are not candidates for autologous stem cell transplant (ASCT), are eligible. Treatment comprises up to 12, 28-day (d) cycles (C) of MOR208 12 mg/kg IV, weekly during C1–3 (loading dose d4 of C1); every second week C4–12 + LEN 25 mg po d1–21, C1–12. Pts progression-free after 12 cycles receive up to 12 additional cycles of MOR208 (every second week). The primary endpoint is the overall response rate (ORR) by central radiology assessment. Secondary endpoints include disease control, duration of response, progression-free and overall survival, safety, and response by cell of origin and other biomarkers. A preplanned safety evaluation was undertaken. **Results:** 31 of 80 planned pts were enrolled prior to data cutoff (3 January 2017). Median age was 74 years (range 47–82); 45% of pts received ≥2 prior lines of therapy; 23% had rituximab refractory disease; 74% had Ann Arbor stage ≥III disease; 65% had elevated lactate dehydrogenase level, and 52% had a poor revised International Prognostic Index (3-5). The most common treatment-emergent adverse events (any grade/grade ≥3 [% pts]) were neutropenia (39/26), anemia (23/0) thrombocytopenia (16/6), infections (26/10) diarrhea (13/0), pyrexia (13/0), and rashes (13/6). Of 26 response evaluable pts (median follow-up 3.3 months), ORR (investigator assessed) was 58% (15 pts), with 7 (27%) complete responses. Median time to response was 1.8 months. **Conclusions:** The combination of MOR208 + LEN is well tolerated and shows promising activity in pts with R-R DLBCL. Accrual and follow-up of pts is ongoing, as are cell of origin and other biomarker analyses. Clinical trial information: NCT02399085.

7515 Poster Discussion Session; Displayed in Poster Session (Board #277), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Updated results of single-agent ibrutinib in recurrent/refractory primary (PCNSL) and secondary CNS lymphoma (SCNSL). *First Author: Christian Grommes, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: PCNSL is an aggressive primary brain tumor with median progression free survival (PFS) after upfront methotrexate-based chemotherapy of 2-3 years. Outcome and treatment options are poor for recurrent/refractory (r/r) disease. Ibrutinib has shown promising clinical response in Mantle cell lymphoma, CLL, Marginal Zone, and Waldenström. This trial investigates Ibrutinib in patients with r/r PCNSL and SCNSL. **Methods:** Eligible patients had r/r PCNSL or SCNSL, age≥18, ECOG≤2, normal end-organ function, and unrestricted number of CNS directed prior therapies. In patients with SCNSL disease, systemic disease needed to be absent. **Results:** Twenty-five patients were enrolled (3 at 560 mg; 22 at 840 mg). Median age was 68 (range 21-85); 15 were women. Median ECOG was 1 (0: 2, 1: 15, 2: 8). 64% had PCNSL and 36% SCNSL; 68% had recurrent disease. Seventeen had parenchymal disease, 3 isolated cerebrospinal fluid (CSF) involvement and 5 both. Seven grade 4 adverse events were observed in 7 patients neutropenia (in 3 patients), lymphopenia (2), sepsis (1), and ALT elevation (1). Fourteen patients developed 20 grade 3 toxicities, including lymphopenia in 5 patients, hyperglycemia in 3, ALT elevation in 2, thrombocytopenia in 2, lung infection in 2, AST elevation in 1, neutropenia in 1, urinary tract infection in 1, colitis in 1, febrile neutropenia in 1 and fungal encephalitis in 1. The most common toxicities at any grade were hyperglycemia, thrombocytopenia and anemia of which most were grade 1/2. No grade 5 events have been observed. After a median follow-up of 414 days (range 289-674), 22/25 patients were evaluated for response (3 did not complete at least 15 days of drug treatment). Over all response was 68% (17/22; 77% (17/22) in patient that completed at least 15 days of drug treatment) with 10 CR, 7 PR, 2 SD and 3 PD as best response. The median PFS is 4.6 months (5.4 months in patients that completed at least 15 days of drug treatment; longest: 15.3 months). The median overall survival has not been reached. **Conclusions:** Patients with CNS lymphoma tolerate Ibrutinib with manageable adverse events. Clinical response was seen in 68% of CNS lymphoma patients. Clinical trial information: NCT02315326.

7516 Poster Discussion Session; Displayed in Poster Session (Board #278), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Phase I clinical trial on pomalidomide and dexamethasone in treating patients with relapsed/refractory primary central nervous system lymphoma (PCNSL) or primary vitreoretinal lymphoma (PVRL). *First Author: Han W. Tun, Mayo Clinic, Jacksonville, FL*

Background: PCNSL is a diffuse large B cell lymphoma confined to the CNS. Pomalidomide (POM) is a novel immunomodulatory agent with excellent CNS penetration (~40%) based on CNS PK analysis in rats and pre-clinical therapeutic activity against CNS lymphoma. **Methods:** A Phase I clinical trial was undertaken to determine the maximal tolerated dose (MTD) of POM, safety profile and overall response rate (ORR). Treatment consists of POM daily for 21 days every 28 days in combination with dexamethasone 40 mg PO weekly for two cycles followed by POM alone in subsequent cycles until progression or intolerance. 4 dose escalation levels of POM (3mg, 5mg, 7mg, and 10 mg) were planned. Thromboprophylaxis with oral anticoagulant or aspirin was required. MTD determination has been completed and expansion of the MTD cohort is ongoing. Therapeutic responses were evaluated per the international PCNSL collaborative group (IPCG) criteria after 2 cycles of treatment. The trial is registered with ClinicalTrials.gov (#NCT01722305). **Results:** 21 of 25 patients accrued were eligible for assessment. The MTD was determined to be 5 mg qd for 21 days every 28 days. Two DLTs were seen at dose level 3 (Grade 3 dyspnea and grade 4 thrombocytopenia). One DLT was seen in the expanded MTD cohort (Grade 4 neutropenia and lymphocytopenia). ORR for the study (9/21) was 43% (95% CI- 22%, 66%) with 4 CR, 1 CRu and 4 PR. 3 responders completed 2, 4, and 6 cycles before progression. 6 responders have completed 4, 5, 6, 10, 12, and 32 cycles and remain on treatment. ORR for the MTD dose level was (5/12) 42% (95% CI-15%, 72%) with 3 CR and 2 PR. 2 patients had stable disease (SD). Pseudoprogression was seen in 1 patient. Overall, grade 3/4 toxicity was hematologic (neutropenia, anemia, and thrombocytopenia) in 38.1% and non-hematologic in 33.3% (fatigue, pneumonia, sepsis, syncope, dyspnea, hypoxia, respiratory failure and maculo-papular rash). Percent CSF/blood ratio of POM was determined to be 19% in 1 patient. **Conclusions:** Pomalidomide treatment is feasible with therapeutic activity against relapsed/refractory PCNSL and should be further developed. Clinical trial information: NCT01722305.

7517 Poster Discussion Session; Displayed in Poster Session (Board #279), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Outcomes by CD30 expression in patients with CTCL receiving brentuximab vedotin (BV) vs physician's choice (PC) in the Phase 3 ALCANZA study. *First Author: Youn H. Kim, Department of Dermatology, Stanford University School of Medicine and Stanford Cancer Institute, Stanford, CA*

Background: The Phase 3 ALCANZA study showed significant, durable responses with CD30-directed antibody-drug conjugate BV vs PC of methotrexate (MTX) or bexarotene (Bex) for CD30-positive (CD30+) cutaneous T cell lymphoma (CTCL). Uniform CD30 expression is characteristic of primary cutaneous anaplastic large cell lymphoma (pcALCL), but is variable among other subtypes including mycosis fungoides (MF). We examined activity of BV and MTX / Bex by CD30 expression in pts treated on the ALCANZA study. **Methods:** Adults with previously treated CD30+ MF or pcALCL were enrolled. MF pts had ≥2 skin biopsies from separate lesions, pcALCL had ≥1. Patients were scored CD30+ if ≥1 biopsy had ≥10% CD30+ lymphoid cells using an investigational Ventana diagnostic test, centrally assessed by one pathologist. We compared the proportion of MF subgroup pts (n=50 per treatment arm) with objective response lasting ≥4 months (ORR4; ALCANZA primary endpoint) and PFS in pts with all biopsies ≥10% CD30+ ($CD30_{min}$ ≥10%) vs ≥1 biopsy <10% CD30+ ($CD30_{min}$ <10%). Pts were randomized 1:1 to BV 1.8 mg/kg IV, Q3W, or PC for up to 16 three-week cycles. **Results:** 125/184 (68%) MF and 44/47 (94%) pcALCL pts were screened and scored CD30+. High inter-lesional variability in CD30 expression was seen in MF pts; 55/125 CD30+ MF pts (44%) had ≥1 biopsy with low (<10%) or undetectable CD30. 100/125 CD30+ MF pts were eligible and enrolled. In the BV arm, ORR4 was higher in MF pts with $CD30_{min}$ ≥10% vs <10%; median PFS with BV was higher in the $CD30_{min}$ <10% group (Table). ORR4 with BV was greater than PC over all CD30 expression ranges ($CD30_{min}$ <5%, 38% vs 13%; CD30 ≥5–≤20%, 35% vs 10%; CD30 >20%, 76% vs 7%, respectively). **Conclusions:** Notable inter-patient or inter-lesional variability in CD30 expression was seen in MF pts. Highly superior ORR4 and PFS endpoints were seen with BV over PC regardless of $CD30_{min}$ expression level. Clinical trial information: NCT01578499.

	BV	PC	Difference, % [95% CI]
ORR4, n/N (%)			
$CD30_{min}$ <10%	9/22 (40.9)	2/21 (9.5)	31.4 [2.8, 58.1]
$CD30_{min}$ ≥10%	16/28 (57.1)	3/29 (10.3)	46.8 [20.6, 67.0]
Median PFS (months) [95% CI]			Hazard ratio [95% CI]
$CD30_{min}$ <10%	27.9 [8.6, 27.9]	2.3 [1.6, 3.5]	0.125 [0.044,0.355]
$CD30_{min}$ ≥10%	17.2 [9.8, NE]	3.5 [2.1, 4.6]	0.176 [0.072,0.432]

7518 Poster Discussion Session; Displayed in Poster Session (Board #280), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Preliminary results of a phase Ib study of GS-4059 in combination with entospletinib in patients with B-cell malignancies. *First Author: Christopher Fegan, Cardiff CLL Research Group, School of Medicine, Heath Park, Cardiff, United Kingdom*

Background: GS-4059 (ONO-4059) selectively and irreversibly inhibits Bruton's tyrosine kinase (BTK) and entospletinib selectively inhibits spleen tyrosine kinase (SYK). **Methods:** This ongoing phase 1b study is evaluating the safety and tolerability of GS-4059 combined with entospletinib in patients with previously treated CLL, FL, SLL, MCL, MZL, WM, or non-GCB DLBCL. The study design uses 3+3 dose escalation (Table) withexpansion cohorts at potential phase 2 doses. **Results:** With a median duration of treatment of 22 weeks (range 3-56), 26/32 enrolled patients continue on treatment. The median age was 70 (43–85) years and 59% were men. Patients had the following diseases: CLL (n = 9), non-GCB DLBCL (7), FL (6), WM (5), MCL (2), SLL (2), and MZL (1). The median number of prior therapies was 2 (1–5). Five patients discontinued all study treatment, 4 due to disease progression (DLBCL x 2, MCL, MZL) and one due to withdrawal of consent. There has been 1 death on study due to progressive disease. The maximum tolerated dose was not reached. 90% of patients treated reported a treatment-emergent AE (TEAE) of which 48% were grade ≥3. Grade ≥3 TEAEs that were present in more than 1 patient were neutropenia (4), anemia, thrombocytopenia, pneumonia and AST/ALT elevation (2 each). The TEAEs present in >10% of patients were fatigue (7), petechiae (5), asthenia, constipation, contusion, dyspepsia, neutropenia and rash (4 each). No patients discontinued treatment due to AEs and all 5 patients with interruption of treatment for an AE successfully re-initiated therapy. 17 patients were evaluable for best overall response with the results as follows: 11 with partial responses (2 each with CLL, DLBCL, FL, SLL, WM, 1 with MCL); 4 with stable disease; 2 with progressive disease. **Conclusions:** GS-4059 at up to 160 mg in combination with entospletinib up to 400 mg daily was safe and well tolerated, supporting the continued clinical evaluation of the combination for the treatment of B-cell malignancies. Clinical trial information: NCT02457598 Clinical trial information: NCT02457598.

Dose escalation cohorts.

	GS-4059	entospletinib		GS-4059	entospletinib	
Dose Level	**A**		**n**	**B**		**n**
1	40 QD	200 QD	3	–	–	
2	80 QD	200 QD	6	40 QD	400 QD	3
3	150 QD	200 QD	3	80 QD	400 QD	15
4				160 QD	400 QD	2

7519 Poster Discussion Session; Displayed in Poster Session (Board #281), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: Interim results of an on open-label, phase II study. *First Author: Loretta J. Nastoupil, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Follicular lymphoma (FL) tumors are infiltrated with antitumor T cells, however, their function is impaired by immune checkpoints such as PD-1/PD-ligand pathway. Blocking PD-1 enhances the function of antitumor T cells in FL. In addition, blocking PD-1 on NK cells has been shown to enhance the ADCC effect of NK cells. We reasoned that the combination of pembrolizumab (P), an anti-PD-1 antibody (ab), and rituximab (R), an anti-CD20 ab that induces ADCC, is likely to be synergistic through activation of both the innate and adaptive immune systems and result in enhanced clinical activity in FL. **Methods:** We evaluated P and R in an open-label, non-randomized, single institution, phase II trial (N=30). Key inclusion criteria included adult (age ≥ 18 years), FL grade 1-3a, ECOG 0-1, in relapse after ≥1 prior therapy (tx) and R sensitive disease, defined as a complete (CR) or partial response lasting at least 6 months (mos) after most recent R-containing therapy. Pts received R (375 mg/m^2 IV) on days 1, 8, 15, and 22 of cycle 1 and P (200mg IV) q 3 weeks for up to 16 cycles starting on day 2 of cycle 1. Primary endpoint was overall response rate (ORR). **Results:** 27 pts have initiated therapy, median age 65 (range 42-79), 52% male, 76% had intermediate or high risk FLIPI, 56% met GELF criteria. Median prior tx =1 (range 1-4). Adverse events (AE) regardless of causality were mild, most grade 1-2. Grade 3 AE's included nausea (N=2), infusion reaction (N=2), aseptic meningitis (N=1), pneumonia (N=1). Immune-related AEs included grade 2 diarrhea (N=2), grade 2 pneumonitis (N=1), grade 2 skin rash (N=1). At the pre-planned interim analysis (N=15), ORR was 80%, CR rate was 60%. With a median follow up of 7 mos (range 0.5-17), median DOR, PFS, and OS has not been reached. PD-L1 expression was tested in 8 baseline tumor samples using PD-L1 22C3 IHC pharmDx and was detected in histiocytes in all 8 tumors, present in only 1-8% of tumor cells in 5 tumors. Additional biomarker analyses are ongoing. **Conclusions:** The combination of P and R is well tolerated in relapsed FL and is associated with high overall and CR rate. These interim results warrant further investigation of this combination in FL. Clinical trial information: NCT02446457.

7520 Poster Discussion Session; Displayed in Poster Session (Board #282), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Combination ibrutinib (Ibr) and venetoclax (Ven) for the treatment of mantle cell lymphoma (MCL): Primary endpoint assessment of the phase 2 AIM study. *First Author: Constantine Si Lun Tam, Peter MacCallum Cancer Centre; St Vincent's Hospital; University of Melbourne, Melbourne, Australia*

Background: Both ibr and ven have activity in relapsed/refractory (R/R) MCL, but complete remissions (CR) are attained in <25% with either. We sought to determine the activity of the combination in an investigator-initiated, phase 2 study. **Methods:** Enrolment of 24 patients (pts) with R/R (n=23) or frontline (n=1) MCL completed in 09/16. Pts received 4 weeks of ibr (560mg/d), followed by introduction of ven (weekly ramp-up to target 400mg/d). The primary endpoint was CR rate at week 16, as assessed by PET/CT, BMAT, flow & molecular MRD, and endoscopy (if baseline gut involvement). Response was calculated separately with and without knowledge of the PET result by IWG criteria (Cheson JCO 2007), in order to compare with published studies (ibr, 9% CR at wk16; ven, best CR rate 21%). **Results:** Median age of pts was 68 (range, 47-81) years. For the R/R pts (n=23), median lines of prior therapy was 2 (1-6), 48% were refractory to last treatment, and 30% had failed previous autologous SCT. As of data cutoff on Jan 11 2017, 18 pts remain on therapy, and 6 stopped treatment due to progressive disease (4), adverse event (1) or unrelated death (1). At week 16, ORR was 71% (63% CR) and 80% of complete responders were flow-cytometry negative in the marrow (sensitivity 10^{-3} to 10^{-4}). Using CT without PET, the comparison responses were CR 42%, CRu 17%, PR 17% (ORR 78%). After a median follow-up of 8.3 (range 1.4-17.7) months, the 8-month estimates of PFS and OS months are 74% and 81%. Adverse events ≥20%, irrespective of attribution, were fatigue (71%), diarrhea (67%), nausea (50%), URTI (38%), gastro-esophageal reflux (33%), neutropenia (33%), cough (25%) and bruising (21%); with the exception of neutropenia (25% grade 3-4), these were predominantly grade 1-2 in severity. Tumour lysis syndrome occurred in 2 pts with high tumour burden, leading to revision of the protocol ven starting dose from 50mg, to 20mg/d. **Conclusions:** The combination of ibr and ven was tolerable and achieved CR rate of 63% at week 16 in pts with MCL. The efficacy results compare favorably with historical results, and warrant further phase III investigation. Clinical trial information: NCT02471391.

7521 Poster Session (Board #283), Mon, 8:00 AM-11:30 AM

Innovative approach to determine overall survival (OS) benefit for orphan diseases using case match control analyses (CMCA): The PROPEL experience of pralatrexate in patients with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL). *First Author: Owen A. O'Connor, Columbia University Medical Center, New York-Presbyterian Hospital, New York, NY*

Background: The challenges in conducting randomized studies in orphan diseases poses limitations on our ability to identify the most promising treatments. Randomized studies in this setting can take protracted periods of time to complete, can be very expensive while not offering the promise of significant commercial return, and could become irrelevant as the pace of scientific advancement continues. The majority of drugs approved in this setting are often approved on surrogate end-points like progression free survival (PFS) or complete response (CR) rates in single arm studies. CMCA are statistically stronger than single arm studies, and can be highly informative in this setting. **Methods:** We established an integrated international database of patients with R/R PTCL to clarify the OS advantage of pralatrexate using original data from the PROPEL study, an international, multicenter phase II study in patients with R/R PTCL. The propensity score was used to match cases and controls. Cases were matched based on histology, number of previous treatments received, age at diagnosis and sex. **Results:** With 1:1 ratio match, we identified 83 cases and 83 controls. In total, 83 patients out of 109 treated on the PROPEL study were successfully matched. OS was plotted for each of the two study populations. The survival curves for the control population were found to be nearly identical to that reported for this population from other datasets. The overall survival was 4.04 months (95% CI 2.83, 5.78), which is consistent with historical controls describing this population. The median OS in for the pralatrexate treated cohort in this analysis was 16.6 months (95% CI: 11.99-25.56). The OS was a highly statistically significant difference between these two populations, with a hazard ratio of 0.426 (95% CI: 0.296-0/61). This difference held up for each of the major histologic subsets, including PTCL-NO and angioimmunoblastic PTCL. **Conclusions:** This approach can be used to better understand how new drugs in orphan diseases perform in heterogeneous patient populations. Clinical trial information: NCT00364923.

7522 Poster Session (Board #284), Mon, 8:00 AM-11:30 AM

Ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (GA101) (iFCG) for previously untreated patients with chronic lymphocytic leukemia (CLL) with mutated IGHV and non-del (17p). *First Author: Nitin Jain, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pts with mutated *IGHV* (*IGHV*-M) have favorable long-term outcomes after FCR. **Methods:** We designed an investigator-initiated phase II trial with ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG) for previously untreated pts with *IGHV*-M CLL (NCT02629809). The intent was to limit FC to 3 courses, potentially reducing short- and long-term toxicity, while maintaining efficacy through addition of ibrutinib and obinutuzumab. Key eligibility included age ≥18, *IGHV*-M, no del17p. Pts received 3 courses of iFCG. G-CSF was not mandated. Primary endpoint: CR/CRi with bone marrow (BM) MRD-neg (4-color flow-cytometry) after 3 courses of iFCG. Pts meeting primary endpoint received ibrutinib with obinutuzumab (iG) for C3-6, then ibrutinib C7-12. Pts not achieving primary endpoint received iG (C4-12). All pts who are MRD neg at 1 year will stop all therapy, including ibrutinib. Pts MRD+ at 1 year may continue ibrutinib. Historic C3 BM MRD-neg with FCR in *IGHV*-M 26% (Strati, Blood 2014). Target BM MRD-neg after iFCG x3 is 45%. Sample size 45. **Results:** 23 pts started treatment. Median age 59 yrs (25-71). Prognostic markers [del13q (n=17), negative (n=3); trisomy 12 (n=3)]. 18 pts completed 3 courses of iFCG and had initial response assessment (the remaining 5 pts too early). All 18 pts had a response; 14/18 (78%) achieved MRD-neg in BM at 3 month with 7/18 achieving CR/CRi (all MRD neg). No pt has progressed, and all but one continue to receive treatment. Of the 23 pts, 11 pts had G3-4 neutropenia and 5 pts had G3-4 thrombocytopenia. 4 pt had neutropenic fever. 1 pt who achieved MRD-neg CR developed pulmonary MAC infection, and declined further therapy. 1 pt had atrial fibrillation. G3 ALT developed in 3 pts. FC was dose reduced in 10 pts; ibrutinib dose-reduced in 2 pts. **Conclusions:** iFCG achieves high rate of MRD-neg remission after 3 courses. Pt enrollment continues, and updated results will be presented at the ASCO meeting. Clinical trial information: NCT02629809.

	Response at 3 Month		Best Response	
	N=18	Marrow MRD	N=18	Marrow MRD
ORR	18/18 (100)	14/18 (78) neg	18/18 (100)	16/18 (89) neg
CR/CRi	7 (39)	7/7 (100) neg	9 (50)	9/9 (100) neg
PR	11 (61)	7/11 (64) neg	9 (50)	7/9 (78) neg

7523 Poster Session (Board #285), Mon, 8:00 AM-11:30 AM

Results of a phase II multicenter study of obinutuzumab plus bendamustine in pts with previously untreated chronic lymphocytic leukemia (CLL). *First Author: Jeff Porter Sharman, Willamette Valley Cancer Institute and Research Center/US Oncology Research, Springfield, OR*

Background: Bendamustine (B) + rituximab (R; BR) is a commonly used 1L treatment for CLL. The CLL10 study reported an ORR of 96% and CR of 31% with BR. Obinutuzumab (GA101; G) is a glycoengineered, type II anti-CD20 monoclonal antibody. A randomized Phase III trial in 1L CLL pts showed that G significantly improved PFS and CR rate compared with R, when used in combination with chlorambucil (Goede 2014). B + G (BG) was evaluated in a subgroup of CLL pts in the GREEN study (Stilgenbauer 2015). We present results of a Phase II study (NCT02320487) evaluating the efficacy and safety of BG as 1L treatment for CLL pts. **Methods:** 102 pts with previously untreated CLL received BG, consisting of 6 cycles of G (cycle [C] 1: 100mg day (D) 1, 900mg D2, 1000mg D8 and D15; C2–6: 1000mg D1) and B (90mg/m^2: C1, D2 and D3; C2–6, D1 and D2). Each cycle was 28 days. Primary endpoint was CR assessed using iwCLL criteria. Secondary endpoints included ORR, PFS, OS, and MRD. Median follow-up at the time of analysis was 11.0 months. **Results:** Median pt age was 61 yrs (range 35–90); 68.6% were male; 44.1% had Rai stage 3–4. For evaluated pts, IgVH status was 32.9% mutated and 67.1% unmutated. The incidences of trisomy 12, normal cytogenetics, and deletions of 13q, 11q, and 17p were 23.4%, 37.5%, 17.2%, 15.6%, and 6.3%, respectively. Investigator-assessed CR rate was 49.0% (95% CI 39.0–59.1) and ORR was 89.2% (95% CI 81.5–94.5) after 6 cycles. MRD negativity (MRD-) in blood, as measured by 4-color flow cytometry, was achieved in 42.7% of pts at the end of induction response assessment and in 75.5% of pts at any time following treatment. MRD- in bone marrow (BM) was 60.8% in pts with BM samples. The most common AEs (all grades [Gr]) were infusion reactions (72.5%), nausea (52.0%), pyrexia (36.3%), neutropenia (34.3%), fatigue (34.3%), constipation (26.5%), and rash (26.5%). The most common Gr 3–4 AE was neutropenia (26.5%). Incidence of Gr 3–4 infections was 11.8%. Incidence of TLS was 4.9% (all Gr 3). Three pts died; none were deemed related to study treatment or CLL by investigators. **Conclusions:** BG is an effective regimen for 1L treatment of CLL pts, inducing a high CR rate after 6 cycles of therapy. No unexpected safety signals were observed. Clinical trial information: NCT02320487.

7524 Poster Session (Board #286), Mon, 8:00 AM-11:30 AM

Ibrutinib vs chlorambucil: Immunophenotypic and quantitative impacts on circulating immune cells in chronic lymphocytic leukemia (CLL). *First Author: Isabelle Solman, Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA*

Background: Ibrutinib (ibr), a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, is indicated by FDA for treatment (Tx) of patients (pts) with CLL. Following the outcome of the RESONATE-2 trial, ibr was approved as the first chemotherapy-free Tx option for treatment-naïve (TN) pts. In this study, ibr reduced the risk of progression or death by 84% compared with chlorambucil (chl). To assess the impact of ibrutinib vs this traditional chemotherapeutic agent on the immune system, quantitative changes in circulating cells were studied throughout the first year of Tx. **Methods:** Immunophenotypic analyses were performed by flow cytometry on peripheral blood to assess lymphoid and myeloid cells of TN CLL pts who received 420 mg ibr once daily (n=50) or 0.5-0.8 mg/kg chl twice a month (n=30). Medians of statistically significant changes ($p<0.05$, Wilcoxon test) in absolute counts of 1-year paired samples (pre-dose vs 1-year) are reported. **Results:** Chl progressively reduced circulating B, T, NK, NKT cells, myeloid derived suppressor cells (MDSC), and monocytes by 69%-99%. All development stages of $CD4^+$ and $CD8^+$ T cells, except stem cell memory T cells (T_{SCM}), decreased by 51%-90%. Regulatory T cells (Treg) and $PD1^+$ T cells also decreased similarly; however, long-term activated T cells (T_{LA}) were not impacted. On the other hand, ibr mainly reduced B cells (90%), MDSC (61%) and some T cells, specifically T_{LA}, $PD1^+$ T cells, Treg and effector T cells (27-52%). Naïve T cells, T_{SCM}, central memory T cells and NK cells were spared throughout the full year of Tx. Classical monocytes were increased (+187%), while non-classical monocytes and intermediate monocytes remained relatively steady. **Conclusions:** Chl, a traditional chemotherapy, affected non-specifically most immune cell subsets in circulation, although surprisingly it did not affect T_{LA} which have been reported as dysfunctional in CLL. Ibr represents a more targeted Tx approach than cytotoxic chemotherapy; essentially B cells, abnormal T subsets (T_{LA}, $PD1^+$T, Treg) and pro-tumor MDSCs were reduced. However, ibr preserved naïve T cells, NK cells and monocytes, which are important for mounting anti-tumor responses. Clinical trial information: NCT01722487.

7525 Poster Session (Board #287), Mon, 8:00 AM-11:30 AM

Persistence of ibrutinib-associated hypertension in CLL pts treated in a real-world experience. *First Author: Lisa M. Gashonia, Abramson Cancer Center, Philadelphia, PA*

Background: Cardiovascular (CV) complications associated with ibrutinib (Ibr) include hypertension (HTN) and atrial fibrillation (AFIB) (incidence 26% and 9%, OBrien, ASH 2016). Unlike clinical trials, Ibr toxicities are the most common reasons for its discontinuation in clinical practice. The incidence of HTN in pts treated with Ibr outside of clinical trial setting and its impact on outcomes is unknown. **Methods:** Retrospective, cohort study of Ibr-treated CLL pts to estimate HTN incidence. Baseline CLL characteristics and co-morbidities were recorded. Blood pressure (BP) measurements were recorded prior to Ibr and sequentially following exposure at specific time points. CV meds were reviewed during a 12 mo follow-up period. The association between Ibr exposure and BP was tested. **Results:** 153 consecutive CLL pts treated with Ibr at a dose of 420 mg/day were identified. Med age was 57 yr (range: 34-87), relapsed CLL (69%), follow-up 14.5 mo. CV pre-Ibr characteristics included: smoking hx (49%), HTN (42%), hyperlipidemia (39%), diabetes (17%), CAD (12%), AFIB (6.8%). Proportion of pts on $\geq$1 anti-HTN med increased from 44% pre-Ibr (20% $\geq$ 2) to 57% during Ibr (30% $\geq$ 2). Med pre-Ibr BP was 127/70 mmHg (range 90-182/48-95mmHg). At 1, 3, 6, 9, 12 mo, med BPs were 137/73, 141/75, 143/76, 140/75, 142/77 (7 mo to peak BP). There was a significant association between Ibr exposure and increased BP ($p<.01$). New HTN was observed in 40% of pts and 36% HTN pts had BP increased above baseline (med baseline 135/70 vs peak 161/80). Incidence of new AFIB was 8.1%. In UV analyses, predictive clinical factors for HTN were not identified. Pre-Ibr HTN (OR 3.0, p .05), CAD (OR 4.3, p .03), prior AFIB event (OR 10.8, p.001), hyperlipidemia (OR 3.4, p.05) were associated with post-Ibr AFIB. **Conclusions:** In the largest real-world series focused on BP in Ibr treated pts, we demonstrate a clear association between Ibr and HTN. Nearly 40% of pts developed HTN within 12 mo of Ibr exposure (vs. 26% in clinical trials over 5 yr). Despite aggressive management (multiple agents), Ibr associated HTN was persistent. These data underscore the critical need for monitoring and management strategies for HTN and follow-up data on future CV events.

7526 Poster Session (Board #288), Mon, 8:00 AM-11:30 AM

Cytogenetic and fluorescence in situ hybridization testing in veterans with chronic lymphocytic leukemia. *First Author: Ahmad Sami Halwani, Huntsman Cancer Institute at the University of Utah, Division of Hematology and Hematological Malignancies, SLC VA IDEAS Center, Salt Lake City, UT*

Background: The presence of deletion 17p (del17), determined by chromosome analysis and/or fluorescence in situ hybridization (FISH), is a strong negative prognostic marker in chronic lymphocytic leukemia (CLL). Prior to the introduction of novel agents (ibrutinib, venetoclax), the clinical utility of cytogenetics/FISH was limited by the absence of chemoimmunotherapy regimens that were proven effective in patients with del17. Testing practices for chromosomal aberrations since the introduction of novel agents have not been reported. We report cytogenetic/FISH trends in a nationwide cohort of veterans diagnosed with CLL. **Methods:** CLL patients diagnosed 2008-2015 and receiving care at VA were identified through the VA Clinical Cancer Registry. Electronic medical records were used to determine cytogenetic/FISH testing (lab records), treatment histories (pharmacy dispensation records), and evidence of system use (heme-onc notes). Cytogenetic/FISH testing was identified by presence of specific keywords in the test name or Logical Observation Identifiers Names and Codes (LOINC) descriptions, then validated by human annotation. The testing rates are reported for the entire cohort, at time of diagnosis, time of regimen initiation (including the 12 months preceding initiation), during the novel era (2014 – 2015) and prior (2008–2013). **Results:** From 2008 to 2015, 3,638 CLL patients were diagnosed and received care at VA. Documented records of treatment regimens were available for 1,562 patients who received a total of 2,929 treatment regimens. Only 24% (998) of patients were tested at any point in time during their care at the VA, 17% (622) were tested at time of diagnosis, and 19% (542) of treatment courses were preceded by cytogenetic/FISH testing. No testing differences existed following the introduction of the novel agents at diagnosis (both ~ 17%), or prior to regimen initiation (20% vs 16%). **Conclusions:** Our study suggests CLL patients diagnosed and receiving care at the VA are not routinely undergoing cytogenetics/FISH testing at diagnosis or prior to treatment. Changing this practice pattern will personalize treatments so that del17 CLL patients receive less toxic and more effective therapies.

7527 Poster Session (Board #289), Mon, 8:00 AM-11:30 AM

Phase 2 trial of brentuximab vedotin and gemcitabine for pediatric and young adult patients with relapsed or refractory Hodgkin lymphoma (HL): A Children's Oncology Group (COG) report. *First Author: Peter D. Cole, The Children's Hospital at Montefiore, Bronx, NY*

Background: AHOD1221 (NCT01780662) tested Brentuximab vedotin (Bv) with gemcitabine (GEM) in children or young adults with HL. The primary objective was to describe the complete response (CR) rate within 4 cycles of therapy. **Methods:** Eligibility criteria included age $\leq$30 years; no prior Bv exposure; and primary refractory HL or advanced stage disease with early relapse. Each 21-day cycle consisted of Bv on day 1 at the recommended phase 2 dose (RP2D), 1.8 mg/kg and GEM 1000mg/m^2 on days 1 and 8. Patients were evaluable for response if they completed 4 cycles of Bv+GEM, had a CR after 2 cycles, or progressive disease at any time. Response was assessed after even cycles, and confirmed by central review. CR was defined by FDG-PET negativity (Deauville 1-2) regardless of residual lesion size. **Results:** 42 patients were treated with Bv+GEM. Median age was 17.4 years (range 5.4-28.7), and 23 (55%) were female. The majority (n=35; 83%) had primary refractory disease or early relapse $<$6 months after completion of primary treatment. Common ($>$10%) adverse events included maculopapular rash (36% in cycle 1), neutropenia (33%) and elevated serum transaminases (21%). GCSF-stimulated peripheral blood stem cell (PBSC) collection was successful in all patients (n=23) for whom it was attempted, with median total collection of 9.4x10^{6}CD34+ cells/kg (range 3.5-36.8). 23 of 40 evaluable patients experienced a CR (58%; 95% CI 42-73%) within four cycles, and 6 had a partial response (PR), for an ORR of 73% (95% CI, 59-86%). For 4 patients with PR or stable disease, all target lesions were Deauville 3 or less after cycle 4, considered a CR by modern response criteria (Cheson et al. Blood 2016;128(21): 2489). **Conclusions:** Bv+GEM is a highly active combination for primary refractory or high-risk relapse of HL, with a CR rate exceeding that seen after either Bv (34%) or GEM (9%) alone. PBSCs can be collected successfully following Bv+GEM, making this an effective reinduction regimen when autologous stem cell transplantation is indicated. Compared to alternate retrieval regimens, Bv+GEM offers the advantage of avoiding agents associated with late treatment sequelae. Clinical trial information: NCT01780662.

7528 Poster Session (Board #290), Mon, 8:00 AM-11:30 AM

Digital sorting and copy number profiling of purified, PD-L1 positive, Reed Sternberg cells in classical Hodgkin lymphoma. *First Author: Chiara Mangano, Menarini Silicon Biosystems, Inc., Bologna, Italy*

Background: Classical Hodgkin Lymphoma (cHL) is one of the disease in which the check-point inhibitors have been demonstrated to be more successful. Lately, it has been reported that in malignant Reed-Sternberg Cells (RSCs), PD-1 ligands (PD-Ls) are overexpressed and that chr.9 amplification correlates with advanced stages of the disease, when the standard therapy have already failed. Unfortunately, the detection of the genetic alterations in RSCs is challenging, as one of the hallmark of cHL is the presence of a small number of malignant cells sparse in an abundant and heterogeneous immune infiltrate. Here we present a method for the isolation and the genetic characterization of purified RSCs, which overcomes the limitations posed by the low-cellularity of cHL biopsies, and could be helpful for earlier detection of genetic alterations and adoption of immunotherapy. **Methods:** FFPE tissue sections from cHL patients were dissociated down to single-cell suspension and stained using anti-CD30 and anti-PD-L1 antibodies. Beyond the positivity to CD30 and PD-L1, RSCs were selected according to morphological criteria such as cell size and the presence of polylobate nuclei compared to surrounding lymphocytes. Target cells were isolated using the DEPArray™ cell sorter, as single cells or in small pools of cells. Recovered cells were whole genome amplified (*Ampli*1™ WGA), and genome-wide copy-number aberrations (CNAs) profiles were obtained using *Ampli*1™ LowPass kit on IonTorrent platform. **Results:** After the dissociation, RSCs maintained cell morphology and therefore, we were able to discriminate them from the heterogeneous immune infiltrate. RSCs appeared as large multinucleated cells with a big central nucleolus surrounded by a clear halo; cell diameter and ploidy were computed from the images. Pools of lymphocytes and pools of CD30+/ PD-L1+ RSCs were isolated. Sequencing results confirmed the expected flat profile for lymphocytes, while RSCs showed an aberrant profile with multiple losses and gains. **Conclusions:** The analysis of purified RSCs, could offer a valuable tool to uncover genetic alterations hidden by cHL immune infiltrate, for earlier adoption of more effective treatment regimens.

7529 Poster Session (Board #291), Mon, 8:00 AM-11:30 AM

Single institution experience of allogeneic stem cell transplantation for Hodgkin lymphoma. *First Author: Mauricio Pineda-Roman, Mount Sinai Hospital, New York, NY*

Background: Hodgkin lymphoma (HL) is curable in the majority of cases without stem cell transplantation (SCT). However, patients(pts) who relapse after chemotherapy require autologousSCT, and about half of those pts relapse. For over 3 decades, allogeneic SCT has been implemented in more refractory HL pts. We present the long term follow up of a group of pts from a our institution who underwent alloSCT for HL. **Methods:** 21 pts with HL transplanted from 2008 to 2015 and disease characteristics (HL type, status at SCT, chemosensitivity), treatment(graft source, donor type, auto and allo SCTdates, GVHD prophylaxis) and outcomes (maximum grade of acute and chronic GVHD, survival (OS) and causes of death) were analyzed. **Results:** 13 males and 8 females received an alloSCT from 2008 to 2015, 11 pts had Nodular sclerosis HL, 6 NOS, 2 mixed cellularity, 1 lymphocyte predominant and 1 lymphocyte depleted. Performance status was 60 to 100, median of 90. 16 grafts were unrelated and 5 HLA identical. 18 pts received PBSC, 2 bone marrow and one double cord transplant. Most pts, 19, had a prior autoSCT, one had 2 prior autoSCT and for one , the allo was the first SCT. One patient was transplanted in unconfirmed first CR, 2 in confirmed CR, 4 in PR without prior CR, 3 in 1strelapse, 5 in 2nd relapse, 5 in 3rd relapse, and one in primary induction failure. All patients had a reduce intensity conditioning: 14 Flu/Mel, 4 Flu/Mel ATG, and one each Flu/TBI/ATG, Flu/TBI, Flu/Cy. Acute GVHD happened in 11 pts: max grade I in 1 , II in 7, III in 1 and IV in 2. 6 pts had extensive chronic GVHD. 12 pts (57.1%) have died (survival range 0.65-43.45 months, mean 13.1, median 6.12). Causes of death were primary disease in 4, infection in 3 pts, GVHD and infection in 2, ARDS, organ failure, pulmonary toxicity in 1 each. 9 pts (42.8%) are alive (survival range 1.63-8.44 years, mean 4.97, median 4.47) **Conclusions:** AlloSCT for pts with relapsed HL is a feasible treatment modality that can lead to long term OS in a significant proportion of pts. Our data is comparable with other published studies for HL alloSCT. The utility of alloSCT should not be dismissed even in the age of Brentuximab and checkpoint inhibitors.

7530 Poster Session (Board #292), Mon, 8:00 AM-11:30 AM

Ongoing phase 1/2 study of INCB050465 for relapsed/refractory (R/R) B-cell malignancies (CITADEL-101). *First Author: Rod Ramchandren, Karmanos Cancer Institute, Detroit, MI*

Background: INCB050465 is a selective PI3Kδ inhibitor with no preclinical hepatotoxicity at clinically relevant doses. We report emerging safety and efficacy data from a phase 1/2 study of INCB050465 in patients (pts) with r/r B-cell malignancies (NCT02018861). **Methods:** The protocol was initiated with a single patient cohort, treated with INCB050465 5 mg QD PO. Subsequent cohorts used a 3+3 design and evaluated doses of 10–45 mg QD. Based on PK/PD, the 20 and 30 mg QD cohorts were expanded. Responses were assessed Q9W by the Lugano Classification or International Working Group on Chronic Lymphocytic Lymphoma (CLL) criteria. **Results:** As of the data cutoff (Nov 1, 2016), 52 pts were treated (median age, 65 y [range, 30–88]; baseline tumors: diffuse large B-cell lymphoma [DLBCL], n=14; follicular lymphoma [FL], n=10; Hodgkin lymphoma [HL], n=9; marginal zone lymphoma [MZL], n=8; CLL, n=6; mantle cell lymphoma [MCL], n=5; 62% had >3 prior systemic regimens). Median duration of therapy was 3.3 mo (range, 0.6–13.4); no DLTs were identified. 67% of pts discontinued therapy (disease progression, 31%; AEs, 25%); 33% had dose interruption; 4% had reduction. Most common nonhematologic AEs (all grade [Gr]; Gr ≥3): nausea (38%; 0%), diarrhea (31%; 6%), vomiting (25%; 0%); Gr ≥3 hematologic AEs: neutropenia (21%), lymphopenia (17%), thrombocytopenia (10%), anemia (4%). 40% of pts had serious AEs, most frequently colitis, diarrhea, hypotension (all n=3). 1 pt had Gr 3 pneumonitis; none had *Pneumocystis jirovecii* pneumonia (PJP) or Gr ≥2 elevated transaminase. Objective responses (ORs) occurred at all doses (Table), except 5 mg QD; 90% were observed at first assessment. **Conclusions:** INCB050465 demonstrated manageable toxicities with no clinically meaningful transaminitis/PJP. OR rates were generally high, with 90% observed at first assessment. Different dosing regimens/ schedules, long-term safety, and disease-specific cohorts are being evaluated. Clinical trial information: NCT02018861.

	N[a]	OR, n (%)	CR,[b] n	PR,[b] n
All pts	45	22 (49)	10	12
NHL	31	19 (61)	10	9
DLBCL	14	5 (36)	3	2
FL	9	7 (78)	2	5
MZL	4	4 (100)	2	2
MCL	4[c]	3 (75)	3	0
CLL	6[c]	2 (33)	0	2
HL	8	1 (13)	0	1

[a] Evaluable pts. [b] Radiologic/metabolic.[c] One MCL and 3 CLL pts had received ibrutinib, of whom 1 CLL pt had a best OR of PR in this study.

7531 Poster Session (Board #293), Mon, 8:00 AM-11:30 AM

Activity of the immunologic doublet of lenalidomide plus obinutuzumab in relapsed follicular lymphoma: Results of a phase I/II study. *First Author: Nathan Hale Fowler, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Relapsed follicular lymphoma (FL) remains a challenge and salvage regimens are associated with toxicity and limited control. Outcomes are linked to the immune microenvironment and lenalidomide and rituximab are highly active in FL. Obinutuzumab has increased ADCC compared to rituximab in preclinical models and is approved for relapsed FL. We hypothesized that the immunologic properties of obinutuzumab and lenalidomide would be synergistic. The study objective was to determine the MTD of lenalidomide with obinutuzumab in relapsed FL and describe the efficacy of the combination. **Methods:** This open label phase I/II study enrolled Gr 1-3a FL. Transformation was excluded. Lenalidomide was given on D 2-22 with 1000mg obinutuzumab on D1, 8, 15, and 22 of cycle 1 and on D1 for up to 12 cycles (28 days/cycle). Obinutuzumab was given every 2 months thereafter for up to 30 months in pts who responded following doublet therapy. During dose escalation, 3 cohorts were planned with 10, 15 and 20mg of lenalidomide. Phase II planned to enroll 30 pts at MTD with efficacy and safety as primary endpoints. **Results:** All 36 pts with FL enrolled (6 in dose escalation and 30 at MTD), and are eligible for efficacy and safety analysis. The median age was 65 with a median of 2 prior therapies. No DLTs were observed in phase I, and 20 mg of lenalidomide was used for phase II. To date, the most common all grade non-heme toxicities were fatigue(83%), diarrhea(67%) and rash(53%). Grade 3+ toxicities included neutropenia (23%), infection (11%) and fatigue (8%). The overall response rate was 100% with 78% (95%CI 60.85-89.88%) of pts attaining complete response (CR/Cru). All pts with rituximab refractory FL (13) responded. At a median follow up of 14 months, 10 pts progressed. The estimated 24 month PFS is 61% (95% CI 43-87%). **Conclusions:** Lenalidomide and obinutuzumab is highly active with durable remissions in relapsed FL, with all pts responding and 78% achieving CR. The majority of pts remain on therapy and the combination appeared safe. Correlatives are ongoing to identify biomarkers of response and frontline studies of the combination are currently enrolling. Clinical trial information: NCT01995669.

7532 Poster Session (Board #294), Mon, 8:00 AM-11:30 AM

Double-blind, randomized phase 3 study to compare efficacy and safety of the biosimilar CT-P10 to rituximab combined with CVP therapy in patients with previously untreated advanced-stage follicular lymphoma. *First Author: Won Seog Kim, Samsung Medical Center, Seoul, Republic of Korea*

Background: CT-P10 is a biosimilar candidate to the innovator rituximab (RTX). In patients with rheumatoid arthritis, CT-P10 has demonstrated equivalence in pharmacokinetics (PK) and efficacy (Yoo, ACR 2016). This study aimed to demonstrate non-inferiority of efficacy and PK equivalence between CT-P10 and RTX in patients with newly diagnosed advanced follicular lymphoma (AFL) (NCT02162771). PK equivalence was confirmed (Coiffier, ASH 2016). **Methods:** A total of 140 patients were randomized in a 1:1 ratio to receive CT-P10 or RTX (375 mg/m^2 i.v) plus CVP (cyclophosphamide, vincristine, and prednisone) every 3 weeks over 8 cycles. Overall response rate (ORR) according to the 1999 IWG criteria over 24 weeks was assessed by the independent review committee. **Results:** Noninferiority of CT-P10 to RTX was shown for the primary efficacy endpoint of ORR. The ORR difference was 4.3% (Table) and the lower bound of the 95% confidence interval was -4.25%. B-cell depleted after the 1st infusion and remained as depleted over 8 cycles in both groups. Overall safety profile of CT-P10 was consistent with that of RTX and the proportion of patients with positive anti-drug antibody was similar in both groups (4.3% and 2.9%) for 24 weeks. Neither progressive multifocal leukoencephalopathy nor Hepatitis B virus reactivation was reported in each group. **Conclusions:** This study demonstrates noninferiority of efficacy of CT-P10 to RTX combined with CVP in previously untreated AFL. CT-P10 was well-tolerated and the safety profile including immunogenicity of CT-P10 was comparable to that of RTX over 8 cycles of induction period. Clinical trial information: NCT02162771.

Summary of efficacy and safety (number [%] of patient).

	CT-P10	RTX
	(N=66)	(N=68)
ORR (CR+CRu+PR)	64 (97.0)	63 (92.6)
Complete response (CR)	20 (30.3)	15 (22.1)
Unconfirmed CR (CRu)	6 (9.1)	8 (11.8)
Partial response (PR)	38 (57.6)	40 (58.8)
	(N=70)	(N=70)
TEAE related to the study drug		
Treatment-emergent adverse event (TEAE)*	37 (52.9)	34 (48.6)
Serious TEAE*	6 (8.6)	4 (5.7)
Infusion-related reaction*	15 (21.4)	17 (24.3)
Infection*	6 (8.6)	9 (12.9)

* Difference between groups is statistically not significant.

7533 Poster Session (Board #295), Mon, 8:00 AM-11:30 AM

Phase 1B of ibrutinib and high-dose methotrexate for recurrent/refractory CNS lymphoma. *First Author: Christian Grommes, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Primary CNS Lymphoma (PCNSL) is an aggressive primary brain tumor. Outcome and treatment options for patients with recurrent/refractory (r/r) disease are poor. We have observed promising efficacy of single agent ibrutinib in r/r PCNSL and secondary CNS lymphoma (SCNSL). In this phase 1B trial, we investigate the toxicity of ibrutinib in combination with high-dose methotrexate (HD-MTX) in r/r PCNSL/SCNSL. **Methods:** Eligible patients had r/r PCNSL/SCNSL or newly diagnosed SCNSL, age≥18, ECOG≤2, normal end-organ function, and with any number and type of prior therapies. In patients with SCNSL disease, systemic disease needed to be absent. HD-MTX was given at 3.5g/m2 every 2 weeks for a total of 8 doses. To minimize adverse events, ibrutinib was stopped on days of HD-MTX infusion and was restarted 5 days after MTX infusion or after completion of MTX-clearance, if clearance of MTX required more than 5 days. Ibrutinib was continued daily after completion of 8 doses of MTX. **Results:** Six patients have been enrolled; 3 received 560mg and 3 received 840mg ibrutinib in combination with HD-MTX. Median age was 62 (range 43-74); median ECOG 1 (0:2; 1:3; 2:1). Two had r/r PCNSL and 4 SCNSL. Three had brain disease, one isolated cerebrospinal fluid (CSF) involvement and two parenchymal and CSF involvement. Three patients had recurrent (2 PCNSL; 1 SCNSL), two refractory (both SCNSL), and one newly diagnosed disease (SCNSL). There were no grade 4 adverse events. Grade 3 events were observed in 5 patients (lymphopenia in 3, ALT elevation in 2, diarrhea in 1, electrolyte changes in 1, hypertension in 1). The most common adverse events were hypokalemia, low WBC, hyperglycemia, ALT and AST elevation. There was no dose reduction of methotrexate or ibrutinib in any patient. After a median follow-up of 130 days, all patients were evaluated for response after 4 doses of HD-MTX, with 4/6 (67%) showing a response: 2 CR, 2 PR, and 1 SD, 1 PD; both non-responders were refractory SCNSL. Ibrutinib concentrations were measured in plasma and CSF. **Conclusions:** Patients with CNS lymphoma tolerate the combination of HD-MTX and Ibrutinib (at 560 and 840mg) well. Continued enrollment into a combination arm that includes rituximab, methotrexate and ibrutinib is ongoing. Clinical trial information: NCT02315326.

7534 Poster Session (Board #296), Mon, 8:00 AM-11:30 AM

Whole body diffusion-weighted MRI to predict treatment outcome after one cycle of immunochemotherapy in aggressive non-Hodgkin lymphoma. *First Author: Katja De Paepe, University Hospitals Leuven, Leuven, Belgium*

Background: Treatment adaptation based on early identification of non-Hodgkin lymphoma (NHL) patients not responding to therapy might improve survival. The role of interim fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) after 2-4 cycles of immunochemotherapy (ICT) herein is experimental as it renders false positive results, due to a rituximab-induced inflammatory response. Whole body diffusion-weighted magnetic resonance imaging (WB-DWI/MRI) was evaluated as a radiation-free imaging technique to predict treatment outcome in NHL after one cycle ICT (2-3 weeks). **Methods:** 47 patients with aggressive NHL (35 DLBCL,2 primary mediastinal BCL,3 unclassifiable BCL, 2 Burkitt,2 MCL, 2 peripheral TCL and 1 extranodal NK-TCL) were enrolled. All had baseline and interim WB-DWI/MRI, and end-of-treatment PET/CT; 39/47 had interim PET/CT. International prognostic index (IPI), immunohistochemical (IHC) markers Ki-67, Bcl-6 and Bcl-2 were evaluated for their predictive value. WB-DWI/MRI was assessed quantitatively with histogram analysis (high b-value signal intensity (SI) and apparent diffusion coefficient (ADC)). Patients were categorized as non-responder when lesions had decreased ADC or insufficient SI decrease between scans. Kaplan-Meier survival analysis was performed with log rank, Cox hazard ratio calculation and multivariate analysis. Outcome measure was disease-free-survival (DFS). **Results:** Median follow-up time was 43 months (4-70 months). 33 patients had complete remission (CR), 5 progression and 9 recurrent disease. WB-DWI/MRI predicted DFS correctly in 45/47 (96%) [log rank p<0.001; hazard ratio (HR) 52, (CI 95% 6-401)]; end-of-treatment PET/CT was correct in 37/47 (79%) [p=0.003;HR 4.3, (1.5-12.4)], and interim PET/CT in 28/39 (72%) [p=0.016;HR 3.9, (1.2-12.5)]. IPI score and IHC parameters were not significantly predictive. Multivariate analysis showed WB-DWI/MRI as the only independent prognostic factor (p<0.001). **Conclusions:** WB-DWI/MRI can accurately predict treatment outcome in aggressive NHL after only one cycle of immunochemotherapy without the burden of radiation exposure. Clinical trial information: NCT01231269.

7535 Poster Session (Board #297), Mon, 8:00 AM-11:30 AM

Copanlisib in patients with relapsed or refractory follicular lymphoma. *First Author: Martin H. Dreyling, University Hospital of LMU, Munich, Germany*

Background: Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (iNHL) subtype, yet treatment options in the relapsed/refractory (r/r) setting are limited. Copanlisib is a pan-Class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant PI3K-α and PI3K-δ activity. We report results from the FL subset of a large phase II study (n=141) in iNHL patients (pts) (NCT01660451, part B). **Methods:** A total of 104 pts with indolent FL (grade 1-3a) relapsed/refractory to ≥2 prior lines of treatment were treated with copanlisib (60 mg IV infusion) administered on days 1, 8 and 15 of a 28-day cycle. The primary endpoint was objective tumor response rate (ORR) per independent radiologic review (Cheson et al., JCO 20:579, 2007). **Results:** Of the 104 pts treated, 62% were refractory; median prior lines 3 (range 2-8), median time from progression 8 wks (range 1-73 wks). 52% were male, 83% white, median age 62 yrs, and 62% ECOG 0. At the time of primary analysis the ORR was 58.7%, comprising 15 pts (14.4%) with complete response (CR) and 46 (44.2%) with partial response. Stable disease was observed in 35 (33.7%) pts and progression of disease as best response in 2 pts. The median duration of response was 370 days (range 0-687), with 43 responders censored at data cut-off. Median duration of treatment was 22 wks (range 1-105); 33 (32%) pts remained on treatment. For all pts, the most common treatment-emergent AEs occurring in >25% of pts included (all grade/grade 3 +): diarrhea (34%/5%), reduced neutrophil count (30%/24%), fatigue (30%/2%), and fever (25%/4%). Hyperglycemia (50%/41%) and hypertension (30%/24%) were transient. The incidence of pneumonitis (8%/1.4%), hepatic enzymopathy (AST 28%/1.4%; ALT 23%/1.4%), opportunistic infection (1.4%) and colitis (0.7%) were low. Six deaths were observed, 3 of which were attributed to copanlisib: one lung infection, one respiratory failure, and one thromboembolic event. **Conclusions:** Copanlisib was highly active as a single agent in heavily pretreated r/r FL pts and resulted in durable responses in the majority of pts. Toxicities were manageable, with a low incidence of severe AEs associated with other PI3K inhibitors, especially hepatic enzymopathy, opportunistic infections, and colitis. Clinical trial information: NCT01660451.

7536 Poster Session (Board #298), Mon, 8:00 AM-11:30 AM

Phase II study of single-agent copanlisib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). *First Author: Georg Lenz, Translational Oncology Medical Clinic, Münster University Clinic, Münster, Germany*

Background: Relapsed/refractory (r/r) DLBCL patients (pts) are characterized by poor prognosis. Copanlisib is a pan-Class I phosphatidylinositol 3-kinase (PI3K) inhibitor, with modest single-agent activity in unselected DLBCL pts. Here we report the treatment effect of copanlisib in r/r DLBCL pts with regards to cell of origin (COO) and molecular biomarker profiles (NCT02391116). **Methods:** Patients with r/r DLBCL and ≥1 prior lines of therapy were eligible. Copanlisib (60 mg IV infusion) was administered on days 1, 8 and 15 of a 28-day cycle. Tumor samples were evaluated for COO, CD79B mutations and > 400 genes by next generation sequencing (NGS). The primary endpoint was objective tumor response rate (ORR; per Lugano Classification, 2014) by COO and CD79B status. **Results:** The full-analysis (FAS) and per-protocol sets (PPS; ≥3 doses, post-baseline scans and NGS/COO data) included 67 and 40 pts, respectively. Pts were 58% male, median age 69 (range 25-93), ECOG status 0/1/2 22%/57%/21%, and heavily pretreated (median prior lines = 3, range 1-13). In the PPS, COO (and mutant CD79B status) analysis identified 22 GCB DLBCL (2 mutant), 16 ABC DLBCL (6 mutant), and 2 unclassifiable. The ORR in the PPS was 25% (10 of 40), with 5 complete responses (CR) and 5 partial responses (PR); stable disease in 12 pts. The ORR was 13.6% with 1 CR in GCB pts and 37.5% with 4 CRs (25%) in ABC pts. Response to copanlisib was 25% in pts with (2/8) and without (8/32) CD79B mutations. Five of 10 ABC DLBCL-wtCD79B pts and one GCB DLBCL-mCD79B responded (ongoing > 17 cycles). NGS analysis in 54 pts detected 348 mutations; BCL2 (54% of pts), TP53 (41%), BCL6 (30%), MYC (22%), CD79B (19%)/A (6%), MYD88 (19%), TNFAIP3 (17%), CARD11 (13%), and NFKBIA (9%). Response to copanlisib was not significantly different based on BCL2, BCL6, MYC, and MYD88 mutations. With a median of 6 cycles (range 1-29), the most common AEs (% all grade/gr3+4) were diarrhea (36/2), nausea (31/2), fatigue (31/3), fever (21/2) and transient hypertension (40/33) and hyperglycemia (34/31). There were 14 gr5 AEs (none drug-related). **Conclusions:** Copanlisib treatment of r/r DLBCL pts resulted in encouraging responses, especially in the ABC subtype, with a manageable toxicity. Clinical trial information: NCT02391116.

7537 Poster Session (Board #299), Mon, 8:00 AM-11:30 AM

Intratumoral G100 to induce systemic immune responses and abscopal tumor regression in patients with follicular lymphoma. *First Author: Christopher Flowers, Winship Cancer Institute, Atlanta, GA*

Background: Follicular lymphoma (FL) is an incurable malignancy with patients (pts) ultimately relapsing following standard therapies. Active immunotherapy has the potential to induce life-long host anti-tumor immunity and disease control. G100 consists of glucopyranosyl lipid-A (GLA), a TLR-4 agonist in a specific formulation. Preclinically, G100 activates dendritic cells, T cells and NK cells, and triggers systemic anti-tumor immunity. In Merkel Cell carcinoma pts, G100 administered intratumorally (IT) induced tumor inflammation and responses including a CR after G100 alone. This is the first study of G100 IT in pts with NHL. **Methods:** Previously treated or naïve pts with FL with an injectable tumor site and distal sites of disease were eligible. In Part 1, G100 cohorts of 5 or 10μg were enrolled in a 3+3 design, followed by a large tumor (> 4cm) cohort at 20μg. Pts received 6-9 doses of G100 IT ~qwk after radiation (RT, 2 Gy x2 doses) to the lesion. A 2nd course of G100 could be given without RT to an additional site. **Results:** As of 31Dec16, all 9 pts in Part 1 dose escalation (3 pts each at 5, 10, or 20 μg/dose) were evaluable for safety and efficacy. An additional 13 pts at 10μg/dose were included in the safety analysis only. No G100-related DLTs or SAEs were observed at any dose level. Of 22 safety pts, all G100 related AEs were grade 1/2 and none occurred in > 2 pts. Tumor biopsies following G100 demonstrated diffuse infiltration of CD8+ T cells in 5/5 pts and T cell repertoire analyses indicated an increased frequency of clonal tumor infiltrating lymphocytes (TILs). Best responses include: 4 PRs (45%), 3 SDs (33%) and 2 pending (22%). Of the 4 PR pts, tumor regression ranged 58-89% including up to 56% shrinkage of abscopal (distal) sites. **Conclusions:** G100 IT was safe, well-tolerated, induced CD8+ T cell infiltration and expansion of TIL clones. G100/RT treated and abscopal lesion regressions were observed signifying the induction or boosting of systemic anti-tumor immunity. The induction of immune responses, favorable safety profile and clinical activity indicate that G100 IT is an active agent that warrants further investigation. Part 2 enrollment continues with randomization to G100/RT ± pembrolizumab. Clinical trial information: NCT02501473.

7538 Poster Session (Board #300), Mon, 8:00 AM-11:30 AM

Elucidation of distinct mutational patterns between diffuse large B cell lymphoma subtypes utilizing circulating tumor DNA. *First Author: Joanne Soo, Duke University School of Medicine, Durham, NC*

Background: Patients with diffuse large B cell lymphoma (DLBCL) exhibit significant differences in clinical outcome based on cell-of-origin (COO). Patients are categorized as having germinal-center-like (GCB) or activated-B-cell-like (ABC) disease based on RNA microarray and histopathological analyses of tumor biopsies. We recently described an accurate sequencing-based method for determination of COO in DLBCL utilizing stereotyped differences in mutations (Scherer et al., 2016). Here, we further explore the mutational patterns in patients with differing molecular subtypes of DLBCL based on sequencing of circulating tumor DNA. **Methods:** We applied cancer personalized profiling by deep sequencing (CAPP-Seq) to pretreatment plasma samples and matched germline from a cohort of 115 patients with DLBCL. We then identified somatic alterations, which were used to determine COO molecular subtypes as previously described. Finally, we compared mutational patterns in patients with GCB and non-GCB DLBCL. **Results:** We detected a significantly greater number of total mutations (GCB: 1766 ± 160 mutations per Mb of targeted sequencing; non-GCB: 1364 ± 150 mutations per Mb of targeted sequencing; $p < 0.05$) and coding mutations (GCB: 145 ± 21 mutations per Mb of targeted sequencing; non-GCB: 28 ± 8.5 mutations per Mb of targeted sequencing; $p < 0.001$), particularly in immunoglobulin (Ig) regions ($p < 0.05$). In addition, GCB and non-GCB samples exhibited distinct mutational patterns within Ig regions. GCB samples were enriched for mutations in regions of switch mu (Sμ) ($p < 0.01$) and IGHV2-70 ($p < 0.01$), while non-GCB samples were enriched for mutations in regions of IGHG3 ($p < 0.03$), IGHV4-34 ($p < 0.03$), and IGLL5 ($p < 0.05$). GCB samples were also significantly enriched for coding mutations in SOCS1 ($p < 0.01$), a gene not included in our original COO classifier. **Conclusions:** Patients with GCB and non-GCB DLBCL exhibit distinct mutational patterns across both Ig and non-Ig loci of the genome. These differences in mutational patterns can be used to classify molecular subtypes noninvasively, potentially providing further utility to noninvasive genotyping and liquid biopsies.

7539 Poster Session (Board #301), Mon, 8:00 AM-11:30 AM

Anti-infective prophylaxis with aciclovir and cotrimoxazole to reduce the rate of infections and therapy-associated deaths in elderly patients with DLBCL undergoing R-CHOP immunochemotherapy. *First Author: Niels Murawski, Saarland University Medical School, Homburg, Germany*

Background: To study if anti-infective prophylaxis with aciclovir and cotrimoxazole is effective in preventing infections in pts. receiving R-CHOP, we compared infections and treatment-related deaths in two prospective DSHNHL trials with different anti-infective strategies. **Methods:** 61-80-yo. pts. in RICOVER-60 study [Lancet Oncol 2008; 9:105-116] received 6 or 8 cycles of CHOP-14 with or without 8 applications of rituximab. Anti-infective prophylaxis consisted of ciprofloxazine (500 mg/d) during days of severe leukocytopenia ($< 1000/mm^3$). In OPTIMAL > 60, pts. were randomized to 6xCHOP-14 or 6xCHLIP-14 (conventional substituted by liposomal vincristine) in combination with rituximab, 8 applications q 2 wks. or 12 applications between days -4 and 238 /2x2 factorial design). In OPTIMAL > 60, anti-infective prophylaxis consisted of cotrimoxazole (2 double strength doses twice every week p. o.) and aciclovir (4 x 400 mg/d p.o.) in addition to ciprofloxazine. **Results:** In RICOVER-60, grade 3&4 infections in 232 patients (IPI = 1 and bulky disease or IPI > 1) receiving 6xCHOP-14+8R were 6% (76/1200) per cycle and 28% (60/218) per patient. With intensified anti-infective prophylaxis in OPTIMAL > 60 there were no differences with respect to infections between the 4 treatment arms. Grade 3&4 infections were 4% (83/1987) per cycle ($p = 0.007$) and 18% (64/365 pts. with toxicity documentation) per patient ($p = 0.004$). Treatment-related deaths (defined as all non-lymphoma associated deaths during and within 2 months after the end of chemotherapy) went down from 15/232 (7%) in RICOVER-60 to 7/385 (2%; $p = 0.003$) in OPTIMAL > 60. **Conclusions:** Anti-infective prophylaxis with cotrimoxazole and aciclovir in addition to ciprofloxazine significantly reduced the rates of severe infections and treatment-related deaths in elderly patients receiving R-CHOP supporting the use of this anti-infective strategy in all DLBCL patients receiving R-CHOP. Clinical trial information: NCT01478542.

7540 Poster Session (Board #302), Mon, 8:00 AM-11:30 AM

Phase II clinical trial of first-line combination of radiation followed by gemcitabine, dexamethasone, and cisplatin (GDP) chemotherapy for early-stage extranodal natural killer/T-cell lymphoma with unfavorable prognostic factors: The GREEN study (NCT02276248). *First Author: Fei Qi, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*

Background: Currently concomitant or sequential chemotherapy with radiotherapy has been recognized as the standard treatment for extranodal natural killer/T-cell lymphoma, nasal type (ENKTL). However, the optimal schedule has not been fully defined. **Methods:** We designed a phase II prospective study to investigate the efficacy and toxicity profile of sequential radiation followed by systemic GDP (gemcitabine, dexamethasone and cisplatin) chemotherapy on previously untreated early-staged (stage IE/IIE) ENKTL patients with at least one unfavorable prognostic factor. The primary endpoint was 2-year progression-free survival (PFS). Secondary endpoints were 2-year overall survival (OS), overall response rate (ORR), and toxicity. **Results:** A total of40 patients were enrolled and completed the entire course of treatment between June 2010 and June 2014. The median age was 38 (range 25-63) years old. All the enrolled patients presented with at least one unfavorable prognostic feature: age $>$ 60 years (5.0%), B symptom (40%), elevated serum LDH (40.0%), regional lymph node involvement (32.5%) and primary tumor invasion (87.5%). At the completion of the whole treatment, ORR was 97.5% and the complete remission rate was 95.0%. Median follow-up time was 43.7 months (range 9.4-72.3 months). 2-, 3-, 5-year PFS rates were 84.7%, 82.1%, 77.5%, and OS rates were 89.9%, 87.1%, 79.7%, respectively. Recurrence within the RT field was observed in four patients and systemic failure in three individuals. Grade 1-2 skin reaction and mucositis were the main toxicity related to radiation. Grade 3-4 neutropenia (12/40), thrombocytopenia (7/40) and anemia (2/40) were observed during GDP chemotherapy. No clinically significant late toxicities were observed during follow-up visits. **Conclusions:** The current results indicates that first-line radiation followed by GDP chemotherapy can be one of the most effective and feasible treatment schedule for early-stage ENKTL patients, especially those with poor prognostic factors. Clinical trial information: NCT02276248.

7541 Poster Session (Board #303), Mon, 8:00 AM-11:30 AM

MYC+ relapsed and refractory (R/R) diffuse large b-cell lymphoma (DLBCL): Impact of additional hits and outcomes with subsequent therapy. *First Author: Narendranath Epperla, Medical College of Wisconsin, Milwaukee, WI*

Background: Translocations involving *MYC* are a hallmark of poor prognosis among patients with newly diagnosed DLBCL. The impact of *MYC* translocations with or without additional "hits" involving *BCL2* or *BCL6* in response to salvage therapy and survival in R/R DLCBL is not well defined. **Methods:** We performed a multicenter retrospective study of 176 patients with R/R DLBCL failing to achieve CR or relapsing within 6 months after completion of upfront chemoimmunotherapy and for whom FISH information on *MYC*, *BCL2* and *BCL6* was available. The objectives were to examine the response to salvage therapy, utilization of hematopoietic cell transplantation (HCT) and survival outcomes in *MYC*- (n = 120), *MYC*+ single hit (SH, n = 28), and *MYC*+ double hit (DH, n = 36) R/R DLBCL. **Results:** Overall response rate to first salvage therapy and utilization of HCT was comparable between the 3 cohorts (Table). 2-year OS was 0% in *MYC*+ SH, 8.8% in *MYC*+ DH and 29.9% in *MYC*- cases (p = 0.001) without difference in OS between SH and DH (P = 0.8). The higher risk of death for *MYC*+ SH (HR 1.79, 95% C.I. 1.03-3.11, P = 0.03) and *MYC*+ DH (HR 1.93, 95% C.I. 1.23-3.00, P = 0.004) persisted after adjustment for covariates. For patients who underwent auto-HCT, 2-year OS was 0% in *MYC*+ SH, 29.3% in *MYC*+ DH and 55.4% in *MYC*- cases (p $<$ 0.001) without significant difference between SH and DH (P = 0.8). All 4 *MYC*+patients who underwent allo-HCT relapsed in $<$ 4 months. **Conclusions:** *MYC*+ R/R DLBCL have similar response to salvage therapy than the *MYC*- counterparts but dismal survival irrespective of additional "hits" and even if HCT can be performed. *MYC*+ R/R DLBCL represents an unmet medical need and should be prioritized for clinical trials with novel agents and innovative cellular therapies.

Table	*MYC*+ SH N = 20 (%)	*MYC*+ DH N = 36 (%)	*MYC*- N = 120 (%)	P
Median age	57	61	58	0.3
Cell of origin -GCB	16 (80)	32 (89)	65 (52)	$<$ 0.001
Upfront therapy				$<$ 0.001
R-CHOP	14 (70)	23 (64)	108 (90)	
More intense	6 (30)	13 (36)	12 (10)	
Int. High/High NCCN-IPI at failure	13 (65)	13 (36)	55 (46)	0.1
Salvage therapy				0.8
ICE (+/- R)	13 (65)	23 (64)	69 (58)	
Response to first salvage therapy				0.2
CR+PR	9 (45)	18 (50)	57 (47)	
SD+PD	9 (45)	9 (25)	29 (24)	
Auto-HCT	7 (35)	13 (36)	48 (40)	0.9
Allo-HCT	1 (5)	3 (8)	15 (12)	0.5

7542 Poster Session (Board #304), Mon, 8:00 AM-11:30 AM

Frequency of secondary malignancies (SM) in patients with large granular lymphocytic leukemia (LGLL): A single institutional experience. *First Author: Leidy Lismeri Isenalumhe, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: Large granular lymphocyte (LGL) disorders represent a spectrum of aberrant T-cell or natural killer cell lymphocytic proliferations. LGLL is classically associated with autoimmune conditions and bone marrow (BM) failure disorders. SM has been reported in association with LGLL in about 10%. The aim of this study is to evaluate the impact of SM on the clinical course of LGLL. **Methods:** This is a retrospective study of LGLL patients (pts) evaluated at Moffitt Cancer Center between January 1995 and May 2016. The diagnostic clinico-pathological criteria consisted of LGL count $>$ 0.5 k/μL with T-cell receptor gene rearrangement. Lower absolute number of clonal circulating LGLs with characteristic immunophenotype associated with BM involvement, cytopenias, splenomegaly and/or associated symptoms were also diagnostic. Pts with myelodysplastic syndrome were excluded. Survival analysis was performed using the Kaplan-Meier method with log-rank test. Chi-square and T-test were used to analyze association among various variables. Significant P-value was considered $<$ 0.05. **Results:** Out of 668 screened pts with LGL expansions in peripheral blood, 261 met criteria for LGLL. SM were present in 44% (116/261) of LGLL pts, of which 38% were hematological and 80% arose prior to onset of LGLL. Most common solid SM included skin cancer (14%), prostate cancer (12%), and breast cancer (12%), while most common hematological SM consisted of non-Hodgkin lymphoma (17%) and chronic leukemia (14%). 5-year overall survival (OS) for all LGLL pts was 75% and 10-year OS 63%. There was a statistically significant difference in 5-year OS between LGLL pts with SM compared to without (p = 0.049), but no difference between both groups in median OS or 10-year OS. Pts diagnosed with SM prior to LGLL had worse 5-year OS (p = 0.031) and 10-year OS (p = 0.05) compared to all other LGLL pts. **Conclusions:** This study showed that the frequency of SM is higher than previously described, especially with onset prior to diagnosis of LGLL. Even though median age of LGLL is around 60 years, it appears that age itself cannot explain this phenomenon. Our results suggest that having a SM is a poor prognostic factor in LGLL patients.

7543 Poster Session (Board #305), Mon, 8:00 AM-11:30 AM

Central line-associated complications during treatment with DA-R-EPOCH therapy for NHL. *First Author: Rachel Julie David, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY*

Background: Certain non-Hodgkin lymphomas (NHL) such as primary mediastinal B-cell, Burkitt's, and high-grade B-cell lymphoma with MYC and BCL2 rearrangements are often treated with infusional dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (DA-R-EPOCH), which requires a central line. We have observed meaningful line-associated complications (LAC) in patients (pts) treated with DA-R-EPOCH. With the ongoing use of this regimen, we sought to identify the rates and correlates of LAC in this population. **Methods:** We retrospectively identified all pts treated with DA-R-EPOCH at the Wilmot Cancer Institute between 3/2011 and 10/2015. Our primary endpoint was the rate of LAC, including venous thromboembolism (VTE), extravasation, and line-associated infection (LAI) diagnosed during DA-R-EPOCH therapy. Our secondary endpoint was the rate of VTE during therapy. Rates and 95% confidence intervals (95% CI) were calculated for all endpoints. Univariate logistic regression was used to calculate odds ratios to evaluate potential predictors. **Results:** 43 pts received DA-R-EPOCH during the study period. 70% of pts were male; median age was 52 years. 17 pts (39.5%, 95% CI 0.25 - 0.56) experienced at least 1 LAC: 15 pts (35%, 95% CI 0.21 - 0.51) had VTE; 3 pts had LAI; and 2 pts experienced extravasations. Grade 3 toxicity was seen in 41% (7/17): 4 pts with VTE, and 3 pts with LAI. Both extravasation events were grade 2, and both occurred with mediports. In univariate analysis, BMI $\geq$ 35 kg/m^2 and receiving therapy via peripherally inserted central catheter (PICC) line were significantly associated with an increased risk of VTE (p=0.04 and p=0.02, respectively). **Conclusions:** 40% of pts receiving DA-R-EPOCH therapy for treatment of NHL developed LAC, almost half of whom experienced grade 3 toxicities. Clinicians need to balance these risks when selecting therapy, particularly with the lack of randomized data to support the DA-R-EPOCH approach in many circumstances. Given observed extravasations, we avoid mediports in favor of PICC lines, however this approach carries a significant risk of VTE. Future studies are needed to evaluate the role of prophylactic anticoagulation in this population.

7544 Poster Session (Board #306), Mon, 8:00 AM-11:30 AM

Phase I dose escalation of ibrutinib and buparlisib in relapsed/refractory diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL). *First Author: Connie Lee Batlevi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In vitro studies of BTK and PI3K inhibitors demonstrate synergy in non-Hodgkin lymphoma (NHL). We embarked on a phase I/Ib investigator-initiated clinical trial evaluating the combination of ibrutinib (BTK inhibitor) and buparlisib (pan-PI3K inhibitor) in relapsed/refractory (R/R) NHL. The completed dose escalation is reported. **Methods:** Patients (pts) were eligible if they had R/R DLBCL, MCL, or FL with ECOG≤2 and adequate organ function. Ibrutinib and buparlisib were given daily by mouth on a 28-day cycle. Dose reductions were permitted after cycle 1. Tumor response was based on Lugano Classification however CR required both PET resolution and ≥ PR by CT. **Results:** As of Dec 16, 2016, 13 pts were enrolled and evaluated for toxicity (DLBCL 5, FL 2, MCL 6). Dose levels and DLT per table. Six pts discontinued treatment for disease progression (DLBCL 4, FL 2). Hematologic AE ≥ grade 3 are anemia (2), leukocytosis (2), and leukopenia (4). Relevant non-hematologic AEs of any grade ≥ 20% across all pts were fatigue (77%), diarrhea (62%), anorexia (54%), rash (46%), hyperbilirubinemia (46%), gastric reflux (46%), CMV reactivation (31%), mood change (31%), and hypertension (23%). Most common related grade 3/4 toxicity is rash (N = 3). No grade 5 toxicities noted. Serious adverse events (SAE) include: grade 2 pleural effusion and grade 2 nausea (N = 1), grade 1 fever with hospitalization (N = 1), grade 2 confusion and grade 4 hyponatremia (N = 1) were unrelated to therapy. Responses noted in 13 pts: MCL (N = 6: CR 4, PR 2), FL (N = 2: SD 2), DLBCL (N = 5: SD 1). One CR was a MCL pt with CR after 2 cycles on combination therapy and continues in remission on ibrutinib alone because of buparlisib toxicity. **Conclusions:** Combination of ibrutinib and buparlisib while generally well tolerated has predicted toxicities of both BTK and PI3K inhibitors. The recommended phase 2 dose is ibrutinib 560 mg and buparlisib 100 mg though dose reductions for tolerability may be needed for long term oral therapies. Promising efficacy is observed in MCL. Clinical trial information: NCT02756247.

Dose Level	N	Ibrutinib (mg)	Buparlisib (mg)	DLT	Best Responses
1	6	420	80	1/6 Grade 2 anorexia	3 CR 1 SD
2	4	560	80	0/4	1 CR 2 SD
3	3	560	100	0/3	2 PR

7545 Poster Session (Board #307), Mon, 8:00 AM-11:30 AM

Clinical activity, safety and tolerability of ASN002, a dual SYK/JAK inhibitor, in patients non-Hodgkin lymphoma (NHL) and solid tumors. *First Author: Drew W. Rasco, START, San Antonio, TX*

Background: ASN002 is a novel, potent inhibitor of Spleen Tyrosine Kinase (SYK) and Janus Kinases (JAK). Pre-clinical studies indicate that ASN002 has low nM IC50s against SYK and JAK, decreases proliferation in ibrutinib-resistant cell lines, and suppresses tumor growth in rodent xenograft models of NHL and other hematologic malignancies. **Methods:** This Phase 1/2 clinical trial in patients with solid tumors and hematologic malignancies evaluates escalating ASN002 oral doses of 10, 20, 30, 40, 50 and' 75 mg BID and 80 and 120 mg QD mg (NCT02440685). Phase 1 allows patients with solid tumors or hematologic malignancies; Phase 2 allows only patients with diffuse large B-Cell lymphoma (DLBCL), follicular lymphoma (FL) or mantle cell lymphoma (MCL). Endpoints include safety, tolerability, pharmacokinetics, serum markers of inflammation, and response using RECIST or Lugano Classification System. **Results:** Twenty-eight patients have enrolled in the DLT phase at doses of 10 mg – 75 mg BID and at 80 mg QD. All patients had multiple prior lines of treatment (range: 2 – 8). ASN002 was well tolerated. No dose limiting adverse events have been reported at these dose levels. Most drug-related adverse events were Gr 1/2 (e.g. headache, fatigue). Steady-state systemic exposure was high (C_{max}, AUC (0-12h) and $T_{1/2}$ at 40 mg BID were 0.7 μM, 6.3 μM.h and 18 h, respectively). High systemic exposure was also observed at 80 mg QD. Robust reduction of CRP, IL-18, MIP1β, VCAM-1, TNFR2 was observed at all doses. Stable disease (RECIST, 9+ months) in a patient with primary peritoneal cancer, about 50% reduction in target lesions at 3 months in a FL patient (Lugano, 6 prior lines) and stable disease and reduction of pruritus in a peripheral T-Cell lymphoma patient after 2 months (Lugano, 2 prior lines) of treatment were observed. ASN002 treatment continues in both lymphoma patients. Accrual of patients continues. **Conclusions:** ASN002 was safe and well tolerated. Encouraging preliminary evidence of efficacy in NHL patients was observed. MTD has not been reached and dose escalation continues. Updated and detailed results will be presented. Clinical trial information: NCT02440685.

7546 Poster Session (Board #308), Mon, 8:00 AM-11:30 AM

Early disease progression in patients (pts) with newly diagnosed localized nasal extranodal NK/T-cell lymphoma, nasal type (ENKL) treated with radiotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (RT-DeVIC). *First Author: Motoko Yamaguchi, Mie University Graduate School of Medicine, Tsu, Japan*

Background: Approximately 25% of all pts with localized nasal ENKL experience disease progression during the first two years (yrs) after diagnosis under new treatments including concurrent chemoradiotherapy. The clinical features of those pts are largely unknown. **Methods:** The database of our study (NKEA project; UMIN000015491) was used for the present analysis. Data from pts with newly diagnosed localized (stage IE and contiguous IIE) nasal ENKL diagnosed between 2000 and 2013 at 31 institutes in Japan and treated with RT-DeVIC were retrospectively analyzed. Progression of disease within 2 yrs (POD24) (Casulo, JCO 2015) was applied as the definition of early progression. **Results:** Of 162 pts, 38 were in the POD24 group (23%) and 124 were in the reference group. Treatment yrs and doses of RT and DeVIC were not associated with the incidence of POD24. With a median follow-up of 5.8 yrs, the overall survival (OS) of the POD24 group was inferior to that of the reference group ($P < 0.00001$; 2-yr OS, 26% vs. 100%; 5-yr OS, 23% vs. 89%). The POD24 group showed the following features more frequently than the reference group: serum soluble interleukin-2 receptor (sIL-2R) level > upper limit of normal (ULN) (25/33, 76%; $P = 0.000012$), C-reactive protein (CRP) > ULN (28/37, 76%; $P = 0.013$), and detectable Epstein-Barr virus (EBV)-DNA in peripheral blood (15/17, 88%; $P = 0.033$). The positive predictive value and negative predictive value of elevated sIL-2R for POD24 were 42% and 90%, respectively; those of elevated CRP were 31% and 87%, respectively; and those of detectable EBV-DNA were 39% and 90%, respectively. Of the 9 pts who were negative for all three factors, none experienced POD24. A multivariate analysis in the POD24 group identified elevated sIL-2R as an independent predictive factor for worse OS (HR 3.16; 95% CI, 1.07 - 9.32). **Conclusions:** Pretreatment sIL-2R, CRP, and EBV-DNA were associated with POD24 among pts with localized nasal ENKL treated with RT-DeVIC. The strong association of elevated sIL-2R with early progression and short OS in the POD24 group provides a rationale for targeting strategies.

7547 Poster Session (Board #309), Mon, 8:00 AM-11:30 AM

Rapid, real-time central pathology review for E1412: A novel and successful paradigm for future National Clinical Trials Network diffuse large B cell lymphoma studies. *First Author: Rebecca L. King, Mayo Clinic, Rochester, MN*

Background: E1412 statistical design is based on results of lenalidomide/RCHOP (R2CHOP) vs RCHOP in ABC-DLBCL as determined by NanoString gene expression profiling (GEP). Central pathology review (CPR) was conducted to confirm diagnosis and to ensure adequate tissue for GEP. Initially, CPR occurred after randomization and treatment initiation. Due to high ineligibility rate (IR), the protocol was amended to include real-time CPR to determine patient eligibility prior to study enrollment. We describe the revision and how it affected the IR. **Methods:** Pre-amendment, CPR was done retrospectively. Post-amendment, CPR was done prior to enrollment, in real time, on a submitted tissue block, H&E, and CD20 slides. Based on CPR, if a diagnosis of DLBCL was confirmed, and sufficient tissue remained for GEP, a patient was deemed eligible and the submitter was notified by fax. Protocol goal was notification within 2 working days (WD) of receipt of materials at the CPR site. **Results:** Pre-amendment, 219 patients were enrolled. Material was typically received at the CPR site 6-9 months after patient registration. The IR with CPR was 36% for all those enrolled, and 26% for patients with adequate tissue for GEP. Post-amendment, 218 patients were submitted for CPR: 145 (67%) were eligible; 73 (33%) were ineligible. Reasons for ineligibility included insufficient tissue (n=27) or a diagnosis other than de novo DLBCL (n=46). Notification of eligibility occurred in a median of 2 WD (Mean 2 WD; Range 1-5 WD). 90% were notified within the protocol goal of 2 WD. GEP for all enrolled was completed within 6 weeks of CPR. **Conclusions:** The success of this novel, real-time CPR serves as a model for the future of NCTN DLBCL trials. When CPR is performed rapidly prior to enrollment, study slots may more accurately reflect the target population and eliminate excess costs. In the precision medicine era, rapid collection of relevant pathology and biomarker data is essential to trial success. Study Coordinated by ECOG-ACRIN Cancer Research Group (Robert L. Comis, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs), supported by NCI grant # CA180820, CA180794, CA180790, CA180799, CA180833.

7548 Poster Session (Board #310), Mon, 8:00 AM-11:30 AM

Significance of MYC rearrangement and chemotherapy type on survival outcomes of patients with central nervous system lymphoma. *First Author: Natalie Sophia Grover, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: Central nervous system lymphoma (CNSL) has a poor prognosis and an optimal treatment regimen has not been established. Due to the rarity of this disease and frequently poor performance status at diagnosis, there have been few prospective therapeutic clinical trials in this patient population. We therefore performed a retrospective analysis of prognostic factors and treatment outcomes of patients with CNSL treated at a single institution. **Methods:** Pathology records were used to identify patients diagnosed with CNSL from 1/1/2005 to 9/1/2016 at the University of North Carolina Cancer Hospital. Information about demographics, disease characteristics, treatment, and outcomes was gathered from the electronic medical record. Overall (OS) and progression free survival (PFS) were estimated using the Kaplan-Meier method. **Results:** We identified 100 patients with CNSL. 49% had primary CNSL (PCNSL). 78% of cases were diffuse large B cell lymphoma. Out of 51 patients evaluated for MYC translocation by FISH, 13 were positive (3 PCNSL and 10 secondary CNSL). Out of 74 patients treated with chemotherapy, 51% received methotrexate (MTX), procarbazine, and vincristine (MPV), with or without rituximab, 28% were treated with other high dose MTX based regimens, with or without rituximab, and 20% received a non-MTX based regimen. There was no significant difference in OS between PCNSL and secondary CNSL (13.7 vs 7.9 months, p = 0.97). Patients with MYC translocation had a worse OS compared to those without MYC translocation (5.1 vs 29.5 months, p = 0.004). Patients treated with MPV had a longer PFS compared to those treated with other high dose MTX based regimens or those who were treated with a non-MTX based regimen (19.1 vs 10.9 vs 3.9 months, p = 0.05), but difference in OS did not reach statistical significance (29.5 vs 22.4 vs 10.6 months, p = 0.12). **Conclusions:** In this single institution analysis of CNSL, MYC translocation was associated with worse survival. MPV was associated with improved PFS compared to other chemotherapy regimens. Further prospective studies are needed comparing MPV to other MTX-based regimens in CNSL.

7549 Poster Session (Board #311), Mon, 8:00 AM-11:30 AM

Oncogenic activation of STAT3 pathway drives PD-L1 expression in natural killer/T cell lymphoma. *First Author: Soon Thye Lim, National Cancer Centre Singapore, Sinagpore, Singapore*

Background: Natural killer/T-cell lymphoma (NKTL) is a rare type of non-Hodgkin lymphoma that occurs more frequently in East Asia and Latin America and is associated with Epstein–Barr virus infection. Recent whole-exome sequencing studies in NKTL have reported recurrent somatic mutations in genes associated with JAK-STAT pathway, however the role of aberrant JAK-STAT signaling in tumor immune escape through PD-L1 regulation is unclear. **Methods:** To determine the prevalence of JAK-STAT pathway alteration in NKTL, we performed targeted sequencing of 188 genes associated with JAK-STAT pathway in 109 NKTL (22 Singapore cases, 79 China cases and 8 cell lines). Single nucleotide variants and micro-indels were called using Freebayes and candidate variants annotated using ANNOVAR. Ba/F3 model system was used to test the transformation capacity of identified variants. Cell lines were evaluated for PD-L1 expression by immunoblotting and flow cytometry. Tissue microarrays were examined for p-STAT3 and PD-L1 expression by immunohistochemistry. **Results:** We identified a total of 284 non-synonymous somatic mutations candidates in 114 genes, including 243 missense, 10 nonsense, 4 splice-site and 27 indel mutations. Recurrent mutations were most frequently located in STAT3 (25/109 cases, 23%) followed by TP53 (16/109 cases, 16%) and JAK3 (8/109 cases, 7%). A total of 18 STAT3 variants were identified including known hotspot mutations and novel mutations in the SH2, coiled coil and DNA-binding domains. Characterization of novel E616K mutant residing in the SH2 domain showed that E616K conferred IL3 independent growth to Ba/F3 cells, increased STAT3 phosphorylation and PD-L1 expression. Consistent with these findings, PD-L1 was over expressed in cell lines harboring STAT3 mutations. A positive correlation between PD-L1 and p-STAT3 expression was also observed in tumor tissue (R = 0.51, P = 0.02). **Conclusions:** We characterized a novel activating STAT3 mutant and demonstrated its ability to drive PD-L1 expression, which may promote tumor evasion from the antitumor immune response. The combination of PD-1/PD-L1 antibodies and STAT3 inhibitors might be a promising and novel therapeutic approach for NKTL in the future.

7550 Poster Session (Board #312), Mon, 8:00 AM-11:30 AM

Comparative double-blind randomized trial of 2 rituximab products in patients with CD20+ diffuse large B-cell lymphoma (DLBCL). *First Author: Sandip Shah, Gujarat Cancer and Research Institute, Ahmedabad, India*

Background: DRL-Rituximab (T) is a proposed biosimilar of the innovator reference rituximab (USA: Rituxan; EU: MabThera). Physicochemical analyses and nonclinical studies have shown T to be comparable with innovator Rituximab. This study evaluated the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety and immunogenicity of T with EU sourced MabThera (R) in DLBCL patients. **Methods:** Multicentre randomized double-blind 2-arm parallel study conducted in patients aged 18-60 yrs, with a centrally confirmed newly diagnosed CD20+ DLBCL, as first line of treatment. Patients received 6 cycles (C), every 21 days, of either T or R at 375 mg/m^2 + CHOP. Primary objective was to compare C1 PK ($AUC_{0\text{-}21d}$ & C_{max}). Overall Response Rate (ORR) was the key secondary objective, with C6 PK parameters, PD parameters (B-cells measured as CD19+ positive cells in peripheral blood- depletion & repletion), treatment-emergent adverse events (TEAEs), and anti-drug antibodies (ADA) as other secondary objectives. PK similarity criterion was 90% CI of geometric mean ratios (GMRs) of $AUC_{0\text{-}21d}$ and C_{max} in C1, within 80-125%. **Results:** 151 patients were randomized (T, 76; R, 75). PK similarity criterion was met. The GMR T/R ratios with 90% CIs for $AUC_{0\text{-}21d}$ & C_{max} were 100.0% (87.7, 114.0) & 96.2% (88.7, 104.4), respectively. Per protocol, ORR with 95% CI was 82.1% (69.6, 91.1) with T and 87.1% (76.1, 94.3) with R. Trough concentration (C5/C6) GMR (90% CI) of 91.3% (86.3, 96.7) for T & 94.0% (88.9, 99.5) for R indicated steady state. C6 $AUC_{0\text{-}21d}$ & C_{max} GMR (T/R [90% CI]) were 88.9% (80.3, 98.5) and 94.6% (88.1, 101.7), respectively. T and R led to comparable B-cell depletion and repletion. Incidence of all grades of TEAEs were comparable. TEAEs ≥Grade 3 were 80.3% in T (n = 61) and 88.0% R (n = 66). Neutropenia was the most common TEAE (overall: T, 75.0%; R, 73.3% & ≥ grade 3: T, 64.5%; R, 64.0%). No neutralizing antibodies were observed in either of the arms. **Conclusions:** These data demonstrate that DRL-Rituximab has comparable PK, PD, efficacy, safety and immunogenicity to MabThera. MabThera already has an established efficacy in longer term follow-up. Clinical trial information: CTRI/2012/11/003129.

7551 Poster Session (Board #313), Mon, 8:00 AM-11:30 AM

Survival outcomes for various treatment modalities in early-stage grade 3 follicular lymphoma (FL3): a National Cancer Database (NCDB) study. *First Author: Upama Giri, University of Tennessee Health Sciences Center, Memphis, TN*

Background: The prognosis, response to therapy and curability of FL3 is controversial. 5-year Overall Survival (OS) in the literature ranges from 35-72% (Ganti 2006). The aim of this study was to compare the OS for patients with early-stage FL3 managed with single- and multi-agent chemotherapy (CT) with and without radiotherapy (RT). **Methods:** We identified patients (pts) diagnosed with stage I & II FL3 between 2004 – 2012 from the NCDB and categorized into 3 groups based on therapy – pts given single agent CT with or without RT were combined due to small sample sizes (SA±RT), multi-agent CT without RT (MA-RT), and multi-agent CT with RT (MA+RT). We calculated OS for each group using Kaplan-Meier method and compared the results using Log Rank test. Cox regression model was used to identify factors which had significant impact on OS. **Results:** 1,563 pts were identified – 827 (53%) with stage I and 736 (47%) with stage II FL3. Median age was 61 yrs (range 18-90yrs); 750 (48%) males, 813 (52%) females; 1423 (91%) whites, 76 (5%) blacks. 112 (7%) received SA±RT, 886 (57%) MA-RT and 565 (37%) MA+RT. 5-year OS for MA+RT (95%) was significantly more than MA-RT (87%; HR 0.33, P<0.001) or SA±RT (88%; HR 0.38, P=0.007). Cox regression indicated that age (HR 1.05, P<0.001), sex (HR 0.66 for females, P=0.02), comorbidities (HR 1.60 for Charlson Deyo Score 1, P=0.04; HR 3.07 for Score 2, P=0.001), stage (HR 1.79, P=0.001), insurance status (HR 0.22 for insured, P<0.001) and increasing year of diagnosis (HR 0.92, P=0.03) also had significant impact on OS. Median radiation dose for the MA+RT was 36Gy (interquartile range 30.6 – 36Gy), and the proportion of patients who received greater than 36Gy decreased from 55% in 2004 to 38% in 2012 and at the same time, the proportion of patients who received intensity modulated RT increased from 5% in 2004 to 15% in 2012. Use of MA CT declined (2004 95% v 2012 89%, P=0.02) but there was no significant trend in use of RT (2004 39% v 2012 34%) during the periods studied. **Conclusions:** For pts with early-stage FL3, there was an association of improved survival with the use of MA+RT over other treatment strategies and appear to have outcomes superior to what has been previously reported.

7552 Poster Session (Board #314), Mon, 8:00 AM-11:30 AM

Circulating tumor DNA assessment in patients with diffuse large B-cell lymphoma following CAR-T therapy. *First Author: Saurabh Dahiya, Stanford University School of Medicine, Stanford, CA*

Background: Circulating tumor DNA(CTD) have been used for disease monitoring in Diffuse Large B Cell Lymphoma(DLBCL) (Kurtz ASCO 2016). Role of CTD assessment in DLBCL patients treated with CAR-T therapy has not been studied. We prospectively analyzed CTD of dynamics measured by next generation sequencing(NGS) of BCR using ClonoSeq MRD(Adaptive Biotechnologies), before and after CAR-T therapy to determine feasibility and clinical utility. **Methods:** At Stanford, 7 patients were enrolled on ZUMA-1 clinical trial NCT02348216, treating chemo-refractory DLBCL patients with anti-CD19, CAR-T. Complete radiologic data and CTD analysis was collected for six subjects. Tumor-DNA was extracted from archival paraffin-embeded tissue & analyzed using the NGS-based assay. PCR amplification of IGH-VDJ, IGH-DJ & IGK regions using universal consensus primers was performed followed by NGS to determine the tumor clonotype(s). Blood collected at day 0,7,14,28,60 & 90 days in relation to CAR-T infusion was used to detect CTD by ClonoSeq quantification of clonotypes. **Results:** Clonotypes were successfully determined for all 6 subjects, and 30 blood samples for 6 patients were prospectively analyzed. All patients had measurable disease burden pre-CAR-T infusion. CTD dynamics correlated with PET-CT outcomes in 100% of the patients. Increasing CTD temporally preceded progressive disease(PD) before PETCT recognition in 4 of 5 patients and was always increasing when PETCT showed PD. Preceding CTD quantification correlated with disease volume increase. One patient achieved durable KTE-19 complete response(CR) and detectable CTD became undetectable on day 14(and on subsequent samples) following CAR-T infusion, corresponding to 1 & 3 month PETCT CR. Additionally, the burden of disease measured by lymphoma molecules per ml allowed volumetric response assessment in all the patients who experienced massive reduction in tumor volume, but by traditional response definition had partial response. **Conclusions:** ClonoSeq CTD provides precise total tumor quantification of DLBCL in the CAR-T cell setting. This technology may overcome fundamental limitations of DLBCL imaging(cost, radiation exposure & limited repetition).

7553 Poster Session (Board #315), Mon, 8:00 AM-11:30 AM

Clinicopathologic characteristics and outcomes of transformed diffuse large B-cell lymphoma in hepatitis C virus-infected patients: A case-control study of 84 patients. *First Author: Jeff Hosry, Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Chronic hepatitis C virus (HCV) infection is associated with development of marginal zone lymphoma (MZL) and diffuse large B-cell lymphoma (DLBCL). Preliminary data showed particular characteristics of HCV-associated DLBCL; such as frequent transformation from indolent lymphomas and aggressive oncologic courses. We studied herein the clinicopathologic characteristics and outcomes of HCV-infected patients (pts) with transformed DLBCL. **Methods:** In this case control study, the medical records and pathology reports of HCV-infected (cases) and HCV-uninfected (controls) pts with transformed DLBCL seen at our institution (6/2004 - 5/2015) were reviewed. Included pts had a concomitant or a history of a low grade lymphoma. To determine their clinicopathologic characteristics, cases were compared to controls at a ratio of 1:3. To determine predictors of oncologic relapse, we compared pts with DLBCL relapse after first line chemotherapy to those who did not relapse in univariate and logistic regression analyses. **Results:** Twenty-one cases were compared to 63 controls. Compared to controls, cases were younger (median year age [interquartile range], 54 [49-62] *v* 62 [53-66], $P = .01$), had advanced Ann Arbor stages, 3-4 (95% *v* 76%, $P = .05$), and upper gastro-intestinal involvement (48% *v* 25%, $P = .05$). Immunophenotypically, cases had more CD10-negative B-cells (76% *v* 43%, $P = .008$) and CD5-positive B-cells (39% *v* 7%, $P = .004$) compared to controls, consistent with an activated B-cell phenotype. A comparison between pts who relapsed after first line chemotherapy (n = 42) and those who did not (n = 40) revealed that having CD5-positive B-cells was the only factor associated with DLBCL relapse in univariate (24% *v* 6%, $P = .03$) and multivariate analyses (OR = 10.7, $P = .02$). **Conclusions:** HCV-infected pts with transformed DLBCL are younger, present with advanced stages, are more commonly CD5-positive, and have an activated B-cell phenotype, suggesting more frequent transformation from MZL compared to HCV-uninfected pts. The higher frequency of CD5-positive B-cells might explain the higher DLBCL relapses previously described in HCV-infected pts.

7554 Poster Session (Board #316), Mon, 8:00 AM-11:30 AM

Survival outcomes for various treatment modalities in advanced-stage grade 3 follicular lymphoma (FL3): A National Cancer Database (NCDB) study. *First Author: Upama Giri, University of Tennessee Health Sciences Center, Memphis, TN*

Background: The prognosis, response to therapy and curability of FL3 is controversial. 5-year Overall Survival (OS) in the literature ranges from 35-72% (Ganti 2006). The aim of this study was to compare the OS for patients with advanced-stage FL3 managed with various treatment modalities. **Methods:** We identified patients (pts) diagnosed with stage III & IV FL3 between 2004 – 2012 from the NCDB and categorized them into 3 groups based on therapy – pts given single agent chemotherapy with or without radiotherapy were combined due to small sample sizes (SA±RT), multi agent chemotherapy without radiotherapy (MA-RT), and multi agent chemotherapy with radiotherapy (MA+RT). We calculated OS using Kaplan-Meier method and compared the results using Log Rank test. Cox regression model was used to identify other factors which had significant impact on OS. **Results:** 2,808 pts were identified – 1,508 (54%) with stage III and 1,300 (46%) with stage IV disease. Median age was 60 yrs (range 21-90yrs); 1,331 (47%) males, 1,477 (53%) females; 2,559 (91%) whites, 142 (5%) blacks. 170 cases (6%) were treated with SA±RT, 2,508 (89%) with MA-RT and 130 (5%) with MA+RT. There was no significant difference in 5-year OS between MA-RT (83%) and MA+RT (82%; HR 1.07, P=0.76). There was no difference between SA±RT (73%) and MA+RT (82%; HR 0.62, P=0.069) likely due to small sample sizes, but survival for MA-RT (83%) was significantly higher than SA±RT (73%; HR 1.78, p<0.001). Cox regression indicated that age (HR 1.04, P<0.001), sex (HR 0.77 for females, P=0.008), comorbidities (HR 1.48 for Charlson Deyo Score 1, P=0.001; HR 2.59 for Score 2, P<0.001), stage (HR 1.29, P=0.007), insurance status (HR 0.65 for insured, P=0.048) and increasing year of diagnosis (HR 0.91, P<0.001) also had significant impact on OS. Use of MA chemotherapy declined (2004 96% v 2012 91%, P=0.008) but there was no significant trend in use of radiotherapy (2004 5% v 2012 3%) during the periods studied. **Conclusions:** MA chemotherapy in pts with advanced-stage FL3 was associated with improved survival compared to SA therapy, and radiation does not appear to influence outcomes. Outcomes were superior to what has been previously reported.

7555 Poster Session (Board #317), Mon, 8:00 AM-11:30 AM

A single institutional experience of 261 patients with large granular lymphocytic leukemia (LGLL). *First Author: Magali Van den Bergh, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: LGLL is a rare clonal lymphoproliferative disorder of post-thymic T-cell or natural killer (NK)-cell lineage associated with cytopenias, splenomegaly, autoimmune disorders, and recurrent mucocutaneous infections. Treatment is dictated by the presence of these manifestations and consists of immunosuppressive therapy. **Methods:** This is a retrospective analysis of clinical and laboratory features, treatment modalities, and outcomes of LGLL patients evaluated at Moffitt Cancer Center between 1995 and 2016. Continuous and categorical variables were tested via Kruskal-Wallis ANOVA and Fisher's Exact Test. Kaplan-Meier curves were used for overall survival (OS). P-values were two-sided with significance set at < 0.05. **Results:** We identified 261 patients with LGLL (91.6% T, 8.4% NK). Median age was 66 years [21-90] and M:F ratio 1.2:1. Median follow up was 3.07 years [0-21.88]. 42.9% presented with anemia, 37.1% neutropenia, 30.7% thrombocytopenia, 29.1% bicytopenia and 6.9% pancytopenia. Transfusion dependence was noted in 20.3%, splenomegaly in 27.2% and bone marrow (BM) involvement in 69.3%. 24.9% had autoimmune diseases and 9.2% autoimmune cytopenias. 45.6% were observed while the remainder required at least 1 line of therapy. 5-yr and 10-yr OS were 75.0% and 63.1% respectively. There was no statistically significant difference in OS, complete response or duration of response based on first line agent (methotrexate, cyclophosphamide, cyclosporine A). However, there was a statistically significant improved partial response with methotrexate versus other therapies (p=0.01). A marginally significant association between severe anemia/transfusion dependence and poor overall response rate (p=0.075) to any therapy was noted. There was no statistically significant difference in OS based on absolute LGL count. Mean number of therapies was 1.08 (range 0-6) and was higher in those with LGL count <0.5 k/μL (p=0.0078), BM involvement (p<0.0001), and splenomegaly (p<0.0001). **Conclusions:** In this large retrospective study, we described the frequency of LGLL-associated manifestations and their impact on the course of LGLL. We confirmed that there is no difference in OS among first line therapies.

7556 Poster Session (Board #318), Mon, 8:00 AM-11:30 AM

Results of GROC-rev salvage regimen: Gemcitabine, rituximab, and oxaliplatin chemotherapy with revlimid for relapsed/refractory aggressive non-Hodgkin lymphoma (NHL). *First Author: Fernando Cabanillas, Auxilio Mutuo Cancer Center, San Juan, PR*

Background: Currently there is no optimal salvage regimen for relapsed/refractory NHL (R/R NHL). Prognosis of pts who fail to achieve CR to salvage therapy is dismal. We sought to improve the CR rate by adding Lenalidomide (L) to GROC (ASCO #8530, 2008). **Methods:** Primary endpoint was rate of conversion to CR after switch to L for pts whose best response to GROC was <CR. Secondary endpoint was progression free survival (PFS) of all pts as well as those who achieve <CR on chemotherapy and were crossed over to L.Pts who failed to achieve at least PR after GROC x2 and those who didn't achieve CR after GROC x6, were crossed over to L 25 mg x 3 weeks q 28 days. CRs were maintained on L x 2 yrs. **Results:** 34 pts were enrolled of which 32 are evaluable. Median age: 61 and 56% males. Histologies included DLBCL (81%), PTCL (9%), follicular grade 3-B (9%). Stage was III-IV in 75% and median IPI=2. Best overall response rate (ORR) at any point during treatment= 19/32 (59%) and CR 13/32 (41%). ORR before crossover to L=13/32 (41%) and CR= 8/32 (25%). There were 24 who failed to achieve CR on GROC (19 who didn't respond at all and 5 whose maximum response was PR). Of these, 21 crossed over to L and 7 (33%) responded (CR in 5, PR in 2). The fact that 5 pts attained a CR to L thus improving the CR rate from 25% to 41% after exhibiting refractoriness to GROC is noteworthy. Of the 7 responders to L, all are alive and only 1 relapsed. At 2 yrs., overall survival (OS) was 48% and PFS 35%. This compares favorably with our previous GROC study without L in which 2 yr. OS= 33% and PFS 29%. In total, 11 pts were eligible for ASCT after chemo plus L and 8 were transplanted (3 refused). Of these eight, 6 remain in CR at 11, 18, 21, 22, 52, 74 mos. At 2 yrs, PFS for transplanted pts is 73% and for those whose response to GROC before crossover to L was <CR, it is 27 mos. Toxic events included 2 neutropenic fevers, 1 MDS (34 mos. after ASCT) and 1 AML (11 mos. after ASCT). Both of these remain continuously in CR after allo SCT. **Conclusions:** 2 yrOS=48% and PFS=35% with GROC-Rev are the best observed with any salvage regimen we have tested. L is active as a single agent in 29% of cases whose best response to GROC was <CR. A larger study is desirable to confirm these data. Clinical trial information: NCT01307592.

7557 Poster Session (Board #319), Mon, 8:00 AM-11:30 AM

Interim metabolic tumor volume to predict response in diffuse large B-cell lymphoma. *First Author: Prioty Islam, Emory University School of Medicine, Atlanta, GA*

Background: DLBCL is a heterogeneous disease with varied clinical outcomes following treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). [^{18}F] fluorodeoxyglucose (FDG) – positron emission tomography (PET)/computed tomography (CT) imaging is ubiquitously used in monitoring of DLBCL. PET-derived metrics for analysis of tumor FDG uptake include: tumor maximum standardized uptake value (SUV); metabolically active tumor volume (MTV); and total lesion glycolysis (TLG), calculated from the intensity of FDG uptake in tumor volume. We evaluated the predictive value of interim SUV, MTV and TLG for patients (pts) with DLBCL treated with R-CHOP. **Methods:** Pts with DLBCL treated at Emory University 2005-2016 were eligible. Cases were included if there was a diagnosis of DLBCL confirmed by record review, available information on date of diagnosis, date of last contact or date of death. Analyses were restricted to patients who received R-CHOP and had PET/CT scans available at baseline, Cycle 2 or 4 and end of treatment. Maximum SUV, MTV, and TLG were calculated using MIM software for tumor with an SUV threshold of > 4. Logistic regression analysis was used to calculate the predictive value of interim PET/CT metrics on end of treatment response. **Results:** Pre-treatment PET/CT scans for 42 patients were identified, along with 28 interim and 31 post-treatment scans. The mean pre-treatment MTV was 303ml (range 4 – 1,327) and mean TLG was 3188 (range 28 – 16,176). MTV and TLG were undetectable in 79% of interim scans and 74% of the post-treatment scans. A Deauville score of 3 or less was observed in 71% of the interim PET/CT scans and 56% of the post-treatment scans. A positive interim MTV was correlated with a positive post-treatment MTV and post-treatment Deauville score at 0.58 and 0.66, respectively, and a positive interim MTV result was a significant predictor of a positive post-treatment MTV result ($p = 0.02$). **Conclusions:** PET-derived metrics of assessing interim tumor response to therapy offer significant predictive value for end of treatment response, and can guide a response-adapted treatment approach for DLBCL pts that builds on the R-CHOP backbone.

7558 Poster Session (Board #320), Mon, 8:00 AM-11:30 AM

Allogeneic hematopoietic stem cell transplantation for mantle cell lymphoma in a heavily pretreated patient population. *First Author: Daniel Allen Kobrinski, Loyola University Medical Center, Maywood, IL*

Background: Allogeneic hematopoietic stem cell transplantation (allo-SCT) is the only potential curative treatment option for patients with MCL due to its potent graft-versus-lymphoma (GVL) effect. Survival following allo-SCT for MCL is variable due to high rates of non-relapse mortality (NRM). **Methods:** We retrospectively identified all patients who were treated with an allo-SCT for MCL at Loyola University Medical Center between January 1, 1999 and January 1, 2016. Probability estimates for overall survival (OS) and non-relapse mortality (NRM) at 5 years were calculated from the date of allo-SCT to the date of patient death or last known follow-up. Significance was determined using a cox proportional hazard (CPH) model. Rates of acute graft-versus-host disease (aGVHD) and relapse were also reported. **Results:** Patient characteristics (n = 29) are listed in Table. Median follow-up in surviving patients is 10 years (range 5-14 years). A majority of patients (n = 23, 79%) had 3 or more lines of treatment prior to allo-SCT. The 5 year rates of OS and NRM for all patients are 42% and 53%, respectively. Univariate analysis showed a lower risk of death in patients who received TBI-based conditioning (HR: 0.19, 95 CI: 0.04 – 0.81, p = 0.03), and those who had HLA-matched related donor (MRD) transplants (HR: 0.29, 95 CI: 0.11 – 0.79, p = 0.02). Patients who received more than 3 lines of prior treatment had a higher risk of death (HR: 2.77, 95% CI: 1.05-7.34, p = 0.04). Low rates of grade III/IV aGVHD (n = 4) and relapse (n = 4) occurred in our patient population. Two patient deaths were attributable to aGVHD, and the majority of other deaths were due to treatment-related toxicities. **Conclusions:** In an era of numerous effective non-curative salvage therapies, the optimal timing of allo-SCT for MCL needs further clarification. Our data supports early opposed to delayed allo-SCT for select high-risk patients with MCL who have a MRD.

Patient characteristics (N = 29)

	N (%)
Sex	
Male	22 (76%)
Median age in yrs (range)	54 (30-66)
Median lines of treatment prior to allo-SCT (range)	3 (1-6)
MIPI at allo-SCT	
High	14 (48%)
Type of conditioning	
RIC	23 (79%)
Myeloablative	6 (21%)
Donor type	
MRD	15 (52%)
MUD	6 (21%)
UCB	8 (27%)

7559 Poster Session (Board #321), Mon, 8:00 AM-11:30 AM

***MYC/BCL2/BCL6* triple hit lymphoma: A study of 33 patients who had an aggressive clinical course similar to patients with double hit lymphomas.** *First Author: Shaoying Li, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Large B cell lymphomas with *MYC, BCL2*, and *BCL6* rearrangements, designated as triple hit lymphoma (THL), are uncommon. Large series studies of THL are scant and studies comparing THL to different types of double hit lymphoma (DHL) are lacking. **Methods:** We studied the clinicopathologic features and prognosis of 33 patients with THL and compared them to 83 patients with *MYC/BCL2* DHL and 13 patients with *MYC/BCL6*DHL. **Results:** There were 21 men and 12 women, with a median age of 63 years (range, 34-85). Six patients had a history of low-grade B cell lymphoma and 27 had *de novo* lymphoma. These tumors were classified histologically as: 21 DLBCL, 10 high grade B-cell lymphoma, one concurrent DLBCL and follicular lymphoma (FL), and one concurrent DLBCL and mantle cell lymphoma. Immunohistochemical analysis showed that these tumors were positive for CD10 (94%), BCL6 (80%), BCL2 (93%), and MYC (69%, 40% as cutoff). 62% of tumors (8/13) with available data showed coexpression of MYC and BCL2. Using the Hans algorithm, 30 of 33 (91%) tumors had a germinal center B cell like (GCB) immunophenotype. All 7 cases tested by conventional cytogenetics showed a complex karyotype. Although *BCL2* was always translocated with IGH, *BCL6* translocated to *MYC* in 2of 7 cases of THL. Twenty-nine patients had treatment information available and all received immune-chemotherapy induction, including 11 with R-CHOP, 14 with R-EPOCH, 3 with R-HyperCVAD, and one with RICE (patient had a history of FL). The clinicopathological features of THL including induction chemotherapy were very similar to both the *MYC/BCL2* DHL and *MYC/BCL6* DHL (all P>0.05). There was no significant difference in median overall survival (OS) between patients with de novo lymphoma and those with a history of low-grade lymphoma (P=0.99). The OS in THL patients was 17.9 months, similar to the OS (17.2 months) of patients with *MYC/BCL6* DHL and those with *MYC/BCL2*DHL (19.9 months) (P=0.60). **Conclusions:** *MYC/BCL2/BCL6* THL is an aggressive B cell lymphoma and >90% of cases have a GCB immunophenotype. THL patients usually have an aggressive clinical course and a poor prognosis, similar to patients with double hit lymphomas.

7560 Poster Session (Board #322), Mon, 8:00 AM-11:30 AM

The outcome of high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements or NOS compared to DLBCL patients from a single institution. *First Author: Joanna Romejko-Jarosinska, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland*

Background: 2016 update of the WHO 2008 classification of lymphoid neoplasms introduced new categories of highly aggressive B lymphomas (BCL): high grade B lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBLR) and HGBL not otherwise specified (NOS). The prognosis for HGBL is generally considered poor, the optimal therapy is unknown. Here we evaluated outcome after first line treatment in patients with a diagnosis of HGBLR, HGBL, NOS, and DLBCL at our institution. **Methods:** Medical records of 591 consecutive patients with aggressive BCL were evaluated, archived pathology reports and samples were reviewed, diagnosis revised if necessary according to 2016 update of WHO classification. We identified 16 cases of HGBLR (3%), 26 cases of HGBL, NOS (4%), and 565 cases of DLBCL (93%). Response to first line therapy, progression free survival (PFS), and overall survival (OS) were calculated and compared between these three entities. **Results:** DLBCL patients were treated with RCHOP between 2005-2012, HGBL patients were treated between 2005-2016 with RDAEPOCH (n = 31, 5%), RCHOP or other regimens. For the first line treatment in patients with DLBCL, HGBLR and HGBL NOS, the overall response/complete response rate was 92%/75%, 81%/56%, 93%/65%, respectively (p = NS). After a median (range) follow up of 42(1-155) months, median PFS and OS for DLBCL was not reached. For both HGBLR and HGLB, NOS patients median PFS was 10 months, median OS was 16 months. The HR for risk of progression in patients with HGBLR vs DLBCL and HGBL NOS vs DLBCL was 2.4 (1.1-4.7), p = 0.01 and 2.0 (1.1-3.5), p = 0.01. The HR for risk of death, for HGBLR vs DLBCL and HGLB NOS vs DLBCL was 2.59(1.32-5.07), $p < 0.01$ and 1.8(0.9-3.3), p = 0.08. The risk of progression and the risk of death in HGBLR vs HGBL, NOS was similar, for PFS: 1.08 (0.46- 2.5), p = NS for OS: 1.2 (0.5 -3,1) p = NS. **Conclusions:** Our data confirms reports by others on poor prognosis for patients with a diagnosis of HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements as well as HGBL, NOS with an increased risk of death and risk of progression compared to DLBCL patients. There was no difference in outcome between HGBL-R and HGBL, NOS patients in our series.

7561 Poster Session (Board #323), Mon, 8:00 AM-11:30 AM

Development of a clinical trial immunohistochemistry (IHC) assay using a novel antibody to CD38. *First Author: Karen Wakamiya, Agilent Technologies, Carpinteria, CA*

Background: CD38 is a type II transmembrane glycoprotein expressed on normal lymphoid and myeloid cells and can be highly expressed in hematologic malignancies. An IHC prototype assay was developed to detect CD38 expression in formalin-fixed, paraffin-embedded (FFPE) tissue specimens from three relapsed or refractory non-Hodgkin's lymphoma (NHL) subtypes: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle cell lymphoma (MCL) for selection of patients for treatment with daratumumab in a Phase 2 clinical trial (NCT02413489). **Methods:** This assay is based on EnVision FLEX IHC technology using CD38, clone DAK-CD38, primary antibody that has been developed and manufactured by Agilent Technologies. The assay staining protocol was developed for Dako PT Link and Autostainer Link 48. Specificity of DAK-CD38 staining was demonstrated by Western blot analysis of cancer cell lysates, as well as IHC on both normal and cancer tissue. Assay precision and robustness were evaluated using commercially procured FFPE DLBCL, FL and MCL specimens. **Results:** CD38 IHC DAK-CD38 detected a broad range of CD38 expression in DLBCL, FL, and MCL specimens. FFPE specimens derived from cancer cell lines exhibited a range of IHC staining intensity and confirmed the reported expression of CD38 in the scientific literature. All precision and robustness results met acceptance criteria for both IHC intensity and percent positive cells staining. **Conclusions:** Our studies demonstrate that the Dako CD38 IHC DAK-CD38 assay is sensitive, specific, precise, and robust for the detection of CD38 expression in DLBCL, FL and MCL. This assay may also have the potential to be used for the detection of CD38 in additional tumor types.

7562 Poster Session (Board #324), Mon, 8:00 AM-11:30 AM

Patterns of use of CNS prophylaxis in DLBCL in a large health system. *First Author: Michael A. Thompson, Aurora Advanced Healthcare, Milwaukee, WI*

Background: Diffuse large B-cell lymphoma (DLBCL) patients (pts) with risk factors based on the R-IPI (Sehn et al. 2007 http://ow.ly/k4Xu308hsBM) and CNS IPI (Schmitz et al. 2016http://ow.ly/dZIb301YyQ4) may relapse in the central nervous system (CNS). NCCN Guidelines (v2.2016) rec lumbar puncture (LP) if 4-6 risk factors present or HIV, testicular, breast, or double expresser and notes optimal management is uncertain. We wished to evaluate the use of CNS px in a large community health system. **Methods:** The Aurora Health Care cancer registry was searched for DLBCL from 1/1/16 to 12/31/16. Pts with CNS px were selected for more detailed analysis for stage, Myc, R-IPI, CNS IPI and cost of px. CNS px was categorized as: 1) intravenous (IV) high dose methotrexate (HD MTX), 2) IT chemo via Ommaya, or 3) IT via LP. Outcomes were CNS px utilization, survival, and costs. **Results:** 146 DLBCL pts were treated (5 R-CHOP, 2 DA-R-EPOCH). CNS px was given in 7/146 (4.8%). Pts were 5 males, 2 females. Median age was 58, (range: 38-76). Median R-IPI was 2.4 (range: 0-5). Median CNS IPI was 2.7 (range: 0-5). HD MTX was used in 3 pts. IT was used in 4 pts, with 0 by Ommaya and 4 by LP. Except for one death, there was no CNS or other recurrences yet. Costs per cycle were (drug + administration): 1) HD MTX: $587+ 3166 (hospitalization and leucovorin) = $3753, 2) IT Ommaya: $20 + 921 = $941 (not including Ommaya surgery), 3) IT LP: $20 + 2460 (includes interventional radiology) = $2480. **Conclusions:** CNS px rate was low across a range of stages and risk scores, which potentially reflects lack of recognition of risk as well as uncertainly about the value including utility (risk reduction) vs cost ($ and pt toxicity). Evaluating for improved utility is necessary, such as lenalidomide (a small molecule with CNS penetration) in R2CHOP (Ayed et al. 2016 http://ow.ly/6s5d308G4I4). If that 6 fold risk reduction holds, the value may be high for lenalidomide added to high risk CNS IPI DLBCL pts therapy.

Treatment	N	Stage	R-IPI	CNS IPI	MYC	Cost ($)/cycle
HD MTX	3	III or IV, IAE, IVAE	0, 2, 3	0, 3, 3	neg, neg, neg	3166
IT Ommaya	0	NA	NA	NA	NA	941
IT LP	4	IAE, IVAE, IIIAE, IVEB	1, 2, 4, 5	1, 2, 5, 5	pos, neg, pos, neg	2480
Lenalidomide 25mg d1-10 q21	0	NA	NA	NA	NA	4514

NA= not applicable

7563 Poster Session (Board #325), Mon, 8:00 AM-11:30 AM

Treatment patterns among elderly follicular lymphoma patients diagnosed between 2000 and 2011: An analysis of linked SEER-Medicare data. *First Author: Ebere Onukwugha, University of Maryland, Baltimore, MD*

Background: There are multiple treatment regimens approved for the management of follicular lymphoma (FL). However, there is limited information available to describe the course of therapy (COT) that patients receive following FL diagnosis. **Methods:** Using the linked Surveillance, Epidemiology, and End Results (SEER) registry & Medicare claims dataset, we analyzed patients 66 years and older diagnosed with FL from 2000 to 2011. In order to characterize FL treatments, we identified first, second and subsequent-lines of therapy listed in the National Comprehensive Cancer Network guidelines 2.2016. We identified the first COT (COT1) as the first regimen that a patient receives after diagnosis. We identified the second and third COT (COT2 and COT3) as new treatment received following/interrupting COT1 or COT2, respectively. Using visual analytics software, we investigated and reported the proportion of patients receiving each COT, the top three regimens within each COT, and the median time to starting a COT from diagnosis or end of a previous COT. **Results:** 10,836 FL patients were identified after applying the inclusion/exclusion criteria. Sixty-two percent (N=6,756) of the patients received FL-directed treatment. Among patients receiving COT1, 65% received COT2. Among patients receiving COT2, 79% received COT3. The table below provides additional information on the COT received. **Conclusions:** Analysis of real-world data indicates that almost 4 out of 10 elderly FL patients do not receive the listed FL-directed treatments. In contrast to rituximab, there was limited use of RCHOP and RCVP after COT1 during the study period. Additional research is needed to understand the differences across demographic groups and associated health outcomes.

Top 3 regimens	Proportion among each COT (%)	Median time to initiation from diagnosis or end of a previous regimen (days)
1st course	-	77
Rituximab	47%	95
RCHOP*	26%	57
RCVP**	19%	62
2nd course	-	77
Rituximab	50%	84
RCVP**	5%	36
RCHOP*	4%	45
3rd course	-	101
Rituximab	53%	103
RCHOP*	2%	59
RCVP**	2%	99

* RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone ** RCVP = rituximab, cyclophosphamide, vincristine, prednisone

7564 Poster Session (Board #326), Mon, 8:00 AM-11:30 AM

Phase 1 trial evaluating MRG-106, a synthetic inhibitor of microRNA-155, in patients with cutaneous t-cell lymphoma (CTCL). *First Author: Francine M. Foss, Yale Cancer Center, Woodbridge, CT*

Background: MRG-106 is an oligonucleotide inhibitor of miR-155, a microRNA with a strong mechanistic link to CTCL, selected based on its activity in mycosis fungoides (MF) cell lines. The objective of this first-in-human study is to evaluate the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK), and preliminary efficacy of MRG-106 in MF patients. **Methods:** This Phase 1 trial employs a dose-escalation design to evaluate either intratumoral (IT, 75 mg/dose) or subcutaneous (SC, $\leq$ 900 mg/dose) administration of MRG-106. Patients were required to have biopsy-proven stage I-III MF and plaque- or tumor-stage lesions. **Results:** Fifteen patients (12M/3F, median age 59 years) have been dosed over 1-4 weeks. All patients tolerated the IT or SC administrations well with only minor local injection reactions in 8 patients. Thirteen of 15 patients completed dosing as scheduled. There were no clinically significant MRG-106 related adverse events with the exception of one grade 3 pruritus. The MTD has not yet been reached. In the IT cohort, a reduction of $\geq$50% in the baseline Composite Assessment of Index Lesion Severity (CAILS) score was observed in the MRG-106 treated lesions in all 4 evaluable patients who completed dosing; such responses were maintained to the End of Study visit (Day 28 or 35). Histological examination of pre- and post-treatment biopsies of the MRG-106-injected lesion from most patients revealed a trend in reduction in neoplastic cell density and depth; 1 patient had a complete loss of the neoplastic infiltrate. Gene expression analysis of the pre- and post-treatment biopsies showed reduction of the PI3K/AKT, JAK/STAT, and NFkB survival pathways and increased cell death consistent with the expected MRG-106 mechanism of action. In the SC cohorts, 3/8 patients had a maximal decrease in their modified Severity-Weighted Assessment Tool (mSWAT) of $>$ 39% indicative of a significant response. One patient at the 900 mg SC dose level had a possible flare of their disease after 3 doses that resolved after 3 weeks. **Conclusions:** Based on favorable clinical safety, efficacy and PK data, additional patients are being accrued. Updated results will be presented as available. Clinical trial information: NCT02580552.

7565 Poster Session (Board #327), Mon, 8:00 AM-11:30 AM

Results of a phase II trial of efficacy and safety of entospletinib (ENTO) in patients with lymphoplasmacytoid lymphoma/Waldenstrom's macroglubulinemia (LPL/WM). *First Author: Sarit E. Assouline, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, QC, Canada*

Background: ENTO is an orally bioavailable, selective inhibitor of spleen tyrosine kinase (Syk, a mediator of B-cell receptor [BCR] signaling). Targeting the BCR-signaling pathway has been a focus in B-cell related hematological malignancies including LPL/WM. **Methods:** This reports the LPL cohort in a phase 2 trial that more broadly evaluated efficacy and safety of ENTO (800 mg BID) in patients with relapsed and refractory (R/R) B-cell malignancies. Tumor response was assessed at weeks 8, 16, 24, and then every 12 weeks. The primary endpoint was PFS at week 24. **Results:** 17 LPL patients (median age 72 years [range: 47–89], 65% male, and median of 3 prior regimens [range: 1–8]) were enrolled. Prior therapies included anti-CD20 antibodies (100%), alkylating agents (71%; bendamustine 24%), purine analogues (24%), and vinca alkaloid (41%). No patient had prior ibrutinib. Median treatment duration was 16 weeks (range: 1-84), with 3 patients continuing on treatment. The most common treatment-emergent AEs (any grade/$\geq$grade 3, independent of causality) were fatigue (53%, 6%), constipation (47%, 0%), nausea (47%, 6%), diarrhea (29%, 6%), insomnia (29%, 0%) and lab abnormalities including neutropenia (53%, 12%), increased creatinine (53%, 0%), increased ALT (41%, 6%) and decreased WBC (41%, 6%). One death due to progressive disease (PD) was reported within 30 days from last dose. 12 (71%) patients were evaluable for tumor response. 5 patients (29%) discontinued prior to initial tumor assessment: PD (n = 2), withdrawal consent (n = 2) and AE (n = 1). ORR was 24% (90% CI: 9%, 46%), with 1 (6%) patient achieving PR, 3 with minor response (18%) and 7 (41%) maintaining stable disease. Reductions of IgM from baseline were greatest in the patient with PR. PFS rate at week 24 was 82% (95% CI: 44%, 95%). Median time to treatment failure and median time to response were 3.7m and 1.9 m respectively. Median duration of response has not been reached. **Conclusions:** ENTO was well tolerated and demonstrated limited activity in patients with R/R LPL. Further development of ENTO in LPL will focus on its role in combination therapies. Clinical trial information: NCT01799889.

TPS7566 Poster Session (Board #328a), Mon, 8:00 AM-11:30 AM

Ironclad: A randomized phase III study of ibrutinib (Ibr) or no consolidation following autologous hematopoietic stem cell transplantation (AutoHCT) for relapsed/refractory activated-B-cell (ABC) subtype diffuse large B-cell lymphoma (DLBCL). *First Author: Charalambos Andreadis, University of California, San Francisco, San Francisco, CA*

Background: Relapsed DLBCL in the rituximab era portends a poor prognosis with only about 25% of patients achieving long-term disease control following 2ndline therapy and AutoHCT. Patients with the ABC subtype have an inferior prognosis at diagnosis than those with GC and are overrepresented at relapse. In order to improve outcomes in ABC-DLBCL, we designed a study targeting disease pathobiology at the time of AutoHCT. Ibr has a safety profile allowing combination with cytotoxic chemotherapy and has single-agent activity with a 37% response rate in patients with relapsed/refractory ABC-DLBCL. **Methods:** This is an intergroup, randomized, placebo-controlled phase III study combining Ibr or placebo with high-dose chemotherapy during conditioning with AutoHCT and for 12 months following AutoHCT. Pts with relapsed or refractory DLBCL have tissue submitted centrally for real-time review and subtype assignment by GEP (Frederick Laboratory). Key eligibility criteria include no more than 3 prior regimens, no active CNS involvement, no need for long-term anticoagulation, and no progression on prior Ibr. Pts with chemosensitive ABC-DLBCL are randomized to Ibr 560 mg or placebo with BEAM or CBV chemotherapy until day 0. After engraftment, pts receive Ibr 560 mg daily or placebo for 12 additional cycles. Pts with progressive disease on placebo can cross over to Ibr monotherapy. An initial safety cohort of 6 pts is being enrolled to evaluate the tolerability of Ibr with concurrent BEAM and CBV therapy. The primary endpoint is superior 2-year PFS (Ha/H0: 67% vs 50%). Secondary endpoints include time to count recovery, post-transplant response rates, OS, PFS, and incidence of 2^{ary}malignancies. In correlative studies, we will assess the prognostic and predictive role of pre-transplant FDG-PET in the setting of Ibr or placebo therapy, the role of emergent BCR pathway mutations, double hit genetics, and pharmacogenetic determinants on treatment outcome and toxicities. We expect to accrue 296 patients over 4 years. An Alliance/BMT-CTN study: NCT02443077 Clinical trial information: NCT02443077.

TPS7567 Poster Session (Board #328b), Mon, 8:00 AM-11:30 AM

COSMOS: MOR208 plus idelalisib or venetoclax in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) previously treated with a Bruton's tyrosine kinase inhibitor (BTKi)—A two-cohort phase II study. *First Author: Clemens-Martin Wendtner, Klinikum Schwabing, Department I of Medicine, Academic Teaching Hospital of University of Munich, Munich, Germany*

Background: Patients (pts) with R/R CLL who discontinue treatment with the BTKi ibrutinib due to progression have a particularly dismal prognosis. A phase I study showed that the Fc-enhanced, humanized, CD19 antibody MOR208 was well tolerated with encouraging single-agent activity in pts with R/R CLL/SLL. In preclinical models, MOR208 showed synergy with idelalisib (an inhibitor of PI3K delta) and venetoclax (an inhibitor of BCL-2), both approved for the treatment of CLL. **Methods:** This two-cohort, phase II study will investigate MOR208 combined with idelalisib (cohort A) or venetoclax (cohort B) in pts with R/R CLL or R/R SLL and includes a safety run-in phase for each cohort, to be evaluated by an Independent Data Monitoring Committee. Key inclusion criteria: aged $\geq$18 years, R/R CLL/SLL while receiving a BTKi therapy or intolerance of such therapy, BTKi administered as a single-agent or in combination for at least 1 month as the most recent prior anticancer therapy, ECOG performance status of 0–2, and adequate organ function. Key exclusion criteria: transformed CLL/SLL or Richter's syndrome, BTKi treatment within 5 days prior to study drug dosing, prior treatment with a CD19-targeted therapy, a PI3K inhibitor (cohort A) or a BCL-2 inhibitor (cohort B). Pts will be treated for a maximum of 24 (28-day) cycles or until disease progression. Treatment will be MOR208 12 mg/kg IV (weekly for the first 3 months, every second week for the next 3 months, and monthly thereafter) in combination with oral idelalisib 150 mg twice-daily or venetoclax administered on a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg. Primary endpoint: overall response rate based on independent review; secondary and exploratory endpoints include: progression-free and overall survival, duration of response, safety, pharmacokinetics, MOR208 immunogenicity, quality of life and minimal residual disease negativity. 120 pts per cohort are planned. Clinical trial information: 2015-002915-14.

TPS7568 Poster Session (Board #329a), Mon, 8:00 AM-11:30 AM

A phase I trial of CD19-targeted EGFRt/19-28z/4-1BBL armored chimeric antigen receptor (CAR) modified T cells in patients with relapsed or refractory chronic lymphocytic leukemia. *First Author: Jae Hong Park, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Despite the recent progress in the therapy of CLL with BTK, PI3Kδ, and BCL2 inhibitors, CLL remains incurable and patients with high-risk disease features (i.e. del17p, complex karyotype) and patients whose disease progress after treatment with the above targeted agents continue to have extremely poor prognosis. CD19-specific chimeric antigen receptor (CAR) T cell therapy with various 2nd generation CARs (19-28z or 19-41BBz) have demonstrated anti-tumor efficacy in CLL but the complete response (CR) rates in CLL have been suboptimal (20-45%) compared to CR rates in ALL (80-90%). The suboptimal activity of the current 2nd generation CAR T cells can be due to the inhibitory tumor microenvironment (TM) of CLL. We believe one approach to over the hostile TM is through the use of CD19-CAR T cells further modified to express a second costimulatory ligand, 4-1BBL. A binding of 4-1BBL to its cognate receptor enhances T cell proliferation, IL-2 secretion, and survival and cytolytic activity of the T cells compared to 19-28z. 19-41BBz and 1928BBz (Zhao Z et al. Cancer Cell 2015;28: 415-428). **Methods:** This phase I dose escalating trial is a single-center clinical trial (MSKCC) to study the safety and efficacy of autologous EGFRt/19-28z/4-1BBL$^+$ CAR T cells in patients with relapsed CLL. Given the concern for potential systemic toxicity the vector includes a "safety switch" in the form of a gene for the expression of truncated form of human epidermal growth factor receptor (EGFRt). Patients with relapsed CLL are eligible for the trial. Patients will receive conditioning chemotherapy of cyclophosphamide followed by escalating doses of CAR T cells ($1x10^5$ – $3x10^6$ CAR T cells/kg). The primary endpoint is safety and maximum tolerated doses of the CAR T ells. Secondary objectives include response assessment by iwCLL criteria. The comprehensive treatment algorithms for CRS and neurotoxicity are based on our CAR T cell experience in other studies. The study will begin enrollment in February 2017 and enroll up to 30 patients. Clinical trial information: Pending.

TPS7569 Poster Session (Board #329b), Mon, 8:00 AM-11:30 AM

KI intolerance study: A phase 2 study to assess the safety and efficacy of TGR-1202 in pts with chronic lymphocytic leukemia (CLL) who are intolerant to prior BTK or PI3K-delta inhibitor therapy. *First Author: Colleen Dorsey, Abramson Cancer Center, Philadelphia, PA*

Background: Although kinase inhibitor (KI) therapies, such as ibrutinib, are generally well tolerated, intolerance is the most common reason for discontinuation (d/c) in practice (~50%, Mato et al, Blood 2016). Additionally KI interruptions (≥ 8 days) can shorten OS (Barr et al, ASCO 2015). Fortunately, data suggest that KIs have non-overlapping toxicity profiles. Therefore, pts who d/c KI due to intolerance, with ongoing CLL response, represent an unmet need. TGR-1202 is a next generation, highly-specific PI3K-delta inhibitor with nanomolar inhibitory potency. TGR-1202 is well-tolerated with a d/c rate due to AEs of 8% as demonstrated in an integrated safety analysis of 165 treated pts (Burris et al, ASCO 2016). **Methods:** A phase 2 investigator initiated study is being conducted to assess the safety and activity of TGR-1202 in CLL pts who are KI intolerant. KI Intolerance is defined as ≥ 1 Gr 3 or ≥ 2 Gr 2 non-heme toxicities, ≥ 1 Gr 3 neutropenia with infection or fever, and/or ≥ 1 Gr 4 heme toxicity leading to KI (BTK and/or PI3K inhibitor) d/c (Table). Toxicities must resolve to ≤ Gr 1 prior to TGR-1202 dosing. Prior KI must be d/c for ≥ 14 days without progression (PD). All eligible pts are treated with TGR-1202 (800mg oral daily) until PD, toxicity or study conclusion. Primary study endpoint is PFS. Secondary endpoints include ORR, duration of response, time to treatment failure and TGR-1202 safety profile. Peripheral blood samples are collected prior to TGR-1202, after 28 days and at PD for correlative analyses to identify markers associated with KI intolerance. The trial commenced 10/1/2016. 55 eligible pts will be enrolled in approximately 12 months with 24 months follow-up. As of 1/2017, 10 study sites are enrolling pts with 10 more to be activated. To date, 10 pts have been enrolled and treated with TGR-1202. Clinical trial information: NCT02742090.

Intolerance stratified by KI class.

BTK toxicities	PI3K toxicities
A-fib	Pneumonitis
HTN	Transaminitis
Bleeding	Rash
Arthralgia	Colitis
Rash	Infection
Diarrhea	
Infection	
Pneumonitis	

Any additional grade ≥ 2 non-heme toxicity not listed will be evaluated by the study chair

TPS7570 Poster Session (Board #330a), Mon, 8:00 AM-11:30 AM

A phase Ia/Ib study of a novel BTK inhibitor, DTRMWXHS-12 (DTRM-12), and combination products, with everolimus and pomalidomide, in pts with CLL or other B-cell lymphomas. *First Author: Jennifer Gill, Abramson Cancer Center, Philadelphia, PA*

Background: Synthetic lethality (SL) relies on the chemical inhibition of two aberrant genes to selectively kill malignant cells. SL is now a clinical reality in an era of multiple targeted agents and advanced genetic testing. We investigated small molecule combinations for SL through in vitro and in vivo screening and optimization studies (Table, US patent 20160324878) and demonstrated the potential of SL through best-in-class combinations of targeted agents, immune modulation and low-dose combinations. We hypothesize that BTK and mTOR inhibition combined with an IMiD target multiple key signaling pathways, improve selective cell kill and address acquired drug-resistance. DTRM-555 is an optimized mechanism-based combination of the novel BTK inhibitor DTRM-12, with everolimus (E) and pomalidomide (P). In xenograft tumor models, DTRM-555 has shown superior efficacy over single agents at lower combined doses (1/18 of DTRM-12, 1/6 of E, and 1/6 of P). **Methods:** We are conducting a phase I, first-in-human multicenter trial exploring DTRM-555 in pts with CLL and B-cell NHL. Phase Ia consists of escalating DTRM-12 monotherapy doses. Phase Ib will explore doublet combination of DTRM-12 plus everolimus, and DTRM-555, the novel triplet combination. Safety is the primary study endpoint. Secondary endpoints include anti-tumor activity and pharmacokinetic studies. Eligible pts are > / = 18 years / ECOG < / = 1 with CLL or B-cell NHL with no available therapies. Treatment is administered for 21 consecutive days of a 28-day cycle, until disease progression or unacceptable toxicity. The trial commenced on 9/27/16. Phase 1a (single subject, 50/100mg respectively) has enrolled 5 pts without DLT and is currently at the 200 mg dose level. Up to 50 pts will be enrolled. Five additional sites are planned to open in the near future across the US. Clinical trial information: NCT02900716.

Viability inhibition of human lymphoma cells by the compounds (%).

TMD-8 cells

	DTRMWXHS-12 concentration		
Treatment	1 μM	0.1 μM	0.01 μM
	61.66	59.59	46.07
Doublet Combination E at 0.1 μM	65.94	67.20	66.17
Double Combination P at 0.1 μM	53.25	49.26	30.27
DTRM-555	76.42	80.77	83.22
Triplet Combination E at 0.1 μM plus P at 0.1 μM			

TPS7571 Poster Session (Board #330b), Mon, 8:00 AM-11:30 AM

B-MIND: MOR208 plus bendamustine (BEN) versus rituximab (RTX) plus BEN in patients with relapsed or refractory (R-R) diffuse large B-cell lymphoma (DLBCL): An open-label, randomized phase II/III trial. *First Author: Grzegorz S. Nowakowski, Mayo Clinic, Rochester, MN*

Background: Patients ineligible for stem cell transplantation (SCT) or who relapse after SCT, and those who fail to respond to second-line or salvage chemotherapy, represent an unmet medical need for which new therapeutic strategies are required. MOR208 is a novel Fc-enhanced, humanized, monoclonal antibody directed against CD19. Significant single-agent activity of MOR208 in patients with R-R DLBCL (Jurczak et al., J Clin Oncol 34, 2016 [suppl; abstr 7545]) and enhancement of MOR208-mediated cytotoxicity by BEN in preclinical studies, provide a strong rationale to study MOR208 + BEN in patients with R-R DLBCL. **Methods:** B-MIND is a randomized (1:1), two-arm, multicenter, open-label, adaptive design, phase II/III study of MOR208 + BEN vs RTX + BEN in adult patients with histologically confirmed DLBCL who have relapsed after or are refractory to 1 to 3 prior lines of therapy and who are not candidates for high-dose chemotherapy and autologous SCT. At least 1 prior therapy line must have included a CD20-targeted therapy. Other key inclusion criteria: age ≥18 years; measurable disease; availability of tumor tissue for central pathology review; ECOG 0–2, and adequate major organ systems function. Key exclusion criteria: primary refractory DLBCL; central nervous system involvement, and known double/triple hit DLBCL genetics. The safety of the combination will be assessed in an initial phase II evaluation. Treatment will comprise 6 cycles of MOR208 (12 mg/kg IV) + BEN (90 mg/m^2 IV) or RTX 375 mg/m^2 IV + BEN. Patients achieving a response after cycle 6 will continue to receive antibody treatment for up to 18 additional cycles. Primary endpoint: progression-free survival (PFS); secondary endpoints include: best overall response, overall survival, safety, quality of life, immunogenicity and pharmacokinetics. Enrollment of 330 patients is anticipated in Europe, US and Asia-Pacific countries. Fourteen patients have been randomized to date. Clinical trial information: NCT02763319.

TPS7572 Poster Session (Board #331a), Mon, 8:00 AM-11:30 AM

Zuma-6: Phase 1-2 multicenter study evaluating safety and efficacy of axicabtagene ciloleucel (axi-cel; KTE-C19) in combination with atezolizumab in patients with refractory diffuse large b-cell lymphoma (DLBCL). *First Author: Frederick Lundry Locke, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: Approximately 1/3 of patients with DLBCL, the most common type of B-cell lymphoma, will become refractory to standard combination chemotherapy and have uniformly poor clinical outcomes (Crump, ASCO 2016). Axi-cel (autologous anti-CD19 chimeric antigen receptor [CAR] T cell therapy) has shown promising response rates in patients with refractory DLBCL compared with standard approaches, although some patients do not respond or progress after an initial response (Locke, *Mol Ther* 2016). Expression of PD-L1 on DLBCL cells and activation-dependent expression of PD-1 on CAR T cells after infusion led to the hypothesis that PD-1 pathway blockade may augment the activity of axi-cel and result in improved clinical outcomes. This study will evaluate safety and efficacy of axi-cel when given with atezolizumab (anti–PD-L1 antibody), delivered sequentially, in patients with refractory DLBCL. **Methods:** Phase 1 will enroll ~3-9 patients to estimate the incidence of dose-limiting toxicities. Phase 2 will enroll ~22 patients to evaluate safety and efficacy, with a primary endpoint of complete response (CR) rate (Cheson 2007). Secondary endpoints include key efficacy outcomes such as objective response rate (CR+partial response [PR]), duration of response, progression-free and overall survival, and safety and biomarker outcomes. Eligible adult patients will have received prior adequate therapy (including anti-CD20 monoclonal antibody and an anthracycline-based regimen) and have an ECOG PS of 0-1 and adequate bone marrow and organ function. Patients with a history of Richter transformation, transformed follicular lymphoma, CNS disease, or active infection are not eligible. Patients will receive fludarabine 30 mg/m^2/d and cyclophosphamide 500 mg/m^2/d $\times$ 3 d, followed by a single infusion of axi-cel (target dose, 2 $\times$ 10^{6}anti-CD19 CAR T cells/kg) followed by atezolizumab 1200 mg given every 21 d for 4 doses (phase 1, first dose to occur 21, 14, and 1 d after axi-cel infusion in cohorts 1, 2, and 3, respectively). The study opened to accrual in September 2016. Clinical trial information: NCT02926833.

TPS7573 Poster Session (Board #331b), Mon, 8:00 AM-11:30 AM

Phase II study of durvalumab (anti-PD-L1 antibody) in combination with R-CHOP or lenalidomide plus R-CHOP in previously untreated, high-risk diffuse large B-cell lymphoma. *First Author: Grzegorz S. Nowakowski, Mayo Clinic, Rochester, MN*

Background: The PD-1/PD-L1 pathway is an important immune checkpoint used by tumor cells and may provide an effective target for enhancing anticancer immune response. In DLBCL, high PD-L1 expression has been identified as a negative prognostic factor for overall survival. Durvalumab (MEDI4736) is a high-affinity human IgG1 monoclonal Ab that selectively blocks PD-L1 binding to PD-1 and CD80, and preliminary preclinical and clinical activity support the study of durvalumab in high-risk DLBCL subtypes. The primary study objective is to explore the clinical activity of durvalumab with R-CHOP in non-activated B-cell–like (non-ABC) and durvalumab with lenalidomide + R-CHOP (R^2-CHOP) in ABC previously untreated DLBCL; secondary objectives are to evaluate safety and identify biomarkers predictive of clinical response. **Methods:** This is a phase II, two-arm, open-label, global, multicenter study of durvalumab combinations in patients with previously untreated, high-risk DLBCL (MEDI4736-DLBCL-001; EUDRA CT 2015-005173-20; NCT03003520). High risk was defined as Ann Arbor stage III/IV or II with bulky disease ($\geq$7.0 cm), along with intermediate-high/high IPI $\geq$3 or NCCN-IPI $\geq$4; patients must also have CD20+ DLBCL, ECOG PS 0-2, and no prior antilymphoma therapy. All patients receive durvalumab + R-CHOP21 in induction cycle 1 simultaneous to cell-of-origin (COO) analysis by gene expression profiling with NanoString technology. Beginning with cycle 2, Arm A (non-ABC) receives durvalumab 1125 mg IV on day 1 with 6 or 8 cycles of R-CHOP21; Arm B (ABC) receives the same durvalumab + R-CHOP21 doses with oral lenalidomide 15 mg/day on days 1-14. Both arms receive durvalumab consolidation 1500 mg IV on day 1 q28d for $\leq$12 months from induction cycle 1, day 1. The primary endpoint is 2-y progression-free survival (PFS); secondary endpoints include clinical response to treatment in biomarker-defined subpopulations (tumor and peripheral blood) and safety as assessed per NCI CTCAE v4.03 criteria. Exploratory endpoints include PFS at 12 mo, complete response, and PK/PD. Recruitment is ongoing, with a target enrollment of 120 patients. Clinical trial information: NCT03003520.

TPS7574 Poster Session (Board #332a), Mon, 8:00 AM-11:30 AM

Phase I/II study of durvalumab (anti–PD-L1 antibody) as monotherapy and in combination in patients with lymphoma or chronic lymphocytic leukemia. *First Author: Thomas E. Witzig, Mayo Clinic, Rochester, MN*

Background: The PD-1/PD-L1 pathway is an important immune checkpoint used by tumor cells to evade immune cell detection and inhibit antitumor responses. PD-1/PD-L1 expression in multiple hematologic malignancies may provide an effective target for enhancing anticancer immune response. Durvalumab (MEDI4736) is a high-affinity human IgG1 monoclonal Ab that selectively blocks PD-L1 binding to PD-1 and CD80, and has shown preliminary evidence of antitumor activity across multiple tumor types. Study objectives are to evaluate durvalumab monotherapy and combinations to determine dose and safety, as well as identify histologies and combinations that show the best complementary antitumor signals for future study. **Methods:** This is a phase I/II open-label, global, multicenter study of durvalumab as a monotherapy and in combination in relapsed/refractory B-cell lymphoma or CLL (MEDI4736-NHL-001; EUDRA CT 2015-003516-21; NCT02733042). Patients must have histologically-confirmed FL, MCL, splenic or nodal MZL, T-cell/histiocyte rich BCL, PMBCL, ALK+ large BCL, transformed large BCL, Richter's transformation, DLBCL (NOS), CLL/SLL, or classical HL during the dose-finding part. Inclusion criteria are ECOG PS 0-2, and $\geq$1 prior antilymphoma therapy. Up to 253 patients may enroll in 4 treatment arms, which include fixed-dose durvalumab 1500 mg Q4W monotherapy or combinations with lenalidomide/rituximab, ibrutinib, or bendamustine/rituximab. The study has 3 parts: dose finding, dose confirmation, and dose expansion. The monotherapy arm does not have a dose finding or expansion part; upon progression, patients may receive combination therapy or involved-field radiation to a single nodal site (evaluating for systemic abscopal antitumor effect). Primary endpoints are safety, identification of recommended phase II dose (phase I, 3+3 design), and overall response rate (ORR; phase II); secondary endpoints include DOR, PFS, and PK/PD. ORR is measured by 2014 IWG criteria for lymphoma or modified 2008 iwCLL criteria for CLL; safety is assessed per NCI CTCAE v4.03 criteria. Recruitment is ongoing, with a target enrollment of 253 patients across 60-80 centers globally. Clinical trial information: NCT02733042.

TPS7575 Poster Session (Board #332b), Mon, 8:00 AM-11:30 AM

Phase 1b/3 study of avelumab-based combination regimens in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL). *First Author: Robert W. Chen, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Approximately 50% of patients (pts) with advanced DLBCL are refractory to or relapse following first line R-CHOP therapy. Pts with R/R DLBCL have limited treatment options and a poor prognosis. This study assesses immunotherapy-based regimens containing avelumab (a fully human IgG1 anti–PD-L1 antibody) in combination with utomilumab (a novel 4-1BB agonist), azacitidine, rituximab, and/or conventional chemotherapy (CT; bendamustine) in pts with R/R DLBCL. **Methods:** JAVELIN DLBCL (NCT02951156) is a global, multicenter, randomized, open-label, 2-component(phase 1b followed by phase 3) study of avelumab-based combination regimens in R/R DLBCL. In phase 1b, up to 84 pts will be randomized 1:1:1 to receive avelumab/rituximab/utomilumab, or avelumab/azacitidine/utomilumab, or avelumab/rituximab/bendamustine. The primary phase 1b objectives are preliminary assessments of dose-limiting toxicities (n = 6 per arm) and efficacy (objective response [OR]; n = 28 per arm). One regimen from phase 1b will be selected for phase 3 evaluation in 220 additional pts randomized 1:1 to the chosen regimen or investigator's choice CT (rituximab/bendamustine or rituximab/gemcitabine/oxaliplatin). The primary phase 3 objective is to demonstrate progression-free survival (PFS) superiority of the avelumab-based regimen over CT. Overall survival is a key secondary endpoint. Eligible pts have completed up to 4 lines of prior rituximab/multiagent CT, and/or have failed autologous stem cell transplantation (ASCT), or are not eligible for intensive CT or ASCT. Other eligibility criteria include ECOG PS $\leq$1 and no prior therapy with a checkpoint inhibitor. Treatment with avelumab, utomilumab, and azacitidine will be continued until the pt no longer receives clinical benefit; rituximab and bendamustine are limited to 8 and 6 cycles, respectively. OR and PFS will be assessed per Lugano disease classification criteria. Other secondary efficacy endpoints include disease control, duration of response, time to response, and minimal residual disease burden. Safety, PK, immunogenicity, pt-reported outcomes, and biomarkers will also be evaluated. Clinical trial information: NCT02951156.

TPS7576 Poster Session (Board #333a), Mon, 8:00 AM-11:30 AM

A multicenter, randomized, double-blind, placebo-controlled phase III study of the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, in combination with rituximab versus placebo in combination with rituximab in patients with treatment-naive follicular lymphoma (PERSPECTIVE). *First Author: Nathan Hale Fowler, Stanford University, Stanford, CA*

Background: Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma. A limited number of chemotherapy-free options exist for patients with treatment-naïve (TN) FL who are older or who have comorbidities. Single-agent rituximab is considered a treatment option for elderly or infirm patients. In a phase 2 study, frontline treatment with ibrutinib in combination with rituximab for 4 weekly doses without maintenance resulted in an ORR of 85% (CR, 35%) with a median follow-up of 22 months and an 18-month PFS rate of 87% (Fowler Blood 2016). The phase 2 study serves as the basis for the randomized, double-blind, placebo-controlled phase 3 PERSPECTIVE (PCYC-1141-CA) trial. PERSPECTIVE will be conducted in two parts and will uniquely test (1) whether frontline treatment with ibrutinib in combination with rituximab results in prolongation of PFS compared to rituximab alone, and (2) whether continuous versus finite treatment with ibrutinib affects PFS outcomes. **Methods:** In the ongoing PERSPECTIVE trial, approximately 440 patients with TN FL meeting at least one Groupe d'Etude des Lymphomes Folliculaires (GELF) criterion will be randomized if they also meet one of the following criteria: age ≥70 years or age 60 to 69 with one or more comorbidities (creatinine clearance 30-59 mL/min or ECOG performance status of 2). Patients will be randomized to receive either ibrutinib or oral placebo once daily. All patients will be given rituximab for 4 weekly doses followed by maintenance. After at least 2 years of treatment in Part 1, patients randomized to ibrutinib who still remain on ibrutinib will be re-randomized in Part 2 to continue ibrutinib or switch to placebo. Key exclusion criteria include any prior treatment for FL, evidence of CNS involvement, or transformation. Analyses will be conducted in two distinct parts, both with a primary endpoint of PFS. The study is open for enrollment with sites planned in the US, EU, and Asia Pacific. Clinical trial information: NCT02947347.

TPS7577 Poster Session (Board #333b), Mon, 8:00 AM-11:30 AM

CheckMate 436: A phase 1-2 study to evaluate safety and efficacy of nivolumab plus brentuximab vedotin in patients with CD30-expressing relapsed/refractory non-Hodgkin lymphomas. *First Author: Paul M. Barr, University of Rochester Medical Center, Rochester, NY*

Background: Nivolumab (nivo) is a PD-1 immune checkpoint inhibitor that augments T-cell activation and host anti-tumor responses. PD-1 blockade has shown promise in B- and T-cell non-Hodgkin lymphoma (NHL),[1] but many patients (pts) with NHL do not respond or progress after response. Combination therapy using anti-tumor agents with complementary mechanisms of action and low immunosuppressive impact may result in more frequent and durable responses. Brentuximab vedotin (BV) is an anti-CD30 antibodydrug conjugate that induces cell cycle arrest and apoptosis, with activity in a range of NHL tumors.[2,3] Tumor cells undergoing BV-induced apoptosis have shown subsequent immune-mediated anti-tumor cytotoxicity.[4] Therefore, nivo and BV may synergize if combined for relapsed/refractory (RR) NHL. **Methods:** CheckMate 436 (NCT02581631) is a phase 12, open-label, international, single-arm study evaluating nivo + BV for CD30-expressing RR NHL (study start: Dec 2015) in pts with RR diffuse large B-cell lymphoma, peripheral T-cell lymphoma (excluding anaplastic large cell lymphoma), and cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome); cohorts with primary mediastinal B-cell lymphoma (PMBL) and mediastinal gray zone lymphoma were made eligible in Sept 2016. Pts with PMBL must be aged ≥15 y (≥18 y for other histologies). All pts must have CD30-expressing disease, defined by CD30 on ≥1% of tumor cells or tumor-infiltrating lymphocytes by immunohistochemistry. In the phase 1 component, 6 pts will receive nivo and BV until disease progression or unacceptable toxicity. In the phase 2 component, ~130 more pts across the 5 histologies will be enrolled and treated at the recommended dose. Primary endpoints: safety, tolerability, and investigator-assessed objective response rate; secondary endpoints: duration of response and complete response (CR), CR rate, and progression-free and overall survival. Accrual is ongoing. References: 1. Lesokhin A et al. *JCO* 2016;34:2698704 2. Jacobsen E et al. *Blood* 2015;125:1394402 3. Horwitz S et al. *Blood* 2014;123:3095100 4. Gardai S et al. *Cancer Res* 2015;75(15 Suppl):2469 [abstract]. Clinical trial information: NCT02581631.

TPS7578 Poster Session (Board #334a), Mon, 8:00 AM-11:30 AM

Phase 1 study of the safety and efficacy of INCB050465 combined with obinutuzumab and bendamustine for relapsed or refractory (R/R) follicular lymphoma (FL) (CITADEL-102). *First Author: Morton Coleman, New York-Presbyterian Hospital, Weill Cornell Medicine, New York, NY*

Background: Aberrant PI3Kδ activation is implicated in B-cell non-Hodgkin lymphomas (NHL) including FL, the most common indolent subtype. INCB050465, a selective PI3Kδ inhibitor, is being evaluated in an ongoing phase 1/2 study as monotherapy for r/r B-cell NHL, including FL (ASH 2016; Abstract 4195). Obinutuzumab plus bendamustine is approved for patients (pts) with rituximab-refractory FL. This phase 1 cohort expansion study will assess the safety, efficacy, and pharmacokinetics of INCB050465 combined with obinutuzumab and bendamustine in pts with r/r FL (NCT03039114). **Methods:** Eligible adults will have documented CD20+ FL r/r to 1–4 prior treatments (must include rituximab), ≥1 measurable lesion (> 1.5 cm in ≥1 dimension), ECOG PS ≤2, and adequate hematologic, hepatic and renal function. Exclusion criteria will include: transformation of FL to aggressive lymphoma or receipt of allogeneic stem cell transplant (SCT) ≤6 months (or having graft-versus-host-disease after allogeneic or autologous SCT ≤3 months) before study start; receipt of any PI3K inhibitor, obinutuzumab, or bendamustine ≤12 months, or rituximab ≤1 month prior to study. Part 1 (safety run-in) will use a 3+3 design. Pts will receive INCB050465 PO at a dose of 20 mg QD continuously for 2 cycles (1 cycle = 4 wks) followed by 20 mg QW. Up to 2 dose reductions will be allowed. Pts will receive obinutuzumab 1000 mg IV (cycle 1: days 1, 8, and 15; cycles 2–6: day 1) and bendamustine 90 mg/m^2 IV (cycles 1–6: days 1 and 2). In part 2 (expansion), the safety and efficacy of INCB050465 (maximum tolerated dose) plus obinutuzumab and bendamustine will be evaluated in 30 pts, including pts treated in part 1 at the dose level deemed safe and tolerated. In both parts 1 and 2, pts not progressing after 6 cycles will be maintained on INCB050465 at the dose deemed safe and tolerated, and will continue on obinutuzumab 1000 mg IV administered on Day 1 of every second cycle for an additional 24 cycles or until disease progression. Response will be assessed using Lugano criteria (FDG-PET; CT/MRI) every 12 wks until cycle 12 and every 16 wks thereafter. The trial is open for enrollment. Clinical trial information: NCT03039114.

TPS7579 Poster Session (Board #334b), Mon, 8:00 AM-11:30 AM

Phase 2 study of the safety and efficacy of INCB050465 in patients with relapsed or refractory (R/R) diffuse large b-cell lymphoma (DLBCL) (CITADEL-202). *First Author: Morton Coleman, New York-Presbyterian Hospital, Weill Cornell Medicine, New York, NY*

Background: Aberrant activation of PI3Kδ is implicated in B-cell malignancies. INCB050465, a highly selective PI3Kδ inhibitor, is demonstrating preliminary efficacy in an ongoing phase 1/2 dose-escalation and expansion study as monotherapy for r/r DLBCL as well as for other r/r B-cell malignancies (ASH 2016; Abstract 4195). This phase 2 study will further evaluate the efficacy and safety of single-agent INCB050465 in pts with r/r DLBCL. **Methods:** In this phase 2, multicenter, open-label study (NCT02998476), eligible adults will have r/r DLBCL diagnosis, defined as receiving 1–5 prior treatments and be ineligible for high-dose chemotherapy or autologous stem-cell transplant (SCT). Pts will also have ≥1 measurable lesion (nodal ≥2 cm or extranodal > 1 cm in longest dimension); Eastern Cooperative Oncology Group performance status ≤2; adequate hematologic, hepatic, and renal function; no mediastinal large B-cell lymphoma or CNS metastases; no allogeneic SCT ≤6 months, or graft-versus-host-disease after allogeneic SCT, or autologous SCT ≤3 months, before first dose; and no prior treatment with PI3K inhibitors. Pts will be enrolled into 2 groups according to prior treatment with a Bruton's tyrosine kinase (BTK) inhibitor (Group A [n = 100, no BTK inhibitor] or B [n≤20, received BTK inhibitor]). Both groups will receive INCB050465 20 mg orally QD for 8 wks; then 20 mg QW until disease progression, death, unacceptable toxicity, or consent withdrawal. The primary endpoint is the objective response rate in Group A (complete/partial response per independent review committee based on Lugano criteria). Secondary endpoints will include duration of response, progression-free survival, overall survival, and safety in Group A (these endpoints will be exploratory in Group B). Other exploratory assessments will include pharmacokinetics and association between genetic characteristics and treatment response in both groups. In a planned interim futility analysis of Group A, the study will be terminated if ≤13 of the first 40 treated pts respond (no futility analysis of Group B will be conducted). The study is currently recruiting (estimated completion date, March 2020). Clinical trial information: NCT02998476.

8000 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Daratumumab (DARA) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in patients (pts) with newly diagnosed multiple myeloma (MMY1001): An open-label, phase 1b study. *First Author: Andrzej J. Jakubowiak, University of Chicago Medical Center, Chicago, IL*

Background: DARA in combination with established standard of care regimens prolongs PFS, deepens responses, and demonstrates a favorable safety profile in relapsed or refractory multiple myeloma (MM). The tolerability and efficacy of DARA-KRd in newly diagnosed MM pts was examined. **Methods:** Newly diagnosed pts regardless of transplantation eligibility were enrolled. Pts received DARA 16 mg/kg QW for Cycles 1-2, Q2W for Cycles 3-6, and Q4W thereafter. All pts received the 1st dose of DARA split over 2 days. Carfilzomib (K) was administered on Days 1, 8 and 15 of each 28-day cycle (20 mg/m^2 on C1D1, 36 or 70 mg/m^2 subsequently based on tolerability of first dose) for ≤13 cycles or elective discontinuation for ASCT. Lenalidomide 25 mg was given on Days 1-21 and dexamethasone 20-40 mg per week. The primary endpoint was tolerability. **Results:** Twenty-two pts (median [range] age, 60 [34-74] y) were enrolled and received a median of 8 (1-10) treatment cycles. Nineteen pts escalated K dose to 70 mg/m^2 by C1D15. Median (range) duration of follow-up was 7.4 (4.0-9.3) months. Six (27%) pts discontinued treatment (1 AE [pulmonary embolism]; 1 PD; 4 other [ASCT]). Serious AEs occurred in 46% of pts, and 14% were possibly related to DARA; 18 (82%) experienced a grade 3/4 TEAE. The most common grade 3/4 TEAEs (>10%) were lymphopenia (50%) and neutropenia (23%); 1 (5%) cardiac grade 3 TEAE was observed (congestive heart failure) which resolved; pt quickly resumed study treatment with reduced K dose. No grade 5 TEAE was reported. All DARA-associated infusion reactions (27% of pts) were grade ≤2. Treatment with DARA-KRd yielded an ORR (≥partial response) of 100% (5% complete response, 86% ≥very good partial response) in 21 response-evaluable pts. The 6-month PFS rate was 100%. **Conclusions:** The addition of DARA to KRd was well tolerated; the overall safety profile was consistent with that previously reported for KRd, with no additional toxicity observed with the addition of DARA. Deep and durable responses were observed. These data support further investigation of DARA-KRd as a frontline treatment regimen. Updated data will be presented based on longer follow up. Clinical trial information: NCT01998971.

8001 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Lenalidomide, doxorubicin hydrochloride and dexamethasone versus bortezomib, lenalidomide, and dexamethasone prior to scheduled stem cell transplant in newly diagnosed myeloma. *First Author: Stefan Knop, Medizinische Klinik und Poliklinik II, Julius Maximilians Universität Würzburg, Würzburg, Germany*

Background: In younger, medically fit patients (pts) with newly diagnosed (ND) multiple myeloma (MM), autologous stem cell transplant (SCT) remains a standard of care. Prior to SCT, induction triplets with at least one of the newer compounds are recommended. Bortezomib (V), lenalidomide (R) and dexamethasone (D; VRD) ranks amongst the most effective treatments. VRD + SCT proved superior over VRD alone in a randomized, controlled trial (RCT). We found encouraging efficacy and low toxicity with RAD (RD and adriamycin) + SCT and decided to compare RAD versus VRD induction in an RCT. **Methods:** The DSMM XIV study was set up according to a double 2x2-factorial design to enroll NDMM pts up to 65 years (yrs). Post-induction (PI) CR rate was the efficacy endpoint for the initial study phase. We hypothesized CR rate with RAD would be non-inferior to an estimated 20% CR with VRD. The study was powered to confirm non-inferiority of RAD at a 10% margin with a one-sided α level of .05. Minimal residual disease (MRD) was analyzed by eight-color flow cytometry (EuroFlow standards) on marrow samples. **Results:** 476 pts were randomized between 05/2012 and 06/2016, 469 of whom (median age 55 (range, 32–65) yrs) received at least one dose of study drug. 18.3% of pts had ISS stage III MM and 17.2%, elevated LDH. 11.3% of pts had del17p; 11.1% had t(4;14); and 4% had t(14;16). 232 pts were randomized to 3 four-week RAD cycles and 237 to 3 three-week VRD cycles, respectively. 89.7% of RAD versus 93.2% of VRD pts completed all induction cycles. PI CR rate was 11.8% (90% CI, 7.9%-16.3%) with RAD versus 13.0% (90% CI, 8.9-18.0) with VRD, (P = .697). 72/317 pts (22.7%) with paired baseline/PI samples achieved negative MRD at a median sensitivity level of $6.73x10^{-6}$. 47 (20.3%) RAD versus 35 (14.8%) VRD pts experienced treatment-emergent SAEs (P = .144). Treatment-related induction mortality was 0% in either arm. **Conclusions:** To the best of our knowledge, this is the first RCT to compare two lenalidomide-based triplets prior to SCT. The endpoint was met with comparable PI CR rates for RAD and VRD, respectively. Tolerability was encouraging in both arms. Follow-up data is needed to analyze time-dependent endpoints. Clinical trial information: NCT01685814.

8002 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

An open-label, single arm, phase IIa study of bortezomib, lenalidomide, dexamethasone, and elotuzumab in newly diagnosed multiple myeloma. *First Author: Jacob Laubach, Dana-Farber Cancer Institute, Boston, MA*

Background: Elotuzumab (elo) is approved for use in combination with lenalidomide (len) and dexamethasone (dex) for relapsed and refractory multiple myeloma (MM). This phase 2a study evaluated the efficacy and safety of elo in combination with len, subcutaneous bortezomib (bortez), and dex. **Methods:** The primary objective of this study was to determine the response rate of newly diagnosed, transplant-eligible MM patients (pts) after four cycles of therapy with elo plus len, bortez, and dex. Pts were newly diagnosed with MM by the revised IMWG criteria. Elo was administered days 1, 8, and 15 of the first two 28 day cycles and days 1 and 11 in cycles 3 and 4. Following cycle 4, pts underwent stem cell mobilization and could then proceed with either autologous stem cell transplant (ASCT) or defer transplant and receive four more cycles of induction therapy with elo plus len, bortez, and dex. Following either ASCT or 8 cycles of induction chemotherapy, pts transitioned to risk-adapted maintenance with elo, len, and dex plus every other week bortez (pts with high-risk cytogenetics, ISS stage II or III) or elo, len, dex (all others). Responses were assessed by the modified Uniform Response Criteria and toxicities graded based on NCI-CTCAE V4. **Results:** 41 patients with a median age of 60 were enrolled and this analysis encompasses response data from 29 patients. The overall response rate (ORR) after four cycles was 100%, with 24% achieving a complete response (CR), 47% achieving a very good partial response (VGPR), and 29% a partial response (PR). The rate of VGPR or better was 71%. The median number of CD34+ stem cells collected was 10.3 x 10^6. The most frequent grade 3 or higher toxicities included thrombocytopenia (15%) and hypophosphatemia (12%). The rate of grade 3 or higher peripheral neuropathy was 2%. Two pts died while on study, one due to complications of septicemia and the other due to respiratory failure. **Conclusions:** The combination of elo plus len, bortez, and dex was effective in newly diagnosed, ASCT-eligible patients. The rate of high-grade toxicities was low, although there were two grade 5 events (septicemia and respiratory failure). Clinical trial information: NCT02375555.

8003 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Carfilzomib-lenalidomide-dexamethasone (KRd) vs carfilzomib-cyclophosphamide-dexamethasone (KCd) induction: Planned interim analysis of the randomized FORTE trial in newly diagnosed multiple myeloma (NDMM). *First Author: Francesca Maria Gay, Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy*

Background: Phase I/II studies showed the safety and efficacy of KRd and KCd in NDMM pts (Jakubowiak Blood 2012, Bringhen Blood 2014). **Methods:** NDMM pts ≤65 yrs were randomized (1:1:1; stratification ISS and age) to: 4 28-day KCd cycles (carfilzomib:20/36 mg/m^2 IV d 1,2,8,9,15,16; cyclophosphamide 300 mg/m^2 d 1,8,15; dexamethasone:20 mg d 1,2,8,9,15,16) followed by MEL200-ASCT and consolidation with 4 KCd cycles; or 4 28-day KRd cycles (carfilzomib and dexamethasone as above; lenalidomide:25 mg d 1-21) followed by MEL200-ASCT and 4 KRd cycles; or 12 KRd cycles. After the 4th induction cycle, all pts received Cyclophosphamide 2 g/m^2, followed by PBSC collection. We report results of the first planned safety interim analysis on induction and mobilization and preliminary efficacy data. We pooled the 2 KRd groups since treatment was the same until mobilization. Data cut-off was October 30, 2016. **Results:** 281 pts were evaluated (KCd, n=94; KRd, n=187). The most frequent grade 3-4 AEs plus SAEs in both arms were hematological (mainly neutropenia) and infections (mainly pneumonia/fever); increased AST/ALT/GGT (mainly reversible) and dermatological (rash) AEs were higher in KRd; cardiac AEs were 2% (atrial fibrillation[1%]/ischemic heart disease[1%]) in KRd vs 1% (atrial fibrillation) in KCd. In KCd, 1 pt died of infection (not treatment-related) vs 3 in the KRd (2 cardiac arrest [1 not treatment-related],1 infection not treatment-related). In the KCd vs KRd arms, 99% vs 95% (P=0.44) of pts mobilized stem cells (median number of PBSC collected:9 vs 6x10^6CD34/Kg with KCd vs KRd); 10% vs 24% (P=0.01) required Plerixafor. Rate of ≥VGPR was 61% with KCd vs 74% with KRd (P=0.05). **Conclusions:** Safety profile was acceptable; more pts required plerixafor in KRd. Rate of VGPR was higher with KRd. Updated data on more patients will be presented at the meeting. Clinicaltrials.gov NCT02203643.

Grade 3-4 AEs/SAEs	KCd	KRd
Hematological	13%	9%
Cardiac	1%	2%
Hypertension	0%	2%
Thromboembolism	0%	1%
Gastrointestinal	0%	3%
AST/ALT/GGT increase	1%*	7%*
Dermatological	0%*	7%*
Infections	6%	9%
Acute Kidney Injury	0%	2%

*p value <0.05

8004 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Carfilzomib weekly-melphalan-prednisone in untreated elderly multiple myeloma: IFM2012-03. *First Author: Xavier Leleu, CHU, Poitiers, France*

Background: Melphalan-prednisone-bortezomib (MPV) is a standard of care upfront for newly diagnosed elderly myeloma (eNDMM). Despite significant improvements on MPV's safety profile, toxicity issues remain. Carfilzomib (K) is a novel generation proteasome inhibitor with a different safety profile from Bortezomib. Carmysap phase I/II study (twice a week Carfilzomib+MP) demonstrated K at 36mg/m² safe and active in eNDMM. We thought to study the K weekly-MP combination in eNDMM. **Methods:** IFM2012-03 is a multicenter phase I/II study in eNDMM (65 and older) aimed to determine the maximum tolerated dose (MTD) of K weekly. 4 cohorts of 6 patients each were recruited at K 36, 45, 56 and 70 mg/m^2 on days 1, 8, 15, 22 IV of 35-days cycles, with oral Melphalan and Prednisone from days 1 to 4 at usual doses. Patients received a 9-cycles induction followed by a K monotherapy maintenance at 36 mg/m^2 IV every 2 weeks for 1 year. 3 dose-limiting toxicities (DLTs) defined MTD at the lower N-1 dose. **Results:** 24 patients were included at K 36, 45, 56 and 70 mg/m². One DLT occurred at 36 mg/m² (grade 4 lymphopenia), one at 45 mg/m² (tumor lysis syndrome with grade 4 renal insufficiency), two at 56 mg/m² (grade 3 cardiac insufficiency and grade 3 febrile neutropenia) and two at 70 mg/m² (grade 3 nausea/vomiting and grade 3 hepatic cytolysis). One patient died from cardiac dysfunction considered related to K at 56 mg/m². 3 patients stopped therapy and 3 others required dose reduction of K. Following DSMB's request a second 6-patients cohort was recruited at 70 mg/m², with increased attention around hyper-hydration and monitoring HTA. We observed no DLT and no grade 3/4 adverse event in this cohort. Median age was 75 years, 56% patients were R-ISS 2 or 3. For the whole cohort (N=30), the overall response rate was 87% including 67% very good partial responses and 44% complete responses. **Conclusions:** The MTD of weekly K in the KMP combination is 70 mg/m² upfront for eNDMM, but it seems reasonable to recommend 56mg/m² after 75 years-old for safety reasons. KMP offers high response rates and possibly greater CR rate. However, since the CLARION study (VMP vs KMP) will not allow KMP's approval in eNDMM in Europe, IFM decided to stop IFM2012-03 after phase I without performing phase II. Clinical trial information: NCT02302495.

8005 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Impact of denosumab (DMB) compared with zoledronic acid (ZA) on renal function in the treatment of myeloma bone disease. *First Author: Noopur S. Raje, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Osteolytic bone disease and renal dysfunction are complications of multiple myeloma. ZA, used for the prevention and treatment of bone complications, can be nephrotoxic. DMB inhibits RANKL and thereby osteoclast function, and is not renally cleared. This international, phase III, randomized, double blind study evaluates the efficacy and safety of DMB compared with ZA in newly diagnosed myeloma patients (pts). **Methods:** Eligible pts were randomized 1:1 to DMB 120mg SC Q4W or ZA 4mg (renally adjusted) IV Q4W along with anti-myeloma therapy. Pts with baseline CrCl<30mL/min were excluded due to ZA dosing restrictions. The primary endpoint was non-inferiority of DMB to ZA with respect to time to first on-study SRE. Overall survival (OS) was a secondary endpoint; progression-free survival (PFS) was an exploratory endpoint. Renal toxicity and safety were assessed. **Results:** 1718 pts were randomized, 859 to each arm. Baseline renal insufficiency (CrCl ≤ 60mL/min) was reported in 26.7% of pts. DMB was non-inferior to ZA ($P = 0.01$) in delaying time to first on-study SRE. Fewer AEs potentially related to renal toxicity were reported with DMB compared to ZA overall (10.0% vs 17.1%, $P < 0.001$) in those with baseline CrCl > 60mL/min (8.8% vs 14.2%) and particularly in those with baseline CrCl ≤ 60mL/min (12.9% vs 26.4%). 12.5% of pts on DMB experienced an increase in creatinine, compared to 20.8% of those on ZA. Median cumulative exposure (Q1, Q3) to DMB was 15.75 months (8.18, 25.79) compared to 14.78 months (7.46, 24.87) for ZA. PFS yielded a HR (95%CI) of 0.82 (0.68, 0.99); descriptive $P = 0.036$. OS HR (95%CI) between DMB and ZA was 0.9 ([0.70, 1.16]; $P = 0.41$), with fewer deaths in DMB (121 [14.1%]) than in ZA (129 [15.0%]). **Conclusions:** DMB achieved the primary endpoint of non-inferiority to ZA in delaying time to first on study SRE in pts with newly diagnosed MM. Pts on DMB had a significantly lower rate of renal AEs compared to ZA; more importantly this rate was 2-fold lower in pts with renal insufficiency (CrCl≤60mL/min). The bone specific benefits in combination with the renal function results and possible prolongation of PFS with DMB therapy is promising. Clinical trial information: NCT01345019.

8006 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Efficacy of daratumumab in combination with lenalidomide plus dexamethasone (DRd) or bortezomib plus dexamethasone (DVd) in relapsed or refractory multiple myeloma (RRMM) based on cytogenetic risk status. *First Author: Katja C. Weisel, Universitaetsklinikum Tuebingen der Eberhard-Karls-Universitaet, Abteilung fuer Innere Medizin II, Tuebingen, Germany*

Background: In 2 randomized phase 3 trials of RRMM patients (pts), DRd (POLLUX) or DVd (CASTOR) significantly improved PFS and deepened responses compared with Rd or Vd alone, respectively. The novel mechanism of action of daratumumab (D) may improve the poor prognosis associated with high-risk cytogenetic abnormalities in RRMM. Therefore, we examined the efficacy of DRd and DVd among RRMM pts with standard (std) or high cytogenetic risk status. **Methods:** Bone marrow aspirates were collected at screening and assessed centrally via next generation sequencing (NGS). Pts with high-risk cytogenetics included those who had ≥1 of the following abnormalities: t(4;14), t(14;16), or del17p; std-risk pts were defined as those confirmed negative for these abnormalities. Efficacy analyses included PFS and ORR. **Results:** Samples from 311/569 pts in POLLUX and 353/498 pts in CASTOR were assessed via NGS. In POLLUX, the median duration of follow-up was 17.3 months. Significantly longer median PFS and numerically higher ORR were observed with DRd vs Rd among high-risk patients, and significant improvements in these outcomes were observed in std-risk patients (Table). In CASTOR, the median duration of follow-up was 13.0 months. Significantly longer median PFS and higher ORR were observed with DVd vs Vd among both high- and std-risk pts (Table). Concordance rates for t(4;14), t(14;16), and del17p were high (88%-98%) between NGS and FISH. Updated data, including subgroup analyses, will be presented. **Conclusions:** In RRMM pts, the addition of D to standard-of-care regimens improved outcomes regardless of cytogenetic risk status. Targeting CD38 by combining D with Rd or Vd appears to improve the poor outcomes associated with high-risk cytogenetic status. See table. Clinical trial information: NCT02136134 and NCT02076009.

	POLLUX				CASTOR			
	High		Std		High		Std	
NGS	DRd (n=28)	Rd (n=37)	DRd (n=133)	Rd (n=113)	DVd (n=44)	Vd (n=51)	DVd (n=123)	Vd (n=135)
Median PFS, mo	NR	10.2	NR	17.1	11.2	7.2	NR	7.0
HR (95% CI)	0.44 (0.19-1.03)		0.30 (0.18-0.49)		0.49 (0.27-0.89)		0.29 (0.20-0.43)	
P	0.0475		<0.0001		0.0167		<0.0001	
ORR, %	85	67	95	82	82	62	85	64
P	0.14		0.0020		0.039		0.0003	
≥CR, %	33	6	52	24	30	9	25	8
≥VGPR, %	63	31	84	51	64	34	64	27

8007 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

A phase Ib study of isatuximab in combination with pomalidomide (Pom) and dexamethasone (Dex) in relapsed/refractory multiple myeloma (RRMM). *First Author: Joseph Mikhael, Mayo Clinic, Phoenix, AZ*

Background: Isatuximab (ISA) is an anti-CD38 monoclonal antibody, which kills tumor cells via multiple mechanisms. Here, we report preliminary data from the dose-escalation cohorts, and the first 3 patients (pts) of the expansion cohort, of a Phase Ib study of ISA plus Pom/Dex in pts with RRMM (NCT02283775). **Methods:** Pts with RRMM (≥2 prior MM therapies, including lenalidomide and a proteasome inhibitor) were sequentially enrolled to ISA 5, 10 or 20 mg/kg (4 weekly doses, then every 2 wks until disease progression or intolerable toxicity) with Pom 4 mg (Days 1–21) and Dex 40 mg (Days 1, 8, 15, and 22; 20 mg if ≥75 yrs old), in 28-day cycles. An expansion cohort was initiated at ISA 10 mg/kg (plus Pom/Dex) based on preliminary safety, efficacy and PK data. Primary objective: determine maximum tolerated dose (MTD). **Results:** 26 pts were analyzed (5 mg/kg [n = 8]; 10 mg/kg [n = 12]; 20 mg/kg [n = 6]), median age 65 (42–80) yrs. Median 4.0 (2–11) prior treatment regimens, with 20 (77%) pts refractory to prior immunomodulatory drug therapy. At data cut-off (Nov 8, 2016), median duration of ISA treatment was 19.0 wks, and 16 pts remained on treatment. 2 pts at 10 mg/kg discontinued therapy due to adverse events (AEs) (grade [Gr] 5 perforated bowel; Gr 3 infusion-associated reaction [IAR]). DLTs reported in 1 pt at each dose level (Gr 4 neutropenia; Gr 4 neutropenic infection; Gr 3 confusional state), and MTD has not been reached. Most common TEAEs, besides IARs, were fatigue (62%), diarrhea (35%), and dyspnea (31%). Most frequent Gr 3/4 hematologic abnormality (laboratory assessment) was neutropenia (Gr 3, 40%; Gr 4, 52%). Gr 3/4 thrombocytopenia was reported in 8 (32%) pts (Gr 3, 16%; Gr 4, 16%). IARs occurred in 12 (46%) pts (Gr ≥3 in 1 pt); only with 1st infusion in 9/12 pts. 16 (62%) pts achieved at least PR (5, 8 and 3 pts at 5, 10 and 20 mg/kg), including 1 CR, 8 VGPR, and 7 PR. Clinical benefit rate (≥ MR) was 73%. Median time to 1st response, 4.2 wks; median duration of response, 25.6 wks. The PK parameters of ISA were not affected by co-administration with Pom/Dex. **Conclusions:** The combination of ISA and Pom/Dex was manageable and clinically active in heavily pretreated RRMM. A Phase III trial of this combination is ongoing. Clinical trial information: NCT02283775.

8008 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Phase I/II dose expansion of a trial investigating bendamustine and pomalidomide with dexamethasone (BPd) in patients with relapsed/refractory multiple myeloma. *First Author: Dharshan Sivaraj, Duke University, Durham, NC*

Background: The combination of bendamustine, pomalidomide, and dexamethasone (BPd) displays promising activity in heavily pretreated RRMM. In the Phase I portion, MTD was 120 mg/m^{2}bendamustine/3mg pomalidomide/40mg dexamethasone. We report our combined findings from the additional phase II expansion cohort for the first phase I/II trial of BPd in patients with RRMM (NCT01754402). **Methods:** All patients had to be refractory to prior lenalidomide as well as be pomalidomide naïve, and must have relapsed or have been refractory to their most recent therapy. Treatment consisted of oral pomalidomide PO QD on days 1-21, intravenous (IV) bendamustine given over 30 minutes on day 1, and dexamethasone 40mg on days 1, 8, 15, and 22 of a 28-day cycle. Bendamustine was administered at 120 mg/m^2 for cycle 1, day 1. **Results:** A total study population of 38 patients was enrolled, with 34 evaluable for toxicity and 32 for efficacy, with 7 patients still receiving treatment. Data cut-off was January 18, 2017. The median age was 67 years, median number of prior regimens was 5, median time from diagnosis was 3.6 years, and median follow-up was 11.7 months. 82% of patients had a prior stem cell transplant, 100% had prior bortezomib, 32% had prior carfilzomib, and all were lenalidomide refractory. Cytogenetic abnormalities included 6 patients with del(17p), 4 with t(4;14), 7 with del(13), and 7 with t(11;14). Patients received a median of 4 cycles of therapy. Best response assessments in 32 evaluable patients showed 3 sCR, 3 VGPR, 17 PR, 7 SD, and 2 PD for an ORR of 72%. The median PFS and OS were 9.6 months and 21.3 months respectively for the entire cohort, with 16 of 32 still alive at follow-up. Grade ≥3 drug-related AEs included fatigue (8%), neutropenia (45%), anemia (26%), thrombocytopenia (24%), and diarrhea (8%). 71% of patients experienced grade ≥3 AEs including neutropenia, anemia, and diarrhea. **Conclusions:** The BPd regimen is relatively tolerable and achieves a promising overall response rate (ORR of 72%) and durable responses in a heavily pretreated lenalidomide–refractory population with prior bortezomib exposure, and a median of 5 lines of prior therapy. Clinical trial information: NCT01754402.

8009 Poster Discussion Session; Displayed in Poster Session (Board #335), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Lenalidomide induction and maintenance therapy for transplant eligible myeloma patients: Results of the Myeloma XI study. *First Author: Graham H. Jackson, Department of Haematology, University of Newcastle, Newcastle-upon-Tyne, United Kingdom*

Background: Immunomodulatory (IMiD) agents are effective therapies for multiple myeloma (MM), with Lenalidomide (Len) having fewer side effects than Thalidomide (Thal), enabling long-term treatment. The optimum IMiD induction and maintenance regimen are unknown. We therefore compared triplet induction regimens of Len vs Thal and examined the role of maintenance Len vs observation, enabling us to explore the interaction of Len induction with Len maintenance. **Methods:** Myeloma XI is a multicenter, randomized controlled trial for newly diagnosed MM, with pathways for transplant eligible (TE) and non-eligible patients. For TE patients the induction question compared Len or Thal plus cyclophosphamide and dexamethasone (CRD vs CTD) continued for a minimum of 4 cycles and to max. response. For patients with a suboptimal response there was a subsequent randomization to a proteasome inhibitor containing triplet or no further therapy prior to ASCT. A maintenance randomization at 3 months post ASCT compared Len till disease progression vs observation. 2042 TE patients underwent the induction randomization (CRD 1021, CTD 1021). After a median follow up of 36.3 months, 965 PFS and 415 OS primary endpoint events had occurred. Secondary endpoints included response and toxicity. **Results:** In TE patients, CRD induction was associated with deeper responses than CTD: ≥VGPR CRD 60% vs CTD 53%. This was associated with a significantly improved median PFS (HR 0.85, 95%CI 0.75, 0.96, CRD 35.9 months vs CTD 32.9, p=0.0116) and 3 year OS: 82.9% vs 77.0% (HR 0.77, 95%CI 0.63, 0.93, p=0.0072). Maintenance therapy with Len was associated with a significantly longer median PFS compared to observation (HR 0.47, 95%CI 0.38, 0.60) across all subgroups including patients with high-risk disease. Exploratory analysis across the TE pathway suggested that CRD induction with Len maintenance was optimum: 60 month PFS CRD-R 50.2%, CTD-R 39.1%, CRD-obs 18.5%, CTD-obs 23.4%. **Conclusions:** CRD was associated with deeper responses than CTD, and with a PFS and OS benefit. The best outcomes were associated with Len induction plus Len maintenance. Our findings support continuing Len therapy through induction until disease progression. Clinical trial information: NCT01554852.

8010 Poster Discussion Session; Displayed in Poster Session (Board #336), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Response status as predictor of survival after autologous hematopoietic cell transplant (AHCT), without or with consolidation (with bortezomib, lenalidomide (Len) and dexamethasone) and len maintenance (AM vs. ACM) versus tandem AHCT and len maintenance (TAM) for up-front treatment of patients (pts) with multiple myeloma (MM): BMT CTN0702-stamina (NCT01109004). *First Author: George Somlo, City of Hope, Duarte, CA*

Background: The Stamina trial primarily aimed to identify the best strategy among AM, ACM, and TAM, leading to longer PFS (LBA-1, ASH, 2016). Here we report on interim, exploratory results of the association between PFS and overall survival (OS) and baseline MM response, risk category, and treatments (Rx). **Methods:** Pts with MM, < 71 years, < 12 mos from diagnosis were randomized to melphalan 200mg/m^2(mel) and AHCT (AM), tandem mel AHCT (TAM), or mel AHCT and 4 cycles of RVD ((ACM). Pts received Len till progression. Pts were stratified by high risk vs. standard (del13q, del17q, t(4;14), t(14;16), t(14;20) and hypodyploid; high β2 microglobulin). Kaplan Meier estimates of PFS and OS were performed as a function of Rx and ≥ very good partial response (VPGR including CRs) vs. < VGPR. Cox proportional hazard models explored associations between PFS or OS and risk category, Rx, and ≥ VPGR vs. < VGPR. **Results:** Between 6/2010-11/2013, 758 pts (AM, N = 257; ACM, N = 254; TAM, N = 247) aged 20-70 years (median 57y) were enrolled (24% high-risk). Baseline ≥VGPR responses were 45.5- 49.8%. PFS at 38 months was similar. For < VGPR, 38-mos PFS with TAM:55.8% (95%CI: 45.8%, 64.7%); ACM: 54.0% (44.7%, 62.5%); AM: 50.1% (40.6%, 58.9%); For ≥VGPR, 38-mos PFS with TAM: 57.1% (46.8%, 66.1%); ACM: 60.1% (50.1%, 68.7%); AM: 55.1% (45.1%, 64.0%). Analyzing response, risk category, and Rx revealed no association between baseline response and PFS (Baseline response < VGPR, hazard ratio (HR): 1.21,95% CI: 0.97-1.52) or OS (baseline response < VGPR, HR 1.02, 95%CI:0.70-1.48). High risk category had an adverse association for PFS (HR 1.62, 95% CI: 1.27-2.07) and OS (HR 1.51 (95% CI:1.01-2.26). **Conclusions:** In this analysis < VGPR at baseline was not associated with PFS or OS. High-risk had an adverse association. Whether accomplishment of CR/minimal residual disease after AM, ACM,or TAM predicts for longer PFS and OS is the subject of ongoing analysis. Clinical trial information: NCT01109004.

8011 Poster Discussion Session; Displayed in Poster Session (Board #337), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Minimal residual disease (MRD) monitoring by multiparameter flow cytometry (MFC) in newly diagnosed transplant eligible multiple myeloma (MM) patients: Results from the EMN02/HO95 phase 3 trial. *First Author: Stefania Oliva, Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy*

Background: MRD detection is a sensitive tool to measure response in MM. We assessed MRD by MFC in newly diagnosed MM patients (pts) enrolled in the EMN02/HO95 phase 3 trial. **Methods:** Pts were ≤65 years old and received Bortezomib-Cyclophosphamide-Dexamethasone (VCD) induction, intensification with Bortezomib-Melphalan-Prednisone (VMP) vs High-Dose-Melphalan (HDM) followed by stem cell transplant, consolidation with Bortezomib-Lenalidomide-Dexamethasone (VRD) vs no consolidation, and Lenalidomide maintenance. MRD analysis was performed in pts achieving at least a very good partial response (VGPR) before starting maintenance (after HDM, VMP or VRD) and during maintenance every 6-12 months; samples were centralized to 3 European labs. MFC was performed on bone marrow according to Euroflow-based methods (8 colors, 2 tubes) with a sensitivity of 10^{-5}. Quality checks were performed to compare sensitivity and to show correlation between protocols (Hofste op Bruinink D *ASH* 2016 abstract 2072). **Results:** 316 pts were evaluable before maintenance: median age was 57 years, 18% (57/316) pts had ISS III and 22% (70/316) had high risk cytogenetic (HR-C) defined as having at least one among del17, t(4;14) or t(14;16); 63% (199/316) had received HDM and 37% (117/316) VMP; thereafter 51% (160/316) had received VRD. 76% (239/316) were MRD negative (MRD-) of whom 64% (153/239) received HDM vs 36% (86/239) VMP, with a median follow-up time of 30 months from MRD enrolment. 3-year PFS was 50% in MRD positive (MRD+) vs 77% in MRD- pts (HR: 2.87, p < 0.001). Subgroup analyses were performed to evaluate the risk factors for MRD+ according to baseline characteristics and therapies: HR-C was the most important risk factor (HR 9.87, interaction-p = 0.001). Finally, 48% of MRD+ pts at pre-maintenance who had a second MRD evaluation after at least 1 year of lenalidomide became MRD-. **Conclusions:** MRD by MFC is a strong prognostic factor in MM pts receiving intensification with novel agents or transplant; lenalidomide maintenance further improved depth of response; HR-C is the most important prognostic factor in MRD+ pts. Clinical trial information: NCT01208766.

8012 Poster Discussion Session; Displayed in Poster Session (Board #338), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Bendamustine with ixazomib and dexamethasone (BID) for double refractory relapsed multiple myeloma (RRMM): Phase I safety and dosing results. *First Author: Binod Dhakal, Medical College of Wisconsin, Milwaukee, WI*

Background: Bendamustine has promising activity in RRMM. This phase I (NCT02477215) study assessed the overall safety and activity of the combination of bendamustine with ixazomib & dexamethasone in pts. with MM pts. refractory to proteasome inhibitors and IMIDs. **Methods:** Design: Open label dose escalation (3+ 3 design) Doses: Bendamustine at escalating doses of 70, 80 and 90 mg/m^2 on days 1,2 of each cycle with weekly ixazomib (4mg) and dexamethasone (40 mg) on days 1,8, 15 in 28-day cycles for up to 8 cycles in responders and 4 cycles if no anti-MM response. Primary end point was safety, maximum tolerated dose (MTD) and the recommended phase II (RP2D) dose. **Results:** As of Jan 2017, the phase I portion is complete (N= 15). The median age was 67 years with 5 (range: 2-10) median number of prior therapies. Prior therapies included bortezomib (100%), lenalidomide (100%), carfilzomib (47%), oprozomib (7%), thalidomide (7%), pomalidomide (7%) and 87% autotransplant. Five (33%) pts. completed their planned courses of therapy (4 or 8 cycles) and 3 (20%) continued on active therapy. Seven (47%) pts. discontinued study treatment (6 related to disease progression). Grade 3/ 4 adverse events were: lymphopenia (67%), neutropenia (27%), thrombocytopenia (33%), decreased WBC counts (13%), hematuria (7%), diarrhea (7%), anemia (7%), lung infection (7%), and skin ulceration (7%). Three (20%) pts. died of myeloma progression. In dose cohort 3 (bendamustine 90 mg/m2), 2 /6 pts. developed hematologic DLTs (neutropenia and thrombocytopenia) meeting MTD; RP2D was determined to be 80 mg/m2. The table below shows responses among pts receiving at least 2 cycles. The median duration of response was not reached at median follow up of 8 months (range, 4-13+) in responders. **Conclusions:** BID has an acceptable safety profile and a promising ORR of 45% and CBR of 73% in pts. with advanced double refractory MM. Clinical trial information: NCT02477215.

Response in 3 cohorts.

Dosing cohort	N	Evaluable (>=2 cycles)	Response
70mg/m2	3	3	1 SD, 2PD
80mg/m2	6	5	2 VGPR, 2PR, 1PD
90 mg/m2	6	3	1PR, 2SD
Total	15	11	ORR -45% (5/11) CBR-73% (8/11)

SD: stable disease; VGPR: very good partial response, PR; partial response, PD: Progressive disease ORR: VGPR+ PR; CBR: VGPR+PR+SD

8013 Poster Discussion Session; Displayed in Poster Session (Board #339), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Replacement of ixazomib for relapsed/refractory multiple myeloma patients refractory to a bortezomib or carfilzomib-containing combination therapy. *First Author: James R. Berenson, Institute for Myeloma and Bone Cancer Research, Los Angeles, CA*

Background: The proteasome inhibitor (PI) ixazomib (Ixz) is the first orally administered PI approved for treating multiple myeloma (MM). It has shown clinical activity as a single agent and when used in other combinations. In this phase 1/2 trial, we evaluated Ixz as a replacement therapy for bortezomib or carfilzomib for MM patients who were refractory to a bortezomib- or carfilzomib-containing combination regimen. **Methods:** This was a phase 1/2, intra-patient, multicenter, open-label trial evaluating the replacement of ixazomib for bortezomib or carfilzomib for MM patients who were refractory in combination with the other agents that the patients had received and failed. Patients received Ixz on days 1, 8 and 15 on a 28-day schedule and the other drugs were administered using the same doses and schedules as they were receiving during their prior regimen. If the Ixz maximum tolerated dose (MTD) for a particular combination regimen was previously determined, then patients were enrolled directly into Phase 2 (PhII). If not, MTD was determined during the Phase 1 (PhI) portion of the trial. **Results:** To date, a total of 40 patients have been enrolled; 37 patients (21 were enrolled in PhI and 16 in PhII) had completed at least one cycle of this treatment. Patients received a median of 5 prior treatments (range, 1-22). The median follow-up time for all patients was 1.6 months (range, 0.1-10.7 months), whereas that of PhII was 2.2 months (range, 0.2-10.7 months). There was no clinical benefit (CBR; 0%) nor any overall response rate (ORR; 0%) for patients receiving Ixz 3 mg (PhI). Nine patients (43%) showed stable disease (SD) while 12 (57%) exhibited disease progression (PD). In PhII (4mg Ixz) portion of the trial, ORR and CBR were both 18.7% with 16 (43.2%) patients showing SD, and 18 (48.6%) patients displaying PD. Common ≥ Gr3 adverse events were anemia (11%), thrombocytopenia (5.4%), hyponatremia (5.4%), dehydration (5.4%) and neutropenia (2.7%). **Conclusions:** Replacement of bortezomib or carfilzomib with Ixz infrequently leads to responses among RRMM patient who have progressed while on proteasome inhibitor -containing combination regimens. Clinical trial information: NCT02206425.

8014 Poster Discussion Session; Displayed in Poster Session (Board #340), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Natural history of t(11;14) multiple myeloma (MM). *First Author: Arjun Lakshman, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: t(11;14) is a standard risk cytogenetic marker in MM. **Methods:** We reviewed 366 patients with MM who had t(11;14) by FISH and 732 age and period-matched controls without t(11;14), seen at our institution from 2004 to 2014 and outcomes were analyzed using time to first progression or death (PFS1) and overall survival (OS). **Results:** For the t(11;14) group at diagnosis, the median age was 63.7 yr (range, 22.1-95.4) with 64.5% of patients being male. Eighty nine (24.3%) patients were above 70 yr of age at diagnosis. 33.8%, 40.3% and 25.9% patients belonged to ISS 1, II and III stages respectively. 13% patients had elevated LDH. Monosomy 17 or del 17p were identified in 10.6% patients. The median follow up period was 56.9 months (m) (95% CI: 54.6-62.2) and 209 (57.1%) patients were alive at last follow-up. Among patients receiving proteasome inhibitor (PI)-based, immunomodulator (IMiD)-based, PI+IMiD based or other agent based induction therapy, 71.2%, 70.3%, 90.4% and 37.5% patients respectively attained ≥PR as best response to induction ($p < 0.01$). During their course, 223 (60.9%) patients underwent stem cell transplant. Median PFS1 and OS were 23.1 (CI: 20.8-27.9) and 78.6 (CI: 66.7-105.9) m respectively. Among the controls, high risk cytogenetics (HRC) was present in 142 (19.4%), and the median OS was 83.8 m (CI: 70.8-97.0) being comparable to t(11;14) group ($p = 0.8$). For all 1098 patients, using a Cox-proportional hazards model with age > 70 years, induction therapy (novel agent-based vs others), cytogenetics [HRC vs t(11;14) without HRC vs no HRC or t(11;14)], and ISS stage III vs II/I as predictors, age > 70 years [HR-2.2 (CI: 1.8-2.8) and $p < 0.01$], ISS III vs ISS II/I [HR-1.4 (CI: 1.1-1.8) and $p < 0.01$] and HRC [HR of 2.1 (CI: 1.6-2.8) vs no HRC or t(11;14) ($p < 0.01$) and 1.9 (CI = 1.4-2.6) for t(11;14) without HRC ($p < 0.01$)were associated with reduced OS. The risk for reduced OS did not differ between t(11;14) without HRC, and those without t(11;14) or HRC [HR-1.1 (CI: 0.9-1.4), $p = 0.4$]. **Conclusions:** Our study characterizes the outcomes of a large cohort of MM patients with t(11;14) at diagnosis. Advanced age, HRC and advanced stage at diagnosis were associated with worse OS in our cohort. t(11;14) MM without HRC does not differ in outcome compared to non-t(11;14) MM without HRC.

8015 Poster Discussion Session; Displayed in Poster Session (Board #341), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Pembrolizumab (Pembro) plus lenalidomide (Len) and low-dose dexamethasone (Dex) for relapsed/refractory multiple myeloma (RRMM): Efficacy and biomarker analyses. *First Author: Enrique M. Ocio, Complejo Asistencial Universitario de Salamanca/IBSAL, Salamanca, Spain*

Background: The PD-1 inhibitor pembro blocks interaction of PD-1 with its ligands PD-L1/PD-L2, activating antitumor immunity. Combination of pembro, len, and dex may provide synergistic antitumor activity in RRMM. **Methods:** Theopen-label, phase 1 KEYNOTE-023 (NCT02036502) study of pembro + len + low-dose dex enrolled patients (pts) with RRMM treated with ≥2 prior therapies (tx). Pts received pembro 200 mg IV Q2W, len 25 mg PO on d1-21, and dex 40 mg PO weekly on each 28-d cycle. Primary end point was safety. ORR was assessed by IMWG 2006. Exploratory biomarker analyses included flow cytometry (FC) (PD-L1, PD-L2 on CD38$^+$CD138$^+$ cells) at screening or predose cycle 1, d 1 bone marrow (BM) aspirate. Absolute and/or relative numbers of circulating immune cells (by FC) and gene expression profile (GEP) (by Nanostring) were evaluated in predose cycle 1, d1 and cycle 2, d1 blood. **Results:** Median age was 61 y; median (range) prior lines of tx was 4 (1-10); 38 (75%) pts were len-refractory and 27 (53%) pts were double refractory. Most common grade ≥3 tx-related AEs (TRAEs) were neutropenia (33%), thrombocytopenia (18%), and anemia (12%). 2 (4%) pts died (hepatic failure, ischemic stroke) because of TRAEs. Immune-related AEs occurred in 5 (10%) pts. No pneumonitis was reported. For response-evaluable pts, ORR was 50% (20/40; 1 sCR, 14 PR, 5 VGPR); 1 had PD. ORR was 38% (11/29) for len-refractory pts. In 16/32 pts with FC-evaluable BM aspirate with >100 CD38$^+$CD138$^+$ cells, all were PD-L1$^+$, while PD-L2 expression was variable. At cycle 2, d1, frequency of circulating HLA-DR$^+$, central (CD45RO$^+$CCR7$^-$), and effector memory (CD45O$^+$CCR7$^+$) CD8$^+$ T cells significantly increased and naive (CD45RA$^+$) CD8$^+$ T cells significantly decreased; all with multiplicity adjusted P values ≤ 0.01. **Conclusions:** Pembro + len + low-dose dex has an acceptable safety profile and antitumor activity in pts with RRMM, including len-refractory pts. PD-L1 was expressed in all pts evaluated by FC, whereas PD-L2 expression was variable. Among the pool of circulating T cells in peripheral blood, HLA-DR$^+$ and memory T-cell subset fractions increased after treatment. Clinical trial information: NCT02036502.

8016 Poster Discussion Session; Displayed in Poster Session (Board #342), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

WT1 heteroclitic epitope immunization following autologous stem cell transplantation in patients with high-risk multiple myeloma (MM). *First Author: Guenther Koehne, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Host T-cells mount immune responses (IR's) against Wilms tumor 1 (WT1) in A*0201^{+}MM pts through formation of WT1 peptide fragment (RMFPNAPYL)/HLA-A*0201 complex. We report initial results from MM pts immunized with the WT1 heteroclitic peptide mixture galinpepimut-S (GPS) after autoSCT. **Methods:** 16 MM pts underwent autoSCT with melphalan conditioning followed by (f/b) lenalidomide maintenance starting 3 months (mos) post-SCT. 13/16 pts presented with high-risk (HR) cytogenetics [t(4;14), t(14;16), del17p, 1q21/25 gain and/or del13q]. GPS was administered with montanide s.c. starting 2 wks post-SCT and q.2 wks thereafter x 6 initial doses f/b boosters q.4 wks x 6 additional doses. GM-CSF was given on days -2 and 0 of each cycle. GPS consisted of 4 peptides: WT1-A1: Y*MFPNAPYL; 427-L (long): RSDELVRHHNMHQRNMTKL; 331-L: PGCNKRYFKLSHLQMHSRKHTG, and 122A1-L: SGQAY*MFPNAPYLPSCLES. 2 of the 4 peptides were mutated at a single residue (*) to induce stronger HLA-binding/reduce tolerance. WT1-specific IR's were assessed by intracellular IFN-g analyses post-challenge with PBMC's pulsed with a 'total pool' of overlapping 15mers along the entire WT1 protein; or each of the 4 WT1 peptides in GPS; or the non-mutated (native) WT1 peptides corresponding to the 2 heteroclitic sequences. **Results:** 16 pts; median follow-up: 18 mos (range: 5-31 mos) for survivors; median age: 61.6 y. Overall survival (OS) and progression-free survival (PFS) (95% CI) at 18 mos: 0.88 (0.73-0.99) and 0.62 (0.42-0.97) respectively. Current median PFS: 23.6 mos (15.2 - not reached). No >G2 systemic side effects were observed, however, all pts developed local nodularity at the site of injections which resolved over 2 – 6 wks. Both CD8+ and CD4+ IR's could be detected at various levels and were induced not only against the heteroclitic peptides (within GPS), but also against the corresponding native WT1 peptide sequences as well as the 'total pool' of WT1-derived overlapping peptides. **Conclusions:** Administration of the novel WT1 heteroclitic peptide immunizer GPS post auto SCT demonstrates favorable safety profile along with encouraging mPFS of currently 23.6 mos in this high-risk MM population. Clinical trial information: NCT01827137.

8017 Poster Discussion Session; Displayed in Poster Session (Board #343), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Development of a fully human T cell engaging bispecific antibody for the treatment of multiple myeloma. *First Author: Ben Buelow, TeneoBio, Inc., Menlo Park, CA*

Background: Although BCMA is a plasma cell specific surface molecule attractive as an antibody target in multiple myeloma, its scarcity on the cell surface may limit the efficacy of a conventional antibody. T-cell engaging bispecific antibody approaches are highly efficacious and are particularly well suited for a membrane target with limited expression, such as BCMA. Teneobio has developed a multivalent antibody platform based on modular human VH domains, which allowed us to build T cell engaging bispecific antibodies with low and high T cell agonistic activities. **Methods:** UniRats were immunized with either CD3 or BCMA antigens and antigen-specific UniAbs were identified by antibody repertoire sequencing and high-throughput gene assembly, expression, and screening. High affinity binding VH sequences were selected using recombinant proteins and cells. In vitro efficacy studies included T-cell activation by cytokine- and tumor cell kill by calcein-release assays. In vivo efficacy of the molecules was evaluated in NSG mice harboring myeloma cells and human PBMCs. **Results:** BCMA-specific UniAbs bound plasma cells with high affinities (100-700pM) and cross-reacted with cynomolgus plasma cells. Strong and weak T cell agonists were identified that bound human T cells with high and low affinities respectively and cross-reacted with cynomolgus T cells. T cell engaging bispecifics with a strong (H929 cytotoxicity:EC_{50}=27pM) and a weak T cell activating arm (H929 cytotoxicity: EC_{50}=1170pM) demonstrated T-cell activation and tumor-cell cytotoxicity in vitro; bispecifics with a weak CD3 engaging arm showed markedly reduced cytokine production even at doses saturating for cytotoxicity. In vivo, BCMAxCD3 bispecific antibodies reduced tumor load and increased survival when co-administered with human PBMCs as compared to controls. **Conclusions:** Our results suggest that T cell engaging bispecifics with low-affinity anti-CD3 arms could be preferred for the treatment of Multiple Myeloma.

8018 Poster Discussion Session; Displayed in Poster Session (Board #344), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Carfilzomib-associated cardiovascular adverse events: A systematic review and meta-analysis. *First Author: Adam Justin Waxman, Abramson Cancer Center, Philadelphia, PA*

Background: The incidence and nature of cardiovascular adverse events (CVAEs) with carfilzomib (CFZ) in multiple myeloma (MM) remain incompletely defined. We performed the first systematic review and meta-analysis of CFZ CVAEs. **Methods:** PubMed was queried for the keywords "carfilzomib," "Kyprolis," and "PX-171." Phase 1-3 clinical trials of carfilzomib in MM with evaluable toxicity data were included. CVAEs were defined as heart failure, hypertension, ischemia, and arrhythmia. All-grade and grade ≥3 CVAEs and study characteristics were recorded. Summary incidence rates and relative risks (for randomized trials) with 95% confidence intervals were calculated using the logistic-normal random-effects model. Subgroup analyses were performed using study level covariates. **Results:** 514 studies were reviewed. 2623 MM patients from 25 eligible studies were included. Incidence rates are summarized in the table. All grade and grade ≥3 CVAEs were seen in 16.8% and 7.6 %, respectively. Phase 2 or 3 studies, carfilzomib doses ≥45mg/m^2, and longer infusion length were study characteristics associated with high-grade cardiac AEs ($p<0.05$). Median age >65, prior MM therapies, and concurrent MM therapies were not associated with CVAEs ($p>.05$). For the three randomized trials, the relative risk of all-grade and grade ≥3 CVAEs were 1.75 and 2.25, respectively ($p<0.001$). **Conclusions:** CFZ is associated with a significant incidence of CVAEs, including heart failure, hypertension, ischemia, and arrhythmia. Phase I studies may be underdetecting CVAEs. Future studies are needed to: identify patients at high-risk for CVAEs, develop optimal monitoring strategies, and explore therapies to mitigate these risks.

Adverse Event	All-Grade Incidence % (95% CI)	p-value	Grade ≥3 Incidence % (95% CI)	p-value
Any Cardiac	16.8 (11.9-22.3)	<0.001	7.6 (5.4-10.1)	<0.001
Heart Failure	4.1 (2.3-6.3)	<0.001	2.6 (1.5-3.8)	<0.001
Hypertension	12.2 (9.7-14.9)	<0.001	4.3 (2.6-6.4)	<0.001
Ischemia	1.4 (0.4-2.8)	<0.001	0.8 (0.4-1.4)	<0.001
Arrhythmia	2.5 (0.4-5.7)	0.002	0.6 (0.1-1.5)	0.007
Cardiac Arrest	–	–	0.0 (0.0-0.2)	0.983

8019 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Evaluation of an oral direct anti-Xa anticoagulant, apixaban, for the prevention of venous thromboembolism in patients with myeloma treated with IMiD* compounds: A pilot study (MYELAXAT). *First Author: Brigitte Pegourie, University Hospital Grenoble-Alpes, Grenoble, France*

Background: The risk of venous thromboembolism (VTE) is higher in myeloma patients recieving IMiD* compounds (IMiD*: registered). A VTE prophylaxis using low-molecular-weight heparin or aspirin is proposed. Apixaban is an oral direct anti-Xa. Several studies have shown the efficiency and safety of apixaban in VTE prophylaxis compared to enoxaparin. The objective of this prospective pilot study was to assess the risk of VTE and bleeding in patients with myeloma treated with IMiD* compounds, using apixaban in a preventive scheme. **Methods:** Myeloma patients requiring Melphalan-Prednisone-Thalidomide in first line, or Lenalidomide-Dexamethasone in relapse, asymptomatic regarding VTE at inclusion, were enrolled between 2014 - 2016. All patients recieved apixaban, 2.5 mg x 2/day for 6 months, and were monthly monitored. Venous (pulmonary embolism – PE, or symptomatic proximal or distal deep vein thrombosis - DVT, or all proximal asymptomatic events detected by systematic proximal bilateral compression ultrasound) or arterial thrombotic events, and bleeding events (ISTH 2005) were registered. Based on meta-analysis of Carrier regarding VTE recurrence, and results from the ADOPT study in medical conditions regarding hemorrhages, < 13 symptomatic VTE events, < 3 severe and < 14 clinically relevant non major (CRNM) bleeding were expected on the treatment period. **Results:** 104 patients were enrolled (mean age 69.8 +/- 7.8yrs), 11 in first line, 93 in relapse. No PE or arterial cardiovascular events were reported. Two venous thrombotic events were registered, i.e an asymptomatic proximal DVT (patient in relapse) and a symptomatic distal DVT, although apixaban was stopped 14 days before, due to Lenalidomide-induced thrombopenia. Only one major and 11 CRNM hemorrhages were reported. **Conclusions:** Referring to the incidence of thromboembolic events in Carrier's meta-analysis, and to hemorrhagic events in medical patients recieving apixaban in primary VTE prophylaxis, apixaban used in a preventive scheme seems to be efficient and safe in preventing VTE in myeloma patients treated with IMiD* compounds. Clinical trial information: NCT02066454.

8020 Poster Discussion Session; Displayed in Poster Session (Board #346), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Prognostic impact of kinetics of circulating plasma cells before and after induction therapy in newly diagnosed multiple myeloma patients undergoing early transplantation. *First Author: Rajshekhar Chakraborty, Mayo Clinic, Department of Hematology, Rochester, MN*

Background: Circulating plasma cells (CPCs) at diagnosis, prior to transplant and at relapse have a negative prognostic impact on survival in multiple myeloma (MM). However, the impact of changes in CPCs along the course of illness has not been defined. **Methods:** We evaluated 247 patients with newly diagnosed MM (NDMM) undergoing early autologous stem cell transplantation (ASCT) in the era of novel agents (2007 to 2015), who had serial evaluation of CPCs at diagnosis and pre-ASCT by 6-color flow cytometry. **Results:** The median age at transplant was 62 years. A total of 117 (47%) patients had no detectable CPCs at both time points (CPC-/-), 82 (33%) had CPCs at diagnosis followed by complete eradication after induction therapy (CPC+/-) and 48 (19%) had detectable clonal CPCs at transplant, with persistence of cells (CPC+/+; n=45) or emergence of new CPCs (CPC-/+; n=3) after induction. The incidence of t(11;14) by iFISH was lower in the CPC-/- group (19%) compared to CPC+/- (29%) and CPC +/+ or -/+ (39%) groups (p=0.033). Conversely, the incidence of hyperdiploidy was significantly higher in patients with CPC-/-, compared to those with CPC+/- and CPC+/+ or -/+ (64%, 44% and 39% respectively; p=0.005). The rate of post-ASCT stringent complete response was 32% in the CPC-/- group, 30% in CPC+/- group and 12% in CPC+/+ or -/+ group (p=0.018). At a median follow-up of 58 months from ASCT, the median progression-free survival (PFS) from transplant in the 3 respective groups was 30, 24 and 14 months and the 5-year overall survival (OS) rates were 83%, 70% and 43% (p<0.001 for both comparisons). On a multivariate analysis, using CPC-/- group as the comparator, PFS and OS was significantly inferior in CPC+/- (RR 1.6; p=0.020 and RR 2.7; p=0.008 for PFS and OS respectively) and CPC +/+ or -/+ groups (RR 2.9; p<0.001 and RR 5.8; p<0.001 for PFS and OS respectively). **Conclusions:** Clonal CPCs are detectable in more than 50% of newly diagnosed MM patients undergoing upfront ASCT. Monitoring for CPCs before initiation of induction therapy and before ASCT by 6-color flow cytometry is highly predictive of outcome in NDMM and should be incorporated into prospective clinical trials.

8021 Poster Session (Board #347), Mon, 8:00 AM-11:30 AM

Acupuncture for symptom reduction in myeloma patients undergoing hematopoietic stem cell transplantation: A randomized, sham-controlled trial. *First Author: Gary E. Deng, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Hematopoietic stem cell transplantation (HCT) is a potentially curative treatment for a number of hematologic malignancies, but is associated with a high symptom burden for patients. We conducted a randomized sham-controlled trial to evaluate the preliminary efficacy and safety of acupuncture as an integrative treatment for managing common symptoms during HCT. **Methods:** Adult patients with multiple myeloma undergoing high dose melphalan followed by autologous peripheral blood HCT were randomized to receive either true or sham acupuncture once daily for five days starting on the day after chemotherapy. Symptom burden was assessed with the MD Anderson Symptom Inventory (MDASI) at baseline, during transplantation, and at 15 and 30 days after transplantation. **Results:** Among 60 participants, symptoms that are significantly reduced by true acupuncture more than sham acupuncture at 15 days include the following: nausea, lack of appetite, and drowsiness (p = 0.042, 0.025, and 0.010, respectively). Patients receiving sham acupuncture were more likely to increase use of pain medication post-transplantation (odds ratio 5.31, p = 0.017). Acupuncture was well tolerated with few attributable adverse events. **Conclusions:** True acupuncture may prevent escalation of symptoms including nausea, lack of appetite, and drowsiness experienced by patients undergoing autologous HCT, and to reduce the use of pain medications. These findings need to be confirmed in a future definitive study. Clinical trial information: NCT01811862.

8022 Poster Session (Board #348), Mon, 8:00 AM-11:30 AM

Autologous stem cell transplant (ASCT) for newly diagnosed multiple myeloma (MM) in the era of novel agents: A meta-analysis of phase III randomized controlled trials. *First Author: Binod Dhakal, Medical College of Wisconsin, Milwaukee, WI*

Background: Given the unprecedented deep response rates with the novel agent induction, the role of high dose therapy (HDT) followed by ASCT in MM pts. has been questioned, and was re-evaluated in a number of randomized clinical trials (RCTs). Although, the results of most studies suggest the continued benefit of HDT/ASCT, some RCTs suggest no overall survival (OS) benefit. We undertook a systematic review and meta-analysis of phase III randomized RCTs evaluating the role of HDT compared to standard therapy (SDT) in the context of novel agent induction **Methods:** We searched the PubMed, Scopus and Cochrane Collection of Controlled Trial databases using the term *myeloma* combined with *autologous* or *transplant* or *myeloablative* or *stem cell* from 2000-2016. A total of 2480 articles identified, of which 4 large phase III RCTs compared upfront HDT with SDT with novel agents use. Two individuals independently extracted the data. Reported hazard ratio (HR) and survival data were pooled using random effects models (STATA v14, College Station, Tx). Heterogeneity was assessed using I^2. **Results:** Four studies comprising 2421 patients were included (Table 1). One study did not report the HR for death and hence OS analysis was limited to 3 studies. The combined hazard for progression with HDT was 0.55 (95% CI 0.40-0.71) (p < 0.005). The combined hazard for death with HDT was 0.65 (95% CI 0.29-1.0) (p = 0.007). Sensitivity and sub-group analysis showed no difference in PFS (p = 0.06) and OS (p = 0.22) with HDT. Significant heterogeneity was demonstrated by I^2 of 71.4% for PFS (p = 0.01) and 68.4% for OS (p = 0.04). **Conclusions:** Based on our analysis, even in the novel agent era, HDT appears to be beneficial and should be considered standard of care for all transplant eligible MM pts.

Baseline characteristics of the trials.

Author	Induction	N	Follow up(m)	Conditioning (HDT)	SDT regimen
Palumbo	Rd	273	51.2	M 200 x2	MPR
Gay F	Rd	256	52	M200 x 2	CRd
Attal M	RVD	700	39	M 200	RVd x2
Cavo M	CyBorD	1192	26	M 200 x 1 or 2	VMPx 4

Abbreviations: R, Lenalidomide. V/Bor, Bortezomib. Cy, Cyclophosphamide. M, Melphalan. P, Prednisone. d: Dexamethasone.

8023 Poster Session (Board #349), Mon, 8:00 AM-11:30 AM

Impact of t(11;14) on outcomes in African American (AA) and non-AA (NAA) patients (Pts) with newly diagnosed multiple myeloma (NDMM): Connect MM registry. *First Author: Cristina Gasparetto, Duke University Medical Center, Durham, NC*

Background: t(11;14) is a common cytogenetic abnormality historically associated with standard-risk and generally favorable MM outcomes, but has shown poor prognosis in some retrospective analyses. Connect MM is a prospective, US, observational, multicenter registry that collects data on management and natural history of NDMM pts in clinical practice. The impact of t(11;14) on survival outcomes was assessed in AA and NAA pts. **Methods:** Adult NDMM pts who completed induction and were tested for t(11;14) by FISH/cytogenetics were grouped by race (AA vs NAA). Endpoints were PFS and OS. Kaplan-Meier analyses were adjusted for differences in cohort, age, ISS stage, transplant intent, t(4;14), hemoglobin, platelets, calcium, creatinine, and diabetes history. Data cutoff was Jul 7, 2016. **Results:** 3011 pts were enrolled in 2 cohorts (Cohort 1: n = 1493, Sep 2009–Dec 2011, median follow-up = 39.3 mos; Cohort 2: n = 1518, Dec 2012–Apr 2016, median follow-up = 16.4 mos). Of 1539 (52%) pts tested for t(11;14), 363 (24%) were t(11;14)-positive, including 53 (26%) of 205 AA and 310 (23%) of 1334 NAA pts. First-line bortezomib exposure was similar across groups. A trend of shorter PFS was observed in AA pts with t(11;14) vs AA without t(11;14) (Table). AA pts with t(11;14) had significantly higher risk of death compared to those without t(11;14) and higher rate of early mortality than NAA pts. No differences in PFS or OS were noted in NAA pts with or without t(11;14). For OS, the interaction between race and t(11;14) status was statistically significant (P= 0.004). **Conclusions:** In Connect MM, the effect of t(11;14) on OS was significantly different between AA and NAA pts. t(11;14) was associated with poorer survival outcomes in AA pts, and thus, may be a risk factor for poor prognosis. Additional analyses will be conducted to elucidate the role of induction treatment, transplant and maintenance in AA and non-AA pts with t(11;14). Clinical trial information: NCT01081028.

	AA N = 205			NAA N = 1334		
	t(11;14)			t(11;14)		
	Yes n = 53	No n = 152	Adj HR (95% CI)	Yes n = 310	No n = 1024	Adj HR (95% CI)
Median PFS, mos	19.1	45.2	0.66 (0.41, 1.04) P = .076	33.1	38.1	1.03 (0.84, 1.25) P = NS
Median OS, mos	NR	NR	0.44 (0.23, 0.84) P = .012	69.3	71.0	1.17 (0.90, 1.54) P = NS

8024 Poster Session (Board #350), Mon, 8:00 AM-11:30 AM

MOR202 with low-dose dexamethasone (Dex) and in combination with pomalidomide/dex and lenalidomide/dex in relapsed or refractory multiple myeloma (RRMM): Interim analysis of a phase I/IIa dose-escalation study. *First Author: Marc Raab, Department of Medicine V, University Hospital Heidelberg and National Center for Tumor Diseases, Heidelberg, Germany*

Background: CD38 is a type II transmembrane glycoprotein expressed by MM cells. MOR202, a human IgG1 CD38 monoclonal antibody, has shown high single-agent activity in preclinical models of MM and synergy in combination with immunomodulatory drugs (IMiDs), lenalidomide (LEN) and pomalidomide (POM). **Methods:** This interim analysis of a multicenter phase I/IIa study reports safety and efficacy data from RRMM patient (pt) cohorts treated with clinically relevant doses of MOR202 (2-hour IV infusion; 4, 8 and 16 mg/kg q1w) + Dex (≤40 mg), or at 8 or 16 mg/kg q1w with an IMiD/Dex. Primary objectives were to evaluate the safety, maximum tolerated dose (MTD) and recommended phase II dose of MOR202. **Results:** As of January 2017, 79 pts had been treated, including 44 in clinically relevant cohorts: 18 received MOR202 + Dex, 15 MOR202 + LEN/Dex and 11 MOR202 + POM/Dex. Pts had received a median of 3, 2 and 3 prior treatment lines, respectively. The MTD of MOR202 was not reached. Combinations were generally well tolerated, with grade ≥3 adverse events (AEs) mainly hematological; 2 pts discontinued due to a MOR202-related AE (one grade 4 thrombocytopenia; one grade 3 acute kidney failure). Infusion-related reactions (all grade 1 or 2) were seen in only 3/44 (7%) pts, and mainly occurred during the first infusion. In the MOR202 + Dex cohort, 5/17 (29%) evaluable pts (receiving at least 1 cycle of treatment) had a response, including 3 with partial responses (PRs) and 2 with very good PRs (VGPRs). Responses were also seen in 11/13 (85%, 8 PRs, 3 VGPRs) evaluable pts in the MOR202 + LEN/Dex cohort and 5/9 (56%, 2 complete responses, 3 PRs) in the MOR202 + POM/Dex cohort. Longest response duration was 17 months (MOR202/Dex). Preliminary analysis showed preservation of high CD38 levels on MM cells under MOR202 therapy. **Conclusions:** In heavily pretreated pts with RRMM, a 2-hour infusion of MOR202 administered at up to 16 mg/kg with Dex or in combination with an IMiD/Dex, showed a favorable safety profile, including excellent infusion tolerability. Promising preliminary efficacy and long-lasting tumor control was seen. Clinical trial information: NCT01421186.

8025 Poster Session (Board #351), Mon, 8:00 AM-11:30 AM

Daratumumab, lenalidomide, and dexamethasone (DRd) vs lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): Efficacy and safety update (POLLUX). *First Author: Nizar J. Bahlis, Tom Baker Cancer Centre, Calgary, AB, Canada*

Background: Daratumumab (D) is a human CD38-targeting mAb that significantly prolongs progression-free survival (PFS) when added to standard-of-care regimens in patients (pts) with RRMM. We examined updated efficacy and safety data from POLLUX (NCT02076009), a randomized phase 3 study of DRd vs Rd in RRMM. **Methods:** Pts with ≥1 prior line of therapy (LOT) received Rd (25 mg PO lenalidomide on days 1-21 of each q4w cycle; 40 mg dexamethasone weekly) ± D (16 mg/kg IV qw for cycles 1 and 2, q2w for cycles 3-6, then q4w until disease progression). Pts refractory to lenalidomide were ineligible. Minimal residual disease (MRD) was assessed on bone marrow samples at time of suspected complete response (CR) and at 3 and 6 months post-suspected CR at sensitivities of 10^{-4}, 10^{-5}, and 10^{-6} via next-generation sequencing (Adaptive Biotechnologies, Seattle, WA). **Results:** Pts received a median (range) of 1 (1-11) prior LOT. 55% received prior IMiDs (18% lenalidomide). Based on previous median follow-up of 17.3 months, DRd significantly prolonged PFS (median: not reached vs 17.5 months; HR, 0.37; 95% CI, 0.28-0.50; $P < 0.0001$) and significantly improved overall response rate (ORR; 93% vs 76%, $P < 0.0001$) vs Rd. DRd induced higher rates of deep responses vs Rd (≥very good partial response [VGPR]: 78% vs 45%; ≥CR: 46% vs 20%; all $P < 0.0001$) and included MRD negativity, which was > 3-fold higher across all 3 sensitivity thresholds for DRd vs Rd (25% vs 6% at the 10^{-5} threshold). MRD-negative pts demonstrated longer PFS vs MRD-positive pts. Follow up for overall survival (OS) is ongoing (OS events: 40 [14%] in DRd and 56 [20%] in Rd). No new safety signals were identified with longer follow up. Updated efficacy and safety data based on approximately 25-months follow up will be presented at the meeting. **Conclusions:** DRd provided significant benefits vs Rd in terms of PFS, ORR, and MRD negativity, and the favorable safety profile of DRd was maintained with longer follow up. These data further validate the use of DRd in RRMM pts who received ≥1 prior therapy. Clinical trial information: NCT02076009.

8026 Poster Session (Board #352), Mon, 8:00 AM-11:30 AM

Loss of heterozygosity in multiple myeloma: A role for PARP inhibition? *First Author: Charlotte Pawlyn, The Institute of Cancer Research, London, United Kingdom*

Background: PARP inhibitors can induce synthetic lethality in tumors characterized by homologous recombination deficiency (HRD). Two PARP inhibitors are approved for the treatment of *BRCA* mutated ovarian cancer. HRD can be detected by evaluating genome-wide loss of heterozygosity (LOH), which is associated with response to PARP inhibition. Myeloma (MM) is a genetically unstable tumor and we hypothesized that LOH could be detected in patient samples, supporting a potential role for PARP inhibition in MM. **Methods:** We analyzed 406 cases at all disease stages: MGUS (n = 7), smoldering MM (SMM, n = 30) newly diagnosed MM (NDMM, n = 71), treated MM (TRMM, n = 64) and relapsed MM (RLMM, n = 234). CD138+ plasma cell DNA underwent targeted next generation sequencing (FoundationOne Heme) interrogating 405 cancer related genes and 3543 single nucleotide polymorphisms (SNPs) across the genome. An algorithm using the minor allele frequencies of the examined SNPs and copy number profile across the 22 autosomal chromosomes identified LOH segments. Events unlikely to be caused by HRD, e.g. whole chromosome or chromosome-arm loss, were excluded. The percentage of genomic LOH for each sample was calculated as the sum of the lengths of included LOH segments divided by the length of the interrogated genome. **Results:** We found evidence of HRD detected by LOH with higher LOH selecting for patients with poor outcome. LOH increases with advancing disease stage from a median of 0.3% in MGUS to 3.1% in RLMM. LOH was highest in the PR and MMSET molecular subgroups and correlated significantly with the gene expression defined risk score GEP70 (R = 0.4, $p < 0.001$) and proliferation index (R = 0.4, $p < 0.001$). Outcome of RLMM patients, the biggest clinical group, was analyzed and patients with LOH above the 3rdquartile (≥5%LOH) had significantly worse overall survival than those with lower levels ($p < 0.001$). LOH correlates and overlaps with other metrics of poor prognosis, suggesting it may be a prognostic marker itself. **Conclusions:** We demonstrated LOH in MM samples, increasing as disease progresses and associated with poor prognosis. These data support the further evaluation of PARP inhibitors in MM patients, particularly in the relapsed setting with a high unmet need for new treatments.

8027 Poster Session (Board #353), Mon, 8:00 AM-11:30 AM

Pomalidomide (POM) + low-dose dexamethasone (LoDEX) after lenalidomide (LEN)-based second-line (2L) treatment (Tx) in patients (Pts) with relapsed/refractory multiple myeloma (RRMM): Analysis of progression-free survival (PFS) by level of disease control. *First Author: David Siegel, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ*

Background: Recent trials of triple therapy in 2L and third-line (3L) Tx excluded pts refractory to LEN. This is not reflective of standard of care in first line and 2L where LEN is given until progressive disease (PD). MM-014 enrolled pts with RRMM and 2L LEN-based Tx failure. Here we report results only from cohort A of pts receiving POM + LoDEX. Cohort B will investigate POM + LoDEX + daratumumab. **Methods:** Adult pts with MM, 2 prior Tx lines, and PD after ≥ 2 cycles of 2L LEN-based Tx received POM + LoDEX. The primary endpoint was overall response rate (ORR). Other endpoints included time to response (TTR), PFS, second primary malignancies (SPMs), and biomarkers. **Results:** Of 51 pts in cohort A, 39 (76.5%) discontinued Tx. Most pts (88.2%) were refractory to their last LEN Tx, (median Tx duration 24.6 mos) and 72.5% had prior bortezomib. At a median follow-up of 13.6 mos, ORR was 29.4% (2.0% complete response, 9.8% very good partial response, and 17.6% partial response [PR]) and median TTR was 1.9 mos; 66% of pts had ongoing response at 1 yr. Minimal response [MR] was reached in 15.7%. Median PFS was 13.8 mos. Pts with ≥ MR had similar Tx durations as those achieving ≥ PR. Additional results in Table. Post-Tx T-cell populations were significantly higher vs baseline ($CD3^+$, 72.6% vs 67.8%; $CD3^+/CD8^+$, 36.9% vs 32.1%). Relative changes from baseline were significantly greater in pts with response vs pts with no response ($CD3^+$, 10.4 vs −0.8; $CD3^+/CD4^+$, 4.2 vs −3.5). **Conclusions:** This update confirms the safety and efficacy of POM + LoDEX following 2L LEN-based Tx failure in pts with RRMM. Hematologic adverse event (AE) rates improved and median PFS was longer with 3L use than previously reported with POM + LoDEX use in later Tx lines. In addition, achieving disease control of ≥ MR led to similar PFS rates as reaching ≥ PR. Clinical trial information: NCT01946477.

Grade 3/4 AEs, %	N = 51
Anemia	25.5
Neutropenia	11.8
Infections	19.6
Pneumonia	9.8
SPMs, %	0
2-Yr PFS, %	
Intent to treat	48.6
≥ PR (n = 15)	69.1[a]
≥ MR (n = 23)	69.4[a]
POM Tx duration by response, mos	
≥ PR (n = 15)	11.5
≥ MR (n = 23)	10.5
MR (n = 8)	7.7
Stable disease (n = 21)	3.7

[a] Subject to survival biases.

8028 Poster Session (Board #354), Mon, 8:00 AM-11:30 AM

Phase 3 ELOQUENT-2 study: Extended four year follow-up (FU) of elotuzumab plus lenalidomide/dexamethasone (ELd) vs Ld in relapsed/refractory multiple myeloma (RRMM). *First Author: Sagar Lonial, Winship Cancer Institute, Atlanta, GA*

Background: Elotuzumab, an immunostimulatory monoclonal antibody, has a dual mechanism of action: directly activating NK cells and tagging myeloma cells for recognition/death via antibody-dependent cell-mediated cytotoxicity. In a 3-y FU, ELOQUENT-2 (NCT01239797) showed a sustained 27% reduction in risk of disease progression/death for ELd vs Ld and OS trend in favor of ELd (Dimopoulos et al, ASH 2015). Here we present extended 4-y FU data (median FU 46 mo). **Methods:** RRMM patients (pts) were randomized 1:1 to ELd or Ld in 28-d cycles until disease progression/unacceptable toxicity. Coprimary endpoints: PFS, ORR. Secondary endpoint: OS. **Results:** Of 646 RRMM pts, 321 were randomized to ELd, 325 to Ld; ~ twice as many pts remain on therapy in ELd vs Ld (17 vs 9%) at data cut-off (Oct 18, 2016). Discontinuation was mainly due to disease progression (both arms 54%). At 4-y FU, ELd had 29% reduction in risk of progression/death vs Ld (HR 0.71, 95% CI 0.59–0.86) and relative improvement of 50% in PFS (21 vs 14%). Pts with ≥VGPR (ELd 112 [35%], Ld 95 [29%]) had greatest reduction in risk of progression/death (HR 0.65, 95% CI 0.46–0.94). ORR was 79% (ELd) vs 66% (Ld). OS will be presented. G3–4 AEs in ≥5% of pts included second primary malignancies (SPMs), vascular diseases, cardiac disorders and infections (ELd vs Ld: 9 vs 6%, 10 vs 8%, 5 vs 8%, 33 vs 26%). Overall rate (any grade) of infection and SPMs was 84 vs 75% and 17 vs 11% for ELd vs Ld. However, pts had longer exposure to ELd vs Ld (median [Q1, Q3] treatment cycles (19 [9, 42] vs 14 [6, 25]). There were fewer deaths with ELd vs Ld (165 vs 186), mainly due to disease progression and infection in both arms. **Conclusions:** Elotuzumab in combination with Ld consistently met its efficacy objectives at 4-y FU. ELd showed durable, clinically relevant improvement in PFS, with 29% reduction in risk of progression/death, consistent with 2-y (30%) and 3-y FU (27%). Safety, including rate of SPMs, was consistent with previous findings, with minimal incremental AEs with addition of elotuzumab to Ld. These data represent the longest median FU of an immuno-oncology agent in MM. Study funding: BMS. Writing support: C Tomas, Caudex, funded by BMS. Clinical trial information: NCT01239797.

8029 Poster Session (Board #355), Mon, 8:00 AM-11:30 AM

HDAC11 as a candidate therapeutic target in multiple myeloma. *First Author: Allison Distler, H. Lee Moffitt Cancer Center, Tampa, FL*

Background: Histone deacetylase (HDAC) inhibitors (HDI) have a therapeutic niche in multiple myeloma (MM) due to their ability to salvage proteasome inhibitor and immunomodulatory drug responsiveness in refractory patients, thus raising interest in this therapeutic class. Selective HDI may further improve therapeutic efficacy. **Methods:** B cell lymphopoiesis was evaluated using Tg-HDAC11-eGFP mice expressing eGFP regulated by the HDAC11 promoter and congenic mouse strains deficient in HDAC11 expression globally (B6.HDAC11$^{-/-}$) or targeted to the B cell lineage (CD19Cre.HDAC11$^{-/-}$). Molecular and pharmacologic means were used to impair HDAC11 in established MM cell lines. Viability was measured by activated caspase-3, Annexin/PI (A/PI) staining, and CCK-8 viability assay. Subcellular localization changes induced by HDI and identification of the novel binding partner IRF4 were assessed by proximity ligation assay (PLA). **Results:** Profound eGFP increases in PC of Tg-HDAC11-eGFP mice suggest HDAC11 influences late stage B cell development. In addition, HDAC11 deficiency results in dramatically reduced PC in the bone marrow and periphery. PC depletion in CD19Cre.HDAC11$^{-/-}$mice suggests activity inherent in B cells rather than via externally derived signals. Quisinostat (QS), an HDI with enhanced HDAC11 selectivity, showed dose-dependent cytotoxicity in 10 MM cell lines (EC50 1-10nM). This activity was synergistic with bortezomib (BTZ) and carfilzomib (CFZ) in RPMI-8226 cells, while synergism was amplified in the BTZ-resistant RPMI-8226-B25 cell line. Exposure of RPMI-8226 cells to QS decreased detection of nuclear, but not cytosolic, HDAC11. Targeted siRNA–mediated silencing of HDAC11 in RPMI-8226 cells activated caspase-3 and reduced viability by A/PI staining. PLA of MM cell lines showed a novel interaction between HDAC11 and IRF4, an essential regulator of PC differentiation and MM survival, unmasking a potential mechanism for HDAC11-induced cytotoxicity in MM. This interaction was disrupted by QS. **Conclusions:** We show that HDAC11 inhibition reduces MM cell survival in vitro. Furthermore, we identify IRF4 as a binding partner for HDAC11 and propose this interaction as a candidate mechanism regulating PC maturation and MM survival.

8030 Poster Session (Board #356), Mon, 8:00 AM-11:30 AM

Cost effectiveness of carfilzomib (CAR), ixazomib (IXA), elotuzumab (ELO), or daratumumab (DAR) with lenalidomide and dexamethasone (LEN+DEX) vs LEN+DEX in relapsed/refractory multiple myeloma (R/R MM). *First Author: Nimer Alsaid, Center for Health Outcomes and PharmacoEconomic Research, College of Pharmacy, University of Arizona, Tucson, AZ*

Background: CAR, IXA, ELO, and DAR in triplet combination with LEN+DEX have shown superior efficacy over LEN+DEX in R/R MM, but their comparative efficacy and cost effectiveness has not been estimated. **Methods:** Network meta-analysis [NMA] and Bücher method were used to indirectly estimate comparative progression-free survival (PFS) efficacy. A 2-state Markov model (progression-free, progressed or death) was specified. Inputs included: cost of chemotherapy, administration, adverse events (AE) management, disease monitoring; utilities for health states; and disutilities for AEs. Incremental cost effectiveness (ICER) and cost utility ratios (ICUR) were calculated for resp. PFS life years (PFS LY) and quality adjusted life years (PFS QALY) gained in base case and probabilistic sensitivity analyses (PSA). **Results:** NMA and Bücher indirect comparison methods yielded similar PFS hazard ratios (HR), revealing superiority of DAR+LEN+DEX over other triplets in terms of PFS (Table). Using the exponential distribution to fit PFS data, our cost effectiveness analysis indicated that all 4 triplet regimens were associated with additional PFS LY and QALY gained over LEN+DEX at additional cost. DAR+LEN+DEX was associated with the greatest PFS LY and QALY gained at the lowest relative cost, yielding superior ICER and ICUR estimates compared to other triplet regimens. **Conclusions:** The superior PFS efficacy of DAR+LEN+DEX is associated with positive cost effectiveness and cost utility in the setting of R/R MM.

Network meta-analysis hazard ratios	CAR+LEN+DEX 0.99 (0.75-1.30) 1.87 (1.28-2.73) 0.69 (0.57-0.83)	IXA+LEN+DEX 0.93 (0.69-1.26) 1.96 (1.34-3.00) 0.74 (0.59-0.93)	ELO+LEN+DEX 1.05 (0.78-1.49) 1.85 (1.29-2.70) 0.70 (0.57-0.86)	DAR+LEN+DEX 0.37 (0.27-0.52)	LEN+DEX
Probabilistic sensitivity analyses: ICER ($/PFS LY) / ICUR ($/PFS QALY)	CAR+LEN+DEX $1,174,511/ $3,523,533 $3,039,067/ $4,558,600 $23,035/$27,100 $558,907/ $707,950	IXA+LEN+DEX $242,233/ $726,700 $173,227/ $221,348 $367,858/ $395,107	ELO+LEN+DEX $166,655/ $201,909 $346,322/ $417,975	DAR+LEN+DEX $230,822/ $279,266	LEN+DEX

8031 Poster Session (Board #357), Mon, 8:00 AM-11:30 AM

Risk stratification of smoldering multiple myeloma (SMM): Predictive value of free light chains and group-based trajectory modeling (GBTM). *First Author: Ajai Chari, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: A serum free light chain ratio (FLCR) ≥ 100 and bone marrow plasma cell (BMPC) ≥ 60% have recently been classified as myeloma defining events to identify a group of SMM patients at high risk (ie. > 50% risk at 2 years) of organ damage. However rates of progression for FLCr range from 30% to 98%. Reasons for the discrepancy include selection/referral bias, patient heterogeneity, and lack of consideration of disease evolution. The objective of this study was to determine the predictive value of baseline FLCR > 100 and BMPC > 60% in our patient population and also to determine the significance of m spike and FLC evolution using GBTM. **Methods:** We retrospectively investigated the predictive value of these events, including involved–uninvolved FLC (dFLC), in 273 consecutive SMM patients seen at our institution between 2010 and 2015. GBTM uses the outcomes of groups of individuals with similar trajectories over time (vs apriori assumptions of % change) to model population trajectories. **Results:** In patients with FLCR ≥ 100 at diagnosis, the median time to progression was 23 mos with 2-year progression of 52%. In patients with BMPC ≥ 60% at diagnosis, median time to progression was 25 months with 2-year progression of 47%. For 111 patients available for analysis, GBTM two distinct trajectories in dFLC during the 1st year. 18% of patients fell into a high risk group experiencing a 171% increase in dFLC at 1 year vs the remaining patients only had a 16% increase. The high risk group had a median TTP of 13.7 mos versus not reached for the remaining (log-rank p = 0.0063). Similarly the 25% of patients who had a 62% increase in mean m spike within 1 year had TTP of 27 mos versus the remaining 75% who had no increase had a median TTP of 84 mos (log rank p = 0.0943). **Conclusions:** Our results not only confirm a more modest 52% 2 year risk of PD with an FLCR > 100 and dFLC > 100, but also suggest that a high risk dFLC trajectory evolution may help identify a SMM high risk group, with a median TTP of only 13.7 mos. Results of multivariate analysis and sensitivity/specificity comparisons of baseline as well as evolving biomarkers will be presented at the meeting.

8032 Poster Session (Board #358), Mon, 8:00 AM-11:30 AM

The impact of body mass index on the risk of early progression of smoldering multiple myeloma to symptomatic myeloma. *First Author: Wilson I. Gonsalves, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Human adipocytes can contribute directly to the *in vitro* growth and progression of multiple myeloma (MM) cell lines. Clinically, an elevated body mass index (BMI) has been associated with an increased risk of MGUS and a shorter time to progression (TTP) of MGUS to MM. However, the impact of BMI on the risk of early progression to MM from a more advanced plasma cell disorder such as smoldering MM (SMM) remains unknown. **Methods:** This study included patients (pts) with a known or new diagnosis of SMM evaluated at the Mayo Clinic, Rochester from January 2000-December 2010. Pts were classified based on their BMI as: normal (< 25) and elevated (>/= 25) BMI. Progression to symptomatic MM was defined by the development of hypercalcemia, renal insufficiency, anemia or lytic bone lesions. **Results:** There were 306 pts with a diagnosis of SMM who were included in this analysis. The median follow up was 106 months. There were 203 (66%) pts who progressed to symptomatic MM at last follow up. The median BMI of the group was 27.5 (Range: 17.2 – 56.4). There were 228 (75%) pts with an elevated BMI. There were 76 (28%) pts who had myeloma defining events (MDEs) such as a serum free light chain ratio > 100 or > 60% clonal bone marrow plasma cells at initial evaluation. MDEs were present in 17% and 33% of pts with a normal and elevated BMI respectively (P = 0.011). The median TTP of SMM to MM in pts with a normal and elevated BMI was 64 and 36 months respectively (P = 0.0006). The 2-year progression rate of SMM to symptomatic MM in pts with a normal and elevated BMI was 16% and 42% respectively (P < 0.0001). Upon limiting the analysis to only SMM pts without MDEs at initial evaluation (N =187), the 2-year progression rate to symptomatic MM with a normal and elevated BMI was 15% and 33% respectively (P = 0.013). In a multivariable model, only elevated BMI (P = 0.004) and increasing clonal bone marrow plasma cells (P = 0.001) was statistically significant in predicting for a 2-year progression to MM. **Conclusions:** SMM pts with an elevated BMI appear to have a higher risk of early progression to MM than those with a normal BMI. This study provides evidence of a potentially modifiable risk factor for the progression of SMM to MM and warrants confirmation in larger studies.

8033 Poster Session (Board #359), Mon, 8:00 AM-11:30 AM

Safety and efficacy of daratumumab-based regimens in elderly (≥75 y) patients (Pts) with relapsed or refractory multiple myeloma (RRMM): Subgroup analysis of POLLUX and CASTOR. *First Author: Maria-Victoria Mateos, University of Salamanca Hospital, Salamanca, Spain*

Background: Daratumumab (D) plus lenalidomide and dexamethasone (Rd; POLLUX) or with bortezomib and dexamethasone (Vd; CASTOR) demonstrated prolonged PFS and tolerability compared with Rd and Vd alone, respectively, in RRMM pts. We examined the safety and efficacy profiles of DRd and DVd in elderly (≥75 y) pts from these phase 3 studies. **Methods:** Pts with ≥1 prior line of therapy were enrolled. All pts in POLLUX were treated until progression; CASTOR pts received 8 cycles of Vd ± daratumumab. Different D (16 mg/kg) dosing schedules were used in POLLUX (qw for cycles 1-2, q2w for cycles 3-6, and q4w thereafter) and CASTOR (qw in Cycles 1-3, q3w for Cycles 4-8, and q4w thereafter). Elderly pts received a reduced dexamethasone dose (20 mg once weekly). **Results:** In POLLUX, 29/286 (DRd) and 35/283 (Rd) were ≥75 y, with 86% and 91% having ECOG status ≤1, respectively. With 17.3 months of median follow up, 10% in DRd and 11% in Rd discontinued due to treatment-emergent adverse events (TEAEs). Common (>10%) grade 3/4 TEAEs for DRd included neutropenia and hypokalemia (Table). Twelve (41%) DRd pts experienced infusion-related reactions (IRR) and 4 (14%) experienced grade 3/4 IRR; none discontinued due to IRR. Median PFS was not reached (NR) in DRd vs 11.4 months in Rd (HR 0.19; 95% CI, 0.06-0.55; *P*=0.0007), and ≥CR % was significantly higher with DRd vs Rd (52% vs 9%; P=0.0002). In CASTOR, 23/251 (DVd) and 35/247 (Vd) were ≥75 y, with 100% and 94% having ECOG status ≤1, respectively. With 13.0 months of median follow up, rates of discontinuation due to TEAEs were similar (15% vs 20%). Thrombocytopenia, fatigue, and pneumonia were common grade 3/4 TEAEs for DVd (Table). Thirteen (65%) pts reported IRR (10% grade 3/4) and no pts discontinued due to IRR. Median PFS was NR in DVd vs 8.1 months in Vd (HR 0.27; 95% CI, 0.12-0.61; *P*=0.0007), and significantly higher ≥CR % was observed in DVd vs Vd (25% vs 3%; *P*=0.0154). **Conclusions:** The safety and efficacy profiles in elderly pts were generally comparable with the overall population in each study. Clinical trial information: NCT02136134 and NCT02076009.

% Grade 3/4 TEAEs	DRd	Rd	DVd	Vd
Neutropenia	45	31	0	3
Hypokalemia	14	3	0	0
Pneumonia	10	11	15	17
Thrombocytopenia	7	14	45	37
Anemia	3	20	10	11
Fatigue	3	3	15	11

8034 Poster Session (Board #360), Mon, 8:00 AM-11:30 AM

Impact of metformin use in the outcomes of multiple myeloma patients post stem cell transplant. *First Author: Narjust Duma, Mayo Clinic, Rochester, MN*

Background: Multiple myeloma (MM), a monoclonal plasma cell disorder, is one of the most common hematologic malignancies in the US. In preclinical studies, metformin demonstrated plasma cells cytotoxicity. However, there is lack of studies translating the effect of metformin into the clinical setting. Therefore, we assessed the clinical effect of metformin in patients (pts) with MM. **Methods:** All MM pts who underwent stem cell transplant (SCT) at the Mayo Clinic Rochester from 2007 to 2012 were reviewed. Patients were grouped based on metformin use. Initial diagnosis at our institution and ≥12 months of follow up were required. Kaplan-Meier method and Cox regression were used for time-to-event and multivariate analysis. **Results:** Out of 687 pts, 78 (11.4%) were using metformin at the time of MM diagnosis. Baseline characteristics in the metformin (Mt) and no-metformin (NMt) groups were similar (Table). Median (M) metformin dose was 2000 mg daily and m duration of metformin use from MM diagnosis was 22 months. Pts on the Mt group achieved higher rates of CR after SCT (41% vs. 29%, p<0.02). Median PFS after SCT was longer in the Mt group, 31.3 months (95% CI: 10.4-52.2) vs. 16.6 months in the NMt group (95%CI: 14.5-18.7) p<0.04. There was a trend towards longer OS in the Mt group, but it was not statistically significant (170 vs. 106 months, p<0.10). In a multivariate analysis of metformin use, age, ISS, LDH, and cytogenetics/FISH, the former was an independent predictor of PFS after SCT (OR: 0.38, 95%CI: 0.20-0.68, p<0.001). **Conclusions:** Metformin use was associated with a better PFS and higher CR after SCT in our MM cohort. A trend towards better OS was also noted in the Mt group. Larger studies are needed to enhance our understanding of the clinic effect of metformin on MM.

Characteristics	Mt No./% (n=78)	NMt No./% (n=609)
Age (M)	61	61
Male	46/59	355/58
Creatinine (M)	0.9	0.9
International Staging System (ISS)		
I	22/28	135/22
II	19/24	175/29
III	15/19	107/18
Unknown	22/28	195/31
Plasma cells circulating index (M)	0.9	0.8
% Bone marrow plasma cells (M)	29	40
LDH (M)	185	184
FISH (normal karyotype)	68/88	533/88
Treatment with cyclophosphamide	16/21	125/21

8035 Poster Session (Board #361), Mon, 8:00 AM-11:30 AM

Synergism of gambogenic acid with bortezomib induce apoptosis of multiple myeloma. *First Author: Runzhe Chen, Department of Hematology and Oncology, Zhongda Hospital, Medical School, Southeast University, Nanjing, China*

Background: Multiple myeloma (MM) is one of the most common primary tumors of the bone marrow that accounts for approximately 10% of all hematological cancer. Gambogenic acid (GNA) is one of the natural compound isolated from gamboge and has demonstrated advantages such as a more potent anticancer effect and less systemic toxicity according to early investigations. In this study, we hypothesized that GNA could synergistically potentiate BTZ-induced apoptosis of MM cells and that combining BTZ and GNA may provide a more effective approach to treat MM. **Methods:** CCK-8 assay, CI isobologram, flow cytometry, western blot, xenograft tumour models, TUNEL and immunochemistry were used in this study to detect to possible mechanisms of apoptosis led by GNA and BTZ *in vitro* and *in vivo*. **Results:** The percentage of MM.1S in G2/M phase after 48h of 4.0nM BTZ, 0.90μM GNA and combination treatment were 31.09±2.16%, 26.68±1.96% and 19.88±1.89% respectively. The percentage of MM.1S in G2/M phase of control group was 17.23±1.65%. The apoptosis rates of MM.1S cells for 48h were 6.57±0.15% in control group, 89.67±5.15% after treatment with 4.0nM BTZ, 97.80±0.81% after treatment with 0.90μM GNA, and 98.9±3.86% after treatment with 4.0nM BTZ plus 0.9μM GNA respectively. All the treatment groups showed a more significant apoptosis rate compared to that of the control group ($p<0.01$). MM.1S tumors were implanted in BALB/Ca nu/nu male mice. The tumor weights of GNA and BTZ plus GNA groups decreased significantly when compared with those of control group ($p<0.01$ and $p<0.001$, respectively) and the tumor weight of combination group was significantly less than that of BTZ or GNA group ($p<0.001$). When mice were treated with BTZ combined with GNA, the tumor inhibition rate was 41.94%, whereas those of mice treated with BTZ or GNA alone were 9.68% and 19.35%, respectively. We also found that the combined treatment could induce more markedly increased apoptosis of MM.1S cells via the activation of PARP cleavage, P53, Caspase-3 cleavage and Bax and inhibition of Bcl-2 expression. **Conclusions:** Our data support that a synergistic antitumor activity exists between BTZ and GNA, and provide a rationale for successful utilization of dual BTZ and GNA in MM chemotherapy in the future.

8036 Poster Session (Board #362), Mon, 8:00 AM-11:30 AM

Daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): Efficacy and safety update (CASTOR). *First Author: Suzanne Lentzsch, Division of Hematology/Oncology, Columbia University, New York, NY*

Background: Daratumumab (D), a human, CD38-targeting mAb, is well tolerated and induces deep and durable responses in patients (pts) with RRMM. We provide an update of CASTOR (NCT02136134), a multicenter, phase 3, randomized study of DVd vs Vd in RRMM. **Methods:** All pts received ≥1 prior line of therapy (LOT) and were administered 8 cycles (Q3W) of Vd (1.3 mg/m^2 SC bortezomib on days 1, 4, 8, and 11; 20 mg PO/IV dexamethasone on days 1-2, 4-5, 8-9, and 11-12) ± D (16 mg/kg IV once weekly in Cycles 1-3, every 3 weeks for Cycles 4-8, then every 4 weeks until progression). Bortezomib-refractory pts were ineligible. Minimal residual disease (MRD) was assessed upon suspected CR and at 6 and 12 months following the first dose at sensitivities of 10^{-4}, 10^{-5}, and 10^{-6}using the ClonoSEQ assay (Adaptive Biotechnologies, Seattle, WA). **Results:** Pts received a median (range) of 2 (1-10) prior LOTs. 66% were previously treated with bortezomib and 21% were refractory to lenalidomide in their last prior LOT. After a median follow-up of 13.0 months, PFS was significantly prolonged with DVd vs Vd (median: not reached vs 7.1 months; HR, 0.33; 95% CI, 0.26-0.43; $P<$ 0.0001). This PFS benefit was seen regardless of number of prior LOTs received, with greatest benefit observed in 1 prior line pts (median: not reached vs 7.9 months; HR, 0.22; 95% CI, 0.14-0.34; $P<$ 0.0001). ORR was also significantly higher for DVd vs Vd (84% vs 63%), along with ≥VGPR (62% vs 29%) and ≥CR (26% vs 10%; $P<$ 0.0001 for all). MRD-negative rates were ≥4-fold higher at all three sensitivity thresholds with DVd vs Vd (10% vs 2% at 10^{-5} threshold). Pts who achieved MRD negativity demonstrated prolonged PFS compared with MRD-positive pts. 37 (15%) and 58 (24%) deaths were observed in DVd vs Vd, respectively, and follow up is ongoing. The most common grade 3/4 TEAE was thrombocytopenia (45% vs 33%). Updated efficacy and safety data will be presented. **Conclusions:** DVd provided significant benefits with respect to PFS, ORR, depth of response, and MRD-negative rate vs Vd. No new safety signals were reported. These data continue to support the use of DVd in RRMM pts and indicate that pts with 1 prior LOT will derive the most benefit. Clinical trial information: NCT02136134.

8037 Poster Session (Board #363), Mon, 8:00 AM-11:30 AM

CALGB/ECOG 100104 (Alliance) study: Lenalidomide (LEN) vs placebo (PBO) maintenance (maint) after stem cell transplant (SCT) for patients (pts) with multiple myeloma—Overall survival (OS) and progression-free survival (PFS) adjusted for treatment (tx) crossover (XO). *First Author: Philip L. McCarthy, Roswell Park Cancer Institute, Buffalo, NY*

Background: At a prespecified interim analysis (Dec 2009), the phase 3 CALGB study results surpassed the prespecified superiority boundary (significantly improved PFS for LEN maint vs PBO after SCT) and the majority of PBO arm pts without progressive disease (PD) crossed over to LEN maint. An updated analysis (cutoff Mar 2015), showed significantly longer OS with LEN maint (HR, 0.56; 95% CI, 0.42-0.76). We examined the effect of LEN vs PBO on OS and PFS from randomization, adjusting for XO effects. **Methods:** The rank-preserving structural failure time model (RPSFTM; Robins, *Commun Stat Theory Methods*, 1991) was used for XO adjustment; the iterative parameter estimation (IPE; Branson, *Stat Med*, 2002) algorithm was used as validation. Survival was portioned assuming a residual LEN effect after discontinuation. A landmark analysis was also performed at the Dec 2009 interim for pts who remained on Tx. **Results:** Pts were randomized to LEN maint (n = 231) and PBO (n = 229) (intent-to-treat [ITT] population); 76 pts without PD crossed over from PBO to LEN. Median time from randomization to XO was 11.5 mos. The relative Tx effect for OS and PFS increased for LEN vs PBO when adjusting for XO using RPSFTM and IPE (Table). The landmark analysis at the Dec 2009 interim (PBO XO, n = 76; No XO, n = 34) showed the Tx effect is not dissimilar to the ITT analysis (HR 0.53; 95% CI, 0.25-1.13). Sensitivity analyses showed consistent results. **Conclusions:** Adjusting for the potential diluting effects of XO reduced median OS and PFS with PBO, and improved the Tx effect in the ITT analyses for OS and PFS for LEN vs PBO maint after SCT. The statistical significance of the ITT analyses was maintained throughout. Support: U10CA180821, U10CA180882, CA180820. Clinical trial information: NCT00114101.

	OS[a]	PFS[a]
	LEN (n = 231) vs PBO (n = 229)	
ITT, Unadjusted	NR vs 79.0 0.56 (0.42-0.76)	58.4 vs 28.9 0.58 (0.46-0.73)
RPSFTM	NR vs 70.9 0.48 (0.34-0.69)[b]	58.4 vs 25.8 0.50 (0.39-0.63)[b]
IPE	NR vs 70.9 0.48 (0.33-0.68)[b]	58.4 vs 25.8 0.48 (0.36-0.63)[b]

[a]Data are median, mos; HR (95% CI). [b]Bootstrapped 95% CI.

8038 Poster Session (Board #364), Mon, 8:00 AM-11:30 AM

Daratumumab-based combination therapies (DCT) in heavily-pretreated patients (pts) with relapsed and/or refractory multiple myeloma (RRMM). *First Author: Arjun Lakshman, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Daratumumab-based Combination Therapies (DCT) with bortezomib (V)/ lenalidomide (R)/ pomalidomide (P) and dexamethasone (d) showed exceptional activity in RRMM in trials. Experience outside of trials since the approval of Daratumumab (D) in 2015 is limited. **Methods:** RRMM pts seen at Mayo Clinic, MN from 12/2015 -12/2016 were reviewed. Pts who received ≥ 1cycle of DCT were included. Time-to-event analyses were done from date of starting DCT. Common terminology criteria for adverse events v4.0 were used to grade toxicities. **Results:** Of 130 pts, 59% were males and median age at DCT initiation was 67 (43-93) years, ECOG performance score was ≥2 in 29%. Pts were classified as mSMART high (22%), intermediate (22%) or standard (56%) risk. Median time from diagnosis to initiation of DCT was 51.3 (5-156) months (m), and median number of prior therapies was 4 (1-14). 14% of pts were refractory to prior D monotherapy. Fifty-three (41%), 34 (26%) and 25 (19%) received DPd, DRd and DVd respectively. Eighteen (14%) pts received 'other' DCT. Median time to first response (≥ PR) was 3.1 m (95% CI 2.1-4.6). Overall response rate was 46%, [CR-2%, VGPR-18%, PR-26%]. Minimal response was seen in 17%, with clinical benefit rate of 62%. Median estimated follow up from initiation of DCT was 5.5 m (CI 4.2-6.1). The median duration of response was 6.1 m [CI 5.1- not reached (NR)]. Median progression free survival (PFS) was 5.5 m (CI 4.1-7.8) and median time to next therapy (TTNT) was 5.9 m (CI 4.6-9.4). Median PFS for DPd, DRd, DVd and other DCTs were 4.6 (CI 2.7-NR), 7.8 (CI 5-NR), 3.9 (CI 2.1-NR) and 3.9 (CI 2.8-8.2) m, respectively (p = 0.3). Median PFS for quadruple refractory (n = 28) MM was 2.8 m (CI 2.2-5.3) vs 5.9 m (CI 4.9-NR) for the rest ($p < 0.01$). Median overall survival (OS) from DCT was NR (CI 11.4-NR). Grade 3 or higher hematological toxicities were seen in 42% of pts. Other toxicities included infections (37%), fatigue (31%), infusion reactions (16%) and diarrhea (10%). **Conclusions:** DCT are effective in RRMM, but the PFS remains short particularly in quadruple refractory pts, reflecting the challenges encountered in managing heavily-pretreated, and often less fit patients, in routine practice.

8039 Poster Session (Board #365), Mon, 8:00 AM-11:30 AM

Semaphorin 4D to suppress bone formation in multiple myeloma. *First Author: Konstantinos Lontos, University of Pittsburgh Medical Center Department of Medicine, Pittsburgh, PA*

Background: Myeloma bone disease is characterized by osteoclast activation and long-term osteoblast suppression. We investigated if Semaphorin 4D (Sema4D; CD100) plays a role in these processes. Sema4D has been shown to be a potent osteoblast inhibitor (Negishi-Koga T et al, Nat Med. 2011). A study recently identified that the breast cancer cell line MDA-MB-231 utilizes Sema4D to create osteolysis (Yang Y et al, PLOS One 2016). There have been previous data that Sema4D is increased in the serum of myeloma patients (Terpos et al, Blood 2012) and that co-culturing myeloma cell lines with osteocytes increases the expression of Sema4D mRNA in both (Suvannasankha et al, Blood 2016). We sought to investigate if myeloma cells are using Sema4D to suppress bone formation and if they affect the levels of Sema4D produced by osteoclasts. **Methods:** We used lentivirus carrying shRNA for Sema4D or control (Scr) to knock down the level of the protein in the 5TGM1 murine myeloma cell line. Knockdown was verified by qPCR and Western Blot. We subsequently co-cultured the 5TGM1 cells with the MC3T3-subclone M4 (MC4) murine stromal cell line for 2 days, removed the myeloma cells and then differentiated the MC4 cells using ascorbic acid and β-glycerolphosphate. At day 5, we analyzed the cells for Runx2 (a critical gene for the differentiation of stromal cells into osteoblasts) expression utilizing qPCR. Also, we performed qPCR in primary osteoclast (OCL) mouse cells differentiating into OCL with RANKL with or without pre-treatment with myeloma-conditioned media for 3 days before the addition of RANKL. **Results:** When 5TGM1-Scr were co-cultured with MC4 cells the expression of Runx2 on day 5 was decreased (p=0.02). Strikingly, the 5TGM1-shSema4D cells when co-cultured with MC4s did not have the same effect and allowed the upregulation of Runx2 expression on day 5 (p=0.01). Myeloma-conditioned media increased Sema4D expression by OCL throughout the 5 days of differentiation 2 to 3-fold (p=0.01 for day 5). **Conclusions:** The myeloma cells seem to be utilizing Sema4D both directly and indirectly to inhibit bone formation. Targeted therapy against Sema4D may improve outcomes and fracture-free survival for multiple myeloma patients.

8040 Poster Session (Board #366), Mon, 8:00 AM-11:30 AM

Impact of post-autologous stem cell transplant (ASCT) maintenance therapy on outcomes in patients (Pts) with newly diagnosed multiple myeloma (NDMM) using the large prospective community-based Connect MM registry. *First Author: Sundar Jagannath, Mount Sinai Medical Center, New York, NY*

Background: Maintenance therapy (MT) improved progression-free survival (PFS) and overall survival (OS) in MM clinical trials. The observational Connect MM registry, which is largely community based, was used to assess impact of MT on outcomes in ASCT-eligible NDMM pts. **Methods:** Adult NDMM pts ≤60 days from diagnosis were eligible for enrollment. Pts receiving induction and ASCT were included and analyzed by 4 MT regimens: No MT, lenalidomide-based (LEN), bortezomib-based (BORT), and LEN+BORT MT. Duration was from 100 days post-ASCT (no MT group) or start of MT until progressive disease, death, discontinuation, or data cutoff. End points were PFS, 2nd PFS, OS, and safety. An exploratory analysis of the impact of baseline characteristics was performed. **Results:** Of 1493 enrolled pts (Cohort 1; Sep 2009 – Dec 2011), 1450 were treated; 81% (n=1173) were in a community setting. A total of 432 (29%) met analysis criteria. Data cutoff was Jan 7, 2016 (median follow-up of 39.3 mo). Median age was 60 y (range, 24-78 y); 60%, men; and 86%, white. 165 pts did not receive MT. Of 267 pts receiving MT, 213 (80%) received LEN; 30 (11%), BORT; and 16 (6%), LEN+BORT. Only LEN MT is presented, as interpretation of other MT data was limited by small sample sizes. Median treatment duration for LEN MT vs No MT was 35.2 vs 26.1 mo, respectively. PFS and OS significantly increased with LEN MT vs No MT (Table); 2nd PFS was similar for both. Exploratory analyses showed generally similar PFS and OS improvements across subgroups (age, ECOG status, ISS stage, risk group, and induction regimen). No new safety signals were observed. **Conclusions:** In ASCT-eligible NDMM pts, PFS and OS improved with LEN MT vs No MT and appeared to be independent of induction regimen. Preliminary analysis of 2nd PFS suggests no impact on the efficacy of 2nd line therapy. These data from a largely community-based setting confirm results from randomized phase III trials. Clinical trial information: NCT01081028.

	LEN (n = 213)	No MT (n = 165)	Hazard Ratio (95% CI)
Median PFS, mo	50.3	30.8	0.62 (0.46, 0.82) *P*= .0009
3-yr PFS	56%	42%	
Median OS, mo	NR	NR	0.54 (0.36, 0.83) *P*= .0050
3-yr OS	85%	70%	

CI, confidence interval; NR, not reached

8041 Poster Session (Board #367), Mon, 8:00 AM-11:30 AM

Rates of peripheral neuropathy (PN) in patients (Pts) with relapsed and refractory multiple myeloma (RRMM) treated with carfilzomib vs comparators in pivotal phase III trials. *First Author: Ruben Niesvizky, Center for Myeloma, New York Presbyterian Hospital-Weill Cornell Medical Center, New York, NY*

Background: PN is a dose-limiting toxicity for some anti-MM agents, such as the proteasome inhibitor (PI) bortezomib (V). Carfilzomib (K), a novel irreversible PI associated with low PN, was evaluated in 2 recent phase 3 studies in RRMM pts. **Methods:** This analysis evaluated PN rates in ASPIRE (K [27 mg/m^2]-lenalidomide [R]-dexamethasone[d] [KRd] vs Rd in relapsed MM; Stewart 2015) and ENDEAVOR (Kd [K 56 mg/m^2] vs Vd in RRMM; Dimopoulos 2016). We evaluated grade ≥2 PN during treatment, patient-reported outcomes (PROs; QLQ-C30 pain, FACT/GOG-neurotoxicity subscales), and progression-free survival (PFS) in pts with BL history of PN. **Results:** In ASPIRE, grade ≥2 PN rate was low (8.9% [KRd] vs 8.0% [Rd]; Table). Pain subscale scores were similar between arms. Median PFS was longer with KRd vs Rd for pts with BL grade ≥2 PN. In ENDEAVOR, grade ≥2 PN rate during the study (prespecified key secondary endpoint) was significantly lower with Kd vs Vd (6.0% vs 32.0%; Table). Pts had significantly improved pain and neurotoxicity subscale scores with Kd vs Vd. PFS improved with Kd vs Vd in pts with BL history of grade ≥2 PN (Table). **Conclusions:** In ENDEAVOR, Kd resulted in less PN vs Vd; in ASPIRE, PN rate was similar for KRd vs Rd. PFS was longer with KRd and Kd vs Rd and Vd, respectively, including in pts with BL grade ≥2 PN. Improved pain and neurotoxicity outcomes with K may be attributed to better disease control and/or lower PN rates. Clinical trial information: NCT01568866, NCT01080391.

PN, PROs, and PFS in ASPIRE, ENDEAVOR.

	ASPIRE		ENDEAVOR	
	KRd	Rd	Kd	Vd
Grade ≥2 PN during study, safety population, %	8.9	8.0	6.0	32.0
OR (95% CI)	1.132 (0.683, 1.876) *p*=0.6850		0.137 (0.089, 0.210) *p*<0.0001	
PRO, LS mean difference				
Pain: QLQ-C30 subscale, ITT (95% CI)	-1.02 (-3.77, 1.73) *p*=0.47		-2.35 (-4.30, -0.39) *p*=0.0186	
Neurotoxicity: FACT/GOG-NTx subscale, safety population (95% CI)	–		0.84 (0.40, 1.28) *p*=0.0002	
PFS by BL history of PN, ITT				
Yes, n	144	137	215	244
Median (95% CI), mo	23.2 (18.0, 25.9)	17.6 (13.9, 26.0)	18.7 (13.88, NE)	9.4 (7.53, 10.39)
HR (95% CI)	0.947 (0.692, 1.296)		0.54 (0.410, 0.715)	
Grade ≥2, n	22	24	71	81
Median (95% CI), mo	24.2 (19.6, NE)	14.8 (7.4, NE)	18.6 (10.20, NE)	5.6 (4.47, 7.40)
HR (95% CI)	0.695 (0.321, 1.507)		0.42 (0.266, 0.677)	

8042 Poster Session (Board #368), Mon, 8:00 AM-11:30 AM

Comparative efficacy of multiple myeloma therapies for treatment of first relapse: A systematic literature review and network meta-analysis. *First Author: Eric M Maiese, Janssen Scientific Affairs, LLC, Horsham, PA*

Background: Treatment for multiple myeloma (MM) in the US has undergone significant advances, with several new therapies recently FDA approved for relapse/refractory MM (RRMM), including carfilzomib+lenalidomide+dex (KRd), carfilzomib+dex (Kd), daratumumab+lenalidomide+dex (DRd), daratumumab+bortezomib+dex (DVd), ixaxomib+lenalidomide+dex (IRd), and elotuzumab+lenalidomide+dex (ERd). These new therapies have shown improvements in clinical outcomes in randomized controlled trials (RCTs). However, with few head-to-head RCTs, there is little comparative evidence to determine the most effective treatment for specific patients. A systematic literature review (SLR) and network meta-analysis (NMA) was conducted to determine the comparative efficacy (progression free survival (PFS)) of MM therapies for treating first relapse. **Methods:** The SLR searched MEDLINE, Embase, and the Cochrane Library for RCTs investigating the efficacy of treatments for RRMM (to August 2016). NMA was conducted on the PFS hazard ratios (HR), where available in RCTs for patients with one prior line of treatment, using Bayesian fixed effects mixed treatment comparisons. **Results:** Data formed two evidence networks. Network 1: RCTs with Rd; Network 2: RCTs with Vd. Analyses found DRd and DVd had the highest probability of being the best treatment (0.96 and 0.89, respectively). Compared to other MM therapies, DRd and DVd had the lowest risk of progression or death (PFS HR <1.0) (Table 1). For example, compared to KRd, DRd had a 41% (PFS HR 0.59) reduced risk of progression or death. **Conclusions:** This analysis provides comparative evidence among treatments where head-to-head RCTs have not been conducted. For treating first relapse, compared to other MM treatments, this analysis found that DRd and DVd had the highest probability of providing the longest progression free survival.

NMA results.

Treatment	PFS HR (95% Credible Interval)
Network 1 - DRd Compared to:	
KRd	0.59 (0.35, 1.01)
ERd	0.55 (0.31, 0.95)
IRd	0.49 (0.29, 0.84)
Rd	0.41 (0.26, 0.65)
Network 2 - DVd Compared to:	
Kd	0.69 (0.37, 1.25)
Vd	0.31 (0.18, 0.52)

8043 Poster Session (Board #369), Mon, 8:00 AM-11:30 AM

Outcomes of secondary cancers among myeloma survivors. *First Author: Jorge J. Castillo, Dana-Farber Cancer Institute, Boston, MA*

Background: With increasing survival, myeloma patients (pts) experience second cancers. We analyzed receipt of surgery and cancer-specific survival (CSS) among myeloma survivors with common solid tumors, in comparison with pts without myeloma. **Methods:** We extracted Surveillance, Epidemiology, and End Results (SEER) data on pts diagnosed with common cancers in 2004-2013. Among them, we identified myeloma survivors, and we matched each to 50 randomly sampled controls with the same cancer by age, sex, race, and year of diagnosis. We then compared CSS, cumulative incidence function (CIF) for death from the index cancer (but not from myeloma), and receipt of surgery (for non-metastastic, stage-matched tumors only) using a Cox (for hazard ratio, HR), Fine-Gray (for subhazard ratio, SHR), and conditional logistic models, respectively. **Results:** Myeloma survivors were significantly older (*P*<.001), and more often black (except in bladder cancer) than pts with respective cancers from the general population. In the case-control analysis, breast (*P*=.002) and lung cancers (*P*=.003) were more often diagnosed at an early stage among myeloma survivors. Receipt of surgery did not significantly differ, except for lower use of prostatectomy in myeloma survivors (odds ratio, 0.59, 95%CI, 0.44-0.81). CSS significantly differed only in lung cancer, and was better among myeloma survivors even when stratified by stage. CIF of cancer death was significantly lower for myeloma cases with lung and colorectal cancer. **Conclusions:** Despite additional competing mortality from recurrent myeloma, myeloma survivors have similar CSS and CIF of death after common cancers compared with other pts. This highlights the need to treat them similarly to other pts, without assuming a poor prognosis. Better outcomes in lung cancer are not fully explained by earlier detection, suggesting a biological difference.

Cancer	*N* myeloma survivors	Median time from myeloma (mo.)	CSS		CIF of cancer death	
			HR	95%CI	SHR	95%CI
Breast	189	40	0.99	0.61-1.61	0.82	0.50-1.35
Prostate	330	40	0.91	0.55-1.49	0.76	0.46-1.25
Lung	286	36	0.64*	0.54-0.75	0.52*	0.44-0.61
Colorectal	198	40	0.86	0.63-1.17	0.67*	0.49-0.91
Melanoma	140	50	0.75	0.40-1.42	0.59	0.32-1.10
Bladder	133	35	0.81	0.50-1.31	0.64	0.40-1.03

* *P*<.05

8044 Poster Session (Board #370), Mon, 8:00 AM-11:30 AM

Racial differences in abnormalities by FISH in minorities with multiple myeloma: A single-center experience. *First Author: Miguel Gonzalez Velez, Rutgers New Jersey Medical School, Newark, NJ*

Background: Racial disparities of FISH abnormalities in multiple myeloma (MM) have been well described in whites (W) but partially described in minorities (M) (Paulus et al, ASH 2016, 4432). We aimed to explore racial-based differences of FISH abnormalities using the largest cohort of m to date. **Methods:** CD-138 selected FISH was done on 799 consecutive patients (pts). Pts without symptomatic MM, and biopsy >6 months after diagnosis were excluded. The abnormalities evaluated included standard and intermediate risk: IGH rearrangements (IGH r), t(4;14), t(11;14), and high risk: t(14;20), t(14;16), del13q, del 17p, 1q21. Chi-square was used for statistical analysis. Due to smaller numbers, all m (Hispanic (H), Black (B), Asian (A) and Other (O)) were included into the same group for statistical analysis. **Results:** 482 pts were eligible, 343 (71%) were W, 52 (10%) H, 50 (10%) B, 19 (3%) A, and 18 (3%) O. Median age was 65 years, 54% were male, and 26% ISS stage 3. There were no were no statistically significant differences in FISH abnormalities between the m (Table1). Overall W had more abnormalities in IGH r, t(4;14), t(11;14), t(14:20), 1q21 gain compared to M. Most notably W had more IGH r (39% vs 28%; p=0.019) and t(11;14) (20% vs 12%; p=0.024). There were no statistically significant differences between W and m in the high risk FISH abnormalities. **Conclusions:** We had significant differences in FISH compared to M. W had more IGH r and t(11;14) than M, and there was no difference in high risk FISH abnormalities between W and M. This study confirms the biological racial disparities that exist in minorities with MM. Further studies with more inclusion of minorities are needed to elucidate these disparities and its effects on risk stratification and outcomes.

$ p-value compares W vs M.

FISH, n (%)	W		H		B		A		O		M		
Total n=482	343		52		50		19		18		139		p-values$
IGH r	135	39%	16	30%	15	30%	4	21%	4	22%	39	28%	<0.019*
t(4;14)	35	10%	4	7%	2	4%	2	10%	2	11%	10	7%	0.39
t(14;16)	21	6%	1	1%	5	10%	0	-	0	-	6	4%	0.43
t(14;14)	72	20%	7	13%	8	16%	2	10%	0	-	17	12%	<0.024*
t(14;20)	6	1%	0	-	0	-	0	-	0	-	0	-	0.11
Del 13q	96	27%	16	30%	18	36%	2	10%	9	50%	45	18%	0.33
Del17p	159	45%	21	40%	22	44%	8	42%	11	61%	62	44%	0.72
1q21 gain	119	34%	12	23%	12	24%	7	36%	7	38%	38	27%	0.11

* means statistical significant (p-value < 0.05).

8045 Poster Session (Board #371), Mon, 8:00 AM-11:30 AM

AFM26 is a novel, highly potent BCMA/CD16A-directed bispecific antibody for high affinity NK-cell engagement in multiple myeloma. *First Author: Thorsten Gantke, Affimed GmbH, Heidelberg, Germany*

Background: Despite recent advances in the treatment of multiple myeloma (MM), novel therapies are needed to achieve long-lasting remissions in a greater number of patients. Natural killer (NK) cells play a key role in the immune response to MM and have been implicated in the clinical efficacy of current standard of care interventions, including IMiDs, proteasome inhibitors, recently approved immunotherapies and autologous stem cell transplantation (ASCT). Numerous strategies are being developed to enhance the natural NK-cell cytotoxicity against myeloma cells, which is frequently dysregulated in MM. Approaches include modulation of activity, through cytokine stimulation or immune checkpoint targeting, and adoptive transfer of culture expanded NK-cells in ASCT-eligible MM. While highly attractive, these approaches are non-targeted, as they rely on the natural cytotoxicity of NK-cells, and may benefit from antigen-specific retargeting and effector activation. AFM26 is a novel tetravalent, bispecific antibody designed to specifically enhance NK-cell anti-MM activity by redirecting NK-cell lysis to BCMA, an antigen expressed on MM cells. **Methods:** NK-cell engagement and cytotoxicity of AFM26 towards MM cell lines and freshly isolated tumor cells from MM patients was characterized *in vitro* and compared with classical antibody formats. **Results:** AFM26 engages NK-cells with superior avidity (K_D: 1-2nM) through bivalent interaction with CD16A (FcγRIIIa) and demonstrates extended cell surface retention that is not affected by high level IgG, as is particularly relevant in MM. Importantly, AFM26 does not induce NK-cell depletion but selectively induces potent and efficacious lysis of MM cells *in vitro*. **Conclusions:** In summary, AFM26 is a promising candidate to enhance NK-cell activity and confer tumor-specificity to NK-cells in MM. Differentiation of AFM26 from classical antibody formats and its potential for combination with cellular NK-cell therapies is highlighted.

8046 Poster Session (Board #372), Mon, 8:00 AM-11:30 AM

Trends in survival and costs among US multiple myeloma patients. *First Author: Eric M Maiese, Janssen Scientific Affairs, LLC, Horsham, PA*

Background: Survival among multiple myeloma (MM) patients has improved over time, but little is known about concurrent changes in healthcare costs. This study examined trends in both survival and healthcare costs over the same time periods in US MM patients. **Methods:** The MarketScan Commercial and Medicare claims dataset was used to identify 5199 adult patients diagnosed with MM from Jan. 2006 to Dec. 2014. Patients had no prior evidence of cancer, were continuously enrolled for >12 months prior to MM diagnosis, and were followed through the earliest event (death, end of enrollment, or end of the study period (9/30/2015)). Multivariate GLM and Cox proportional hazards models estimated healthcare costs and survival probabilities, respectively, for two time periods during which patients were diagnosed with MM (2006-2010 vs 2011-2014) while controlling for demographic and clinical characteristics. The recycled prediction method was used to calculate the incremental cost estimates between the time periods. **Results:** Patients diagnosed in 2011-2014 had a 35% lower risk of death compared to those diagnosed in 2006-2010 (HR [95% CI] = 0.65 [0.57-0.74]. Patients diagnosed in 2011-2014 had 18% (95% CI: 6-31%) higher all cause and 26% (95% CI: 6-50%) higher MM-related per patient per month costs compared to those diagnosed in 2006-2010 (Table). **Conclusions:** Among MM patients, survival has improved at a greater rate than the increase in healthcare costs. In addition to improvements in MM treatment, changes in overall disease management may have contributed to both the increased expenditures and survival improvements observed in this study.

Healthcare costs, by time period of diagnosis.

	2006-2010 (N=2597)	2011-2014 (N=2602)	Cost Ratio
Adjusted* all-cause healthcare costs,** mean (SD)	$13,960 ($5213)	$16,449 ($6142)	1.18^
Adjusted* MM-specific healthcare costs, ** mean (SD)	$7,476 ($5524)	$9,422 ($1438)	1.26^

*Adjusted for age, sex, insurance provider, geographic region, MM treatments, pre-index healthcare costs, baseline comorbidity index, and baseline number of comorbid diagnoses. **Costs per patient per month. ^p<0.01 for time periods 2011-2014 vs 2006-2010.

8047 Poster Session (Board #373), Mon, 8:00 AM-11:30 AM

Risk stratification by detection of clonal circulating plasma cells (CPCs) by multi-parametric flow cytometry (MFC) in light chain amyloidosis (AL). *First Author: Surbhi Sidana, Mayo Clinic, Rochester, MN*

Background: Presence of CPCs by six color MFC is associated with worse outcomes in multiple myeloma (MM). Using a slide based immunofluorescence assay, CPCs are associated with worse prognosis in AL, but outcomes with MFC are not known. **Methods:** We retrospectively analyzed 154 patients (pts) from Jan 2008 – Dec 2015 with AL who had CPCs analyzed by MFC at diagnosis. **Results:** CPCs were present in 42% pts (n = 64, median = 88 per 150,000 events, range 6-17844). Table 1 lists baseline characteristics, treatment and response. In univariate analysis, bone marrow (BM) plasma cells > 15% (p<0.0001), dFLC > 60 mg/dL (p=0.02) and presence of active MM (p=0.0004) were associated with detectable CPCs. In multivariate (MV) model, only BM plasma cells > 15% predicted for presence of CPCs (p=0.02). There was no difference in hematologic or organ response in the 2 groups. Median follow up was 43 months (m). Pts with detectable CPCs had worse survival than those without detectable CPCs (90 m vs. 98 m, p=0.0004). In MV analysis model with Mayo Stage and detectable CPCs, presence of CPCs at diagnosis was independently associated with poor survival (CPCs p= 0.02, Mayo Stage p < 0.0001). **Conclusions:** Presence of detectable CPCs is an independent adverse prognostic factor for survival in AL. Comparatively fewer pts with detectable CPCs underwent early ASCT, which may reflect a more aggressive disease presentation.

	CPCs Present N=64	CPCs Absent N=90	P value
Median age	63 years	62 years	0.8
Cardiac involvement	61% n=39	56% n=50	0.5
Renal involvement	58% n=36	62% n=56	0.6
Liver involvement	8% n=59	11% n=10	0.48
Mayo Stage	.	.	0.13
1	26% (n=16)	43% (n=38)	
2	28% (n=17)	24% (n=21)	
3	15% (n=9)	16% (n=14)	
4	31% (n=19)	18% (n=16)	
Median dFLC (mg/dL)	41	16	0.037
Median BM plasma cells	15%	10%	<0.0001
Active MM	30% n=19	8% n=7	0.0004
Treatment	.	.	
ASCT based	51%(n=31)	72% (n=63)	
Bortezomib based	17% (n=10)	22% (n=19)	
Alkylator/IMiD	30% (n=18)	6% (n=5)	
None	4% (n=2)	.	
Early ASCT	54% n=32	75% n=65	0.01
Response			
>PR	85% (n=28, N=31)	88% (n=58, N=66)	0.68
>VGPR	64% (n=21)	65% (n=43)	0.88
Cardiac response	47% (n=9, N=19)	57% (n=10, N=25)	0.49
Median time to cardiac response (m)	8.8	9	0.98
Renal response	79% (n=19, N=24)	74% (n=36, N=49)	0.59

8048 Poster Session (Board #374), Mon, 8:00 AM-11:30 AM

Factors predicting organ response in light chain amyloidosis (AL). *First Author: Surbhi Sidana, Mayo Clinic, Rochester, MN*

Background: Organ response (OR) in AL is often delayed and difficult to predict early. **Methods:** We retrospectively analyzed 1308 patients (pts) with newly diagnosed AL from 2006 – 2015 to determine factors which could predict for OR. **Results:** Median age was 64 years (yr) and Mayo Stage was: 1 (22%); 2 (23%); 3 (25%); 4 (31%). Organ involvement was: cardiac (74%, n=932); renal (59%, n=738), liver (16%, n=205); gut (24%, n=310) and autonomic (12%, n=152). 59% (n=765) had > 1 organ involved, including 43% (n=567) with > 1 critical organ (heart, kidney, liver) involved. Treatment was: ASCT based (28%, n=330, N=1186), bortezomib based (24%, n=281), alkylator based (33%, n=392), others (5%, n=54) and none (10%). In evaluable pts, VGPR or better rates were: 53% at 6 months (m) (N=625), 72% at 12 m (N=465) and 57% overall (N=688). Table 1 lists OR at various time points. Complete OR in all involved critical organs was seen in: 51% (n=308, N=600), partial response (at least 1 OR when >1 organ involved) in 12% (n=73) and none in 37% (n=219). Complete OR was associated with better overall survival (OS) than partial or no OR (median OS: not reached vs 42 m vs 29 m; P <0.0001). In multivariate model the following variables at baseline or 1 yr mark were predictive of complete OR: lower Mayo Stage (p=0.01), fewer critical organs involved (p=0.007), higher baseline GFR (p=0.03), female sex (Complete OR 60% vs 47%; p=0.04) and VGPR at 1 yr (Complete OR 70% vs. 36%; p <0.0001). Other factors included in the model were age (p=0.9), bilirubin (p=0.1) and transplant (p=0.2). All aforementioned factors were significant in univariate analysis. **Conclusions:** Achievement of response in all involved critical organs is associated with better survival in AL pts than partial or no OR. Various baseline factors and VGPR at 1 yr can predict for achieving complete OR, with 70% pts who achieve VGPR at 1 yr having a complete OR.

Organ response.

	Cardiac Response	Renal Response	Liver Response
At 6 m	17% (n=88, N = 498)*	31% (n=135, N=433)*#	25% (n=22, N=110)*
At 12 m	24% (n=123, N=504)*	40% (n=167, N=421)*#	26% (n=27, N=105)*
Overall OR (in evaluable pts)	50% (n=195, N=394)	67% (n-274, N=409)	43% (n=39, N=90)
Median time	7.7 m	6.4 m	5.8 m

*Including pts who died at landmark time-point #Excluding pts on dialysis at diagnosis

8049 Poster Session (Board #375), Mon, 8:00 AM-11:30 AM

Outcomes according to involved free light chain (FLC) levels in patients with normal FLC ratio after initial therapy in light chain amyloidosis (AL). *First Author: Nidhi Tandon, Mayo Clinic, Rochester, MN*

Background: Complete response in AL is defined as normal FLC ratio with negative serum and urine immunofixation. It is not clear if high involved serum FLC (hIFLC) in a patient with normal ratio may contribute to ongoing amyloid formation and hence affect outcomes. **Methods:** Data of 1308 patients (pts) with systemic AL seen within 90 days of diagnosis, at Mayo Clinic between 2006-2015, was analyzed retrospectively. Among these, 369 pts had 2 consecutive normal FLC ratio values after 1st line treatment and form the study population. Log rank test was used to estimate survival differences. **Results:** Among these 369 pts, pts with hIFLC at 1st reading of normal FLC ratio (hIFLC1; n=170; 46.1%) were compared to those who did not (n=199; 53.9%). At diagnosis, the median age [61.5 vs 60.8 years (y); p=0.2], proportion of males (62.4 vs 58.3%; p=0.4), percentage of pts with renal involvement (73.5 vs 64.8%; p=0.07), in mayo stage I / II / III / IV (32.9% / 23%/ 27.3% / 16.8% vs 43.6 %/ 22.9% / 18.1% / 15.4%; p=0.1), with bone marrow plasma cells >10% (24.2 vs 30%; p=0.2) and with presence of t(11; 14)(48.4 vs 60; p=0.08) was similar, while cardiac (67.5 vs 53.3%; p=0.006) and hepatic (18.2 vs 9.1%; p=0.01) involvement was higher in hIFLC1 group. The median follow-up from diagnosis was 6.1 y (95% CI; 5.6, 6.8). The median progression free survival (PFS) in pts who had hIFLC1 was lower than for those who did not; 2.6 y (95% CI; 1.9, 4.5) vs 5.2 y (95% CI; 4.6, 6.4), p<0.0001, as was the median overall survival [OS; 6.7 y (95% CI; 4.5, 8.3) vs not reached (NR), p<0.0001]. We performed a more stringent comparison for pts with 2 consecutive hIFLC values (hIFLC2; n=112; 30.4%) versus not (n=257; 69.6%). The median PFS (3.2 y; 95% CI; 2.2, 4.5 vs 5.6 y; 95% CI; 4.7, 7.1; p<0.0001) and OS (7.8 y; 95% CI; 6.4, NR vs NR; 95%CI; 9.5, NR; p<0.0001) were significantly reduced in pts with hIFLC2 versus not as well. A multivariate analysis confirmed an impact of hIFLC1 and hIFLC2 on PFS/OS independent of serum creatinine. **Conclusions:** In pts with systemic AL, persistent elevation of the involved FLC predicts for poor prognosis (independent of serum creatinine) even among those who achieved normal FLC ratio after 1st line treatment.

8050 Poster Session (Board #376), Mon, 8:00 AM-11:30 AM

Treatment approaches and outcomes in extramedullary plasmacytomas. *First Author: Gaurav Goyal, Creighton University Medical Center, Omaha, NE*

Background: There is a lack of contemporary studies analyzing the optimum radiation dose and prognostic factors for outcomes of extramedullary plasmacytomas. In this study, we aim to answer these questions by utilizing the National Cancer Data Base (NCDB). **Methods:** This is a retrospective study of patients with histologically confirmed diagnosis of plasmacytoma from 2000-2011 using NCDB. Patients who had bone marrow involvement were excluded from the analysis. Hazard ratios were calculated using the Cox-proportional hazard method. In addition, we utilized survival trees as a novel tool for assessing prognostic effect of factors among four age quartiles (Q): Q1: 18-52, Q2:52-62, Q3:62-72, and Q4: ≥72 years. **Results:** A total of 5,056 patients were included in the study (median age 62 years; range, 52-72 years). Of these, 63% were males. Radiation therapy was received by 3,905 patients, with a median radiation dose of 45 Gy. A radiation dose of ≥40 Gy was associated with improved overall survival (OS) as compared to <40 Gy. Factors associated with worse OS included older age (≥65 years) and bone disease (Table). In survival tree analysis, radiation dose ≥44.5 Gy was associated with better OS in Q1 as compared to lower dose. For Q2 and Q3, disease location played a major role, with improved survival seen in upper aero-digestive and lymph node disease as compared to bone and soft tissue. In Q3, among the bone and soft tissue disease, radiation dose ≥ 43.5 Gy was associated with the better survival as compared to ≤43.5 Gy. In Q4, soft tissue and upper aerodigestive plasmacytomas had better outcomes as compared to bone and lymph node disease. Among the latter group, a radiation dose ≥30.3 Gy was associated with improved OS as compared to lower dose. **Conclusions:** This is the largest study of extramedullary plasmacytomas in the United States. This study shows that dose of radiation has a significant impact on outcomes, in addition to disease location and age.

Factors affecting survival in extramedullary plasmacytoma.

Prognostic variable	Hazard ratio	95% CI
Age ≥65 vs. younger	3.41	2.95, 3.93
Plasmacytoma bone vs. other	1.59	1.35, 1.87
Radiation dose ≥40 Gy vs. <40 Gy	0.21	0.07, 0.65

TPS8051 Poster Session (Board #377a), Mon, 8:00 AM-11:30 AM

Phase 1 study to evaluate the safety and efficacy of immunotherapy with tremelimumab and durvalumab in multiple myeloma patients receiving high dose chemotherapy and autologous stem cell transplant (HDT/ASCT) + peripheral blood lymphocyte (PBL) reinfusion. *First Author: Alexander M. Lesokhin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Multiple myeloma (MM) remains an incurable hematologic malignancy despite the advent of new classes of drugs, including immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies. The success and synergistic activity of immunotherapy (IMT) in solid tumors and hematologic malignancies has fueled their investigation in MM. HDT/ASCT as consolidation or as treatment for relapse remains a cornerstone for improving overall survival. HDT/ASCT transiently eliminates immune-suppressive cell populations and provides a viable IMT platform. Reinfusion of PBLs harvested pre-HDT induces immune responses, supporting its inclusion in IMT combinations. This study evaluates the effect of IMT, using tremelimumab (T), an anti-CTLA-4 monoclonal antibody, and durvalumab (D), an anti-PD-L1 monoclonal antibody, together with autologous PBL reinfusion and starting T ± D at Day 100 and earlier (Day 30) post-ASCT. **Methods:** This ongoing Phase 1, open-label, multicenter study (NCT02716805) evaluates the safety and preliminary efficacy of T and D administered on 2 schedules in MM patients at high risk for relapse as outlined below. Cohort initiation requires dose-limiting toxicity in < 2/6 patients in the previous cohort. The primary endpoint is safety. Secondary endpoints are objective response rate per IMWG, minimal residual disease, progression free and overall survival, and 100-day ASCT-related mortality. Exploratory endpoints include immunological effects and immune response. Enrollment opened 18 Nov 2016. As of 31 Dec 2016, 1 patient is enrolled in Cohort 1; enrollment is ongoing. Clinical trial information: NCT02716805.

Cohort (n=6)	Day -31	Treatment (Day)	Cycle 1*		Cycle 2		Cycles 3-8
1	T	LEU (-10)	Day 100	T	Day 100 +4 weeks	T	D
2	T	HDT (-2)	Day 30	T	Day 100	T	every
3	T + D	ASCT (0)	Day 100	T + D	Day 100 +4 weeks	T + D	4 weeks
4	T + D	PBL reinfusion +T (3)	Day 30	T + D	Day 100	T + D	

Doses: T = tremelimumab 75 mg; D = durvalumab 1500 mg; HDT = melphalan 200 mg/m^{2}IV LEU = leukapheresis
*T ± D starting at either 100 or 30 days post-HDT/ASCT + PBL

TPS8052 Poster Session (Board #377b), Mon, 8:00 AM-11:30 AM

CheckMate 602: An open-label, randomized, phase 3 trial of combinations of nivolumab, elotuzumab, pomalidomide and dexamethasone in relapsed/refractory multiple myeloma. *First Author: Sagar Lonial, Winship Cancer Institute, Atlanta, GA*

Background: Multiple myeloma (MM) cells may evade immune surveillance by suppressing immune responses through the PD-1 pathway, via upregulation of PD-L1.[1]Nivolumab (nivo), a PD-1 immune checkpoint inhibitor that blocks PD-L1 interaction and disrupts MM-mediated PD-1 signaling, demonstrated modest activity as monotherapy in patients (pts) with relapsed/refractory multiple myeloma (RRMM) in a phase 1b study.[2] Pomalidomide, an immunomodulatory drug (IMiD), may sensitize MM cells to PD-1 blockade, and has shown efficacy with dexamethasone (Pd) for RRMM. Elotuzumab (elo), an anti-SLAMF7 monoclonal antibody, directly activates natural killer cells and facilitates antibody-dependent cell-mediated cytotoxicity. Preclinical work suggests PD-1 blockade may enhance elo efficacy[3]; thus nivo + Pd + elo may increase clinical benefit. **Methods:** CheckMate 602 (NCT02726581) is a phase 3, open-label, randomized study of efficacy and safety of nivo + Pd (N-Pd) vs Pd in pts with RRMM. Nivo combined with elo + Pd (NE-Pd) will be evaluated in an exploratory arm. Eligible pts must have measurable MM after ≥2 prior lines of therapy (LoTs) that included an IMiD and proteasome inhibitor, each for ≥2 consecutive cycles, alone or combined, and be refractory to their last LoT. Pts with prior elo are eligible. A planned 406 pts will be randomized 3:3:1 to N-Pd, Pd and NE-Pd, stratified by LoT (2 vs 3+) and International Staging System disease stage (I–II vs III). Pts in the Pd arm may cross over to the NE-Pd arm at disease progression. Pts are enrolled at 119 sites in 13 countries. Coprimary endpoints (N-Pd and Pd arms): objective response rate (ORR) and progression-free survival (PFS), assessed by an independent review committee. Secondary endpoints (N-Pd and Pd arms): time to response, duration of response, investigator-assessed ORR and PFS. Exploratory endpoints include ORR and PFS (NE-Pd arm), and safety/tolerability and minimal residual disease status (all arms). 1. Liu et al. *Blood* 2007;110: 296–304 2. Lesokhin et al. *JCO* 2016;34:2698–704 3. Bezman et al. *Haematologica* 2016;101:161–2 [S450] Study support: BMS. Writing support: A Gill, Caudex, funded by BMS. Clinical trial information: NCT02726581.

TPS8053 Poster Session (Board #378a), Mon, 8:00 AM-11:30 AM

A phase Ib study of atezolizumab (atezo) alone or in combination with lenalidomide or pomalidomide and/or daratumumab in patients (pts) with multiple myeloma (MM). *First Author: Hearn J. Cho, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: The advent of proteasome inhibitors and immunomodulatory drugs (IMiDs) have significantly improved outcomes in MM, and the first monoclonal antibodies for MM have been recently approved (daratumumab, elotuzumab). Despite novel therapies and improved disease management, MM is still considered incurable and most pts relapse, confirming the need for additional treatment options. MM cells express PD-L1, with higher levels observed after relapse and with advanced disease. Additionally, PD-L1–expressing immune cells in the microenvironment promote MM cell survival and potential immune escape. However, anti–PD-1 monotherapy did not result in objective responses in the MM cohort of a Ph I study, suggesting that MM pts need combination therapy. Daratumumab has activity as a single agent, as well as in combination with IMiDs plus dexamethasone and bortezomib plus dexamethasone in R/R MM. Immunomodulatory activity for daratumumab has also been reported. Thus, disruption of the PD-L1/PD-1 pathway may be additive or synergistic. The safety and efficacy of atezo (anti–PD-L1) alone or with lenalidomide or pomalidomide and/or daratumumab will be evaluated in a Ph Ib study of MM pts. NCT02431208. **Methods:** R/R MM pts with ≤ 3 prior therapies will be enrolled in Cohorts A (atezo), B (atezo + lenalidomide), D (atezo + daratumumab) and E (atezo + daratumumab + lenalidomide); MM pts with measurable disease after ASCT (Cohort C: atezo) or ≥ 3 prior therapies (Cohort F: atezo + daratumumab + pomalidomide) will also be enrolled. Cohorts B, D, E and F include a safety run-in (D) or dose escalation phase (B, E, F) and an expansion. Lenalidomide and pomalidomide will be dose escalated and the MTD evaluated in expansion phases. Atezo will be given at 1200 mg IV (A, B, C) or 840 mg IV (D, E, F); pts will get daratumumab at 16 mg/kg IV (D, E, F). All pts will be ECOG PS ≤ 2. Primary endpoints are ORR and the RP2D of lenalidomide and pomalidomide with atezo and daratumumab and the RP2D of lenalidomide with atezo. DOR and PFS are secondary endpoints; safety, PK and the relationship between biomarkers and other endpoints, including efficacy, will be assessed. Pts will be enrolled at 19 US sites. Clinical trial information: NCT02431208.

TPS8054 Poster Session (Board #378b), Mon, 8:00 AM-11:30 AM

Durvalumab (DURVA) plus daratumumab (DARA) in patients (pts) with relapsed and refractory multiple myeloma (RRMM). *First Author: Paul G. Richardson, Dana-Farber Cancer Institute, Boston, MA*

Background: DARA, a monoclonal antibody (mAb) against CD38, is approved for RRMM. Combination treatment (Tx) with DARA + DURVA, a mAb against programmed death ligand-1 (PD-L1), may enhance host anti-MM immunity and response. DARA and PD-L1 mAbs have each demonstrated clinical activity in combination with pomalidomide (POM) + low-dose dexamethasone (LoDEX) in MM. Thus, the phase 2 MEDI4736-MM-003 trial is evaluating DURVA + DARA in RRMM, and, in an exploratory analysis, the addition of POM + LoDEX to DARA + DURVA either upon progressive disease (PD) with DARA + DURVA or as up-front Tx will be assessed. **Methods:** ≈ 144 pts with RRMM are being enrolled. Pts with measurable MM who received ≥ 3 prior anti-MM Txs, including a protease inhibitor and an immunomodulatory agent, or are double-refractory to these 2 agents will be included. Exclusion criteria include allogeneic stem cell transplant (SCT), autologous SCT ≤ 12 weeks, and prior DARA or other CD38 antibody therapies. Primary endpoints are overall response rate (ORR) and safety. Secondary endpoints are time to response, duration of response, progression-free survival, and pharmacokinetics. The study includes a 3 + 3 safety run-in phase to confirm the tolerability of the recommended phase 2 doses (RP2Ds) of DURVA and DARA. Dose-limiting toxicities will be evaluated during the first Tx cycle. Safety and efficacy will be assessed by a Simon 2-stage design (Table). POM + LoDEX may be added to DARA + DURVA in pts who received ≥ 2 cycles of DARA + DURVA and had confirmed PD. Based on preliminary safety and efficacy, the 4-drug regimen may be explored as up-front Tx. Tx with either the 2- or 4-drug regimens will continue until PD or unacceptable toxicity. Pts treated with POM will be followed for second primary malignancies every 6 mos until the end of the trial. To date, 6 pts have enrolled in the run-in phase. Clinical trial information: NCT02807454.

Study Drug in 28-d Cycles	Safety Run-In	Stage 1 (RP2D)	Stage 2[a]	Exploratory	Expansion
DURVA		1500 mg (can be de-escalated to 750 mg) C1 D2; C2+ D1 or D2			
DARA		16 mg/kg C1-2 D1, 8, 15, 22; C3-6 D1, 15; C7+ D1			
POM		—		4 mg/day D1-21	
LoDEX		—		40 mg (20 mg if > 75 yrs old) D1, 8, 15, 22	

C, cycle. [a] If minimum ORR threshold met in Stage 1

TPS8055 Poster Session (Board #379a), Mon, 8:00 AM-11:30 AM

A phase 1/2 study of durvalumab (DURVA) in combination with lenalidomide (LEN) with or without dexamethasone (DEX) in patients (pts) with newly diagnosed multiple myeloma (NDMM). *First Author: Sagar Lonial, Winship Cancer Institute, Atlanta, GA*

Background: LEN + DEX (Rd) is approved for pts with newly diagnosed MM, including those who are transplant non-eligible (TNE). DURVA is a monoclonal antibody to programmed death ligand 1 (PD-L1) that blocks PD-L1 binding to programmed death-1 (PD-1). Preclinical studies showed anti-MM immune responses with PD-1/PD-L1 blockade that were enhanced with LEN (Görgün et al, 2015). Here, we present a phase 1/2, multicenter, open-label trial in progress (MEDI4736-MM-002) designed to evaluate DURVA in combination with LEN ± DEX in a target population of pts who are TNE and/or with high-risk NDMM. **Methods:** Enrollment of up to 138 pts from the US, Canada, and Europe is planned to determine the recommended dose of DURVA (primary endpoint) with LEN ± DEX for the treatment (Tx) of NDMM. Key secondary endpoints include safety, response outcomes, pharmacokinetics, progression-free survival, and overall survival. Pts with previously untreated MM with ≥ 1 of the following will be included: 1 of the CRAB criteria or clonal bone marrow plasma cells ≥ 60% and an Eastern Cooperative Oncology Group performance status of ≤ 2. Pts with a history of primary immunodeficiency will be excluded. Each independent cohort (A, B, C) will enroll 6 pts in parallel in the dose-finding phase (Table). Dose-limiting toxicities will be evaluated during the first cycle of Tx. The optimal regimen will be determined from the dose-finding phase and a parallel dose-expansion phase of up to 40 pts per cohort. Tx will continue until progressive disease or unacceptable toxicity. To date, 15 pts have enrolled. Clinical trial information: NCT02685826.

	28-d Cycle		
Study Drug	**Cohort A TNE and High Risk[a]**	**Cohort B TNE and ≥ 65 Yrs Old**	**Cohort C Post-Transplant and High Risk[a]**
DURVA[b]	1500 mg on D1		
LEN[c]	25 mg		10 mg
DEX	40 mg (20 mg if > 75 yrs old) on D1, 8, 15, 22		Not applicable

[a] Pts with ≥ 1 feature: t(4;14), del(17p), 1q rearrangement, and/or t(14;16); International Staging System stage III disease; or lactate dehydrogenase levels > 2 × upper limit of normal. [b] Can be de-escalated to 750 mg. [c] D1-21; adjustable per creatinine clearance value.

TPS8056 Poster Session (Board #379b), Mon, 8:00 AM-11:30 AM

Phase 2, open-label study of venetoclax in combination with carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma. *First Author: Orlando Bueno, AbbVie Inc., Chicago, IL*

Background: A significant unmet need for multiple myeloma (MM) therapy remains as many patients eventually relapse after or become refractory to current treatment options. Investigation of novel agents and combinations in relapsed/refractory (R/R) patients are therefore critical to advance therapy and improve patient outcomes. Venetoclax is a potent, selective, orally bioavailable inhibitor of BCL-2. Combination of venetoclax with dexamethasone and bortezomib, a proteasome inhibitor that can inhibit MCL-1 indirectly via stabilizing the MCL-1-neutralizing protein NOXA, showed high rates of clinical response in a Phase 1 study. The mechanism of MCL-1 inhibition is thought to be a class effect of proteasome inhibitors. Given the clinical data supporting the combination of venetoclax with a proteasome inhibitor, this study will evaluate whether venetoclax combined with carfilzomib and dexamethasone can provide a well-tolerated and efficacious treatment option for R/R MM patients. **Methods:** This Phase 2, open-label study will assess the combination of venetoclax, carfilzomib, and dexamethasone in patients with R/R MM (NCT02899052). Primary objectives are to assess the safety and tolerability of this combination. Secondary objectives include evaluation of the pharmacokinetics of venetoclax and carfilzomib, preliminary efficacy of the combination (including overall response rate, very good partial response or better rate, progression-free survival, time to progression, and duration of response), and minimal residual disease (MRD) in bone marrow by next generation sequencing. Exploratory objectives will assess pharmacodynamic and predictive biomarkers, MRD by PET, pharmacogenetics, and patient-reported outcomes. Safety and pharmacokinetic profiles of the combination will be evaluated in initial dose escalation cohorts to determine appropriate doses of venetoclax and carfilzomib to be used with dexamethasone; a dose expansion phase will evaluate the safety and efficacy profiles of the combination based on selected doses. Study recruitment began in January 2017, with target enrollment of ~40 patients from 10–15 sites in the United States. Clinical trial information: NCT02899052.

TPS8057 Poster Session (Board #380a), Mon, 8:00 AM-11:30 AM

A phase III, randomized, open-label study of isatuximab (SAR650984) plus pomalidomide (Pom) and dexamethasone (Dex) versus Pom and Dex in relapsed/refractory multiple myeloma. *First Author: Paul G. Richardson, Dana-Farber Cancer Institute, Boston, MA*

Background: Treatment for refractory or relapsed and refractory multiple myeloma (MM) remains an unmet need. Isatuximab (ISA), an anti-CD38 monoclonal antibody with multiple mechanisms of tumor killing, has shown efficacy and an acceptable tolerability profile in Phase 1/2 studies in patients with refractory or relapsed and refractory MM (RRMM) (Richter et al. ASCO 2016; Vij et al. ASCO 2016). **Methods:** This Phase III, prospective, multicenter, randomized, open-label study (NCT02990338; ICARIA-MM) is being conducted to evaluate the clinical benefit of ISA in combination with Pom and low-dose Dex (Pom/Dex) versus Pom/Dex for the treatment of adult patients with RRMM and demonstrated disease progression within 60 days of the last therapy, and who have received at least 2 prior lines of therapy, including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) alone or in combination. Patients will be randomly assigned in a 1:1 ratio to either ISA (10 mg/kg IV on Days 1, 8, 15, and 22 in the 1st cycle; Days 1 and 15 in subsequent cycles) plus Pom (4 mg on Days 1–21) and Dex (40 mg for patients $<$ 75 years of age and 20 mg for patients $\geq$75 years of age, on Days 1, 8, 15, and 22) or Pom and Dex. Treatment cycles will be 28 days each. Patients will continue therapy until disease progression, occurrence of unacceptable adverse events (AEs), or their decision to discontinue the study, whichever comes first. The primary endpoint is progression-free survival (PFS), i.e. time from randomization to progressive disease or death from any cause. Response will be determined by IMWG criteria (2016). Key secondary endpoints include overall response rate and overall survival (OS). Safety evaluations include treatment-emergent AEs/serious AEs (including infusion-associated reactions), laboratory parameters, vital signs and assessment of physical examination. Statistical analyses will be conducted according to a pre-specified plan; approximately 300 patients (150 in each arm) are expected to be enrolled in this study. The first patient was recruited in January 2017. Study funding: Sanofi. Clinical trial information: NCT02990338.

TPS8058 Poster Session (Board #380b), Mon, 8:00 AM-11:30 AM

Novel phase 1a/1b dose-finding study design of CWP232291 (CWP291) in relapsed or refractory myeloma (MM). *First Author: Sung-Soo Yoon, Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea*

Background: CWP291, a novel peptidomimetic small molecule, has potent, selective inhibitory activity on a Wnt gene reporter, decreasing expression of β-catenin target genes, cyclin D1 and survivin. With broad anti-cancer efficacy in vitro, it significantly outperforms lenalidomide as a single agent combination in MM bone marrow engraftment models. **Methods:** This Phase 1a/1b study (NCT #02426723) was designed to define a well-tolerated dose of CWP291 as a single agent in subjects with R/R MM. CWP291 was administered IV over $\geq$30 minutes 2x weekly for 3 weeks out of a 4-week cycle, with standard 3+3 dose escalation design. But an important objective in terms of patient benefit and further clinical development was to explore activity of a combination regimen with lenalidomide. Thus, a novel study design allowed initiation of the Phase 1b as soon as CWP291 achieved a well-tolerated dose as a single agent. Combination therapy would start at one dose level lower. Enrollment of patients onto each arm was guided by Safety Review Committee assessments, including baseline laboratory values, performance status, extent of prior therapy, or prior adverse events related to lenalidomide. **Results:** Initiated September 2015, the starting dose was based on a prior Phase 1 study in AML, 198 mg/m^2. There were 4 sites involved, and 11 patients enrolled over 12 months. Approval of the new design by regulatory authorities and IRBs was completed by November 2016. A well-tolerated single agent dose (297 mg/m^2) was identified, allowing initiation of the Phase 1b at a dose of 198 mg/m^2(one dose level lower) combined with lenalidomide. Four subjects were enrolled in ~2 months to the Phase 1b. Enrollment to both arms is continuing and the status of this study will be updated at presentation. **Conclusions:** The ability to consider combination therapy with a novel drug is clearly a motivation for patient participation in clinical trials; especially true in MM, as multiple new therapies are available. This trial design was approved and allowed based on assessment of individual patient safety and potential benefit. Rapid enrollment in the combination therapy arm may significantly foster development of novel agents with this study design. Clinical trial information: NCT #02426723.

8500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Gefitinib (G) versus vinorelbine+cisplatin (VP) as adjuvant treatment in stage II-IIIA (N1-N2) non-small-cell lung cancer (NSCLC) with *EGFR*-activating mutation (ADJUVANT): A randomized, Phase III trial (CTONG 1104). *First Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: Cisplatin-based adjuvant chemotherapy is standard of care for patients (pts) with stage II-IIIA non-small cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors have shown no benefits in the adjuvant setting for pts with unselected resected NSCLC in the BR19 and RADIANT trials. ADJUVANT (NCT01405079) is the first randomized trial to compare gefitinib (G) with vinorelbine+cisplatin (VP) in completely resected pathological stage II-IIIA (N1-N2) NSCLC with *EGFR*-activating mutation. **Methods:** Completely resected stage II-IIIA (N1-N2) NSCLC pts with *EGFR*-activating mutation were randomized 1:1 to receive G (250 mg once daily) for 24 months or vinorelbine (25 mg/m^2 Day 1 and Day 8) plus cisplatin (75 mg/m^2 Day 1) every 3 weeks for 4 cycles. Stratification factors were lymph node status (pN1/N2) and *EGFR*mutation status. The primary endpoint was disease-free survival (DFS) in the intent-to-treat population. **Results:** A total of 222 pts were randomly assigned (Sep 19 2011 to Apr 24 2014). Baseline characteristics were balanced. At the time of data cutoff, the median duration of treatment was 21.9 months in the G arm, and 4 cycles in the VP arm. The median follow-up period was 36.5 months (range 0.1 to 62.8). G had significantly longer median DFS (28.7 months, 95% confidence interval [CI] 24.9 to 32.5) than VP (18.0 months, 95% CI 13.6 to 22.3; hazard ratio 0.60; 95% CI 0.42 to 0.87; p= 0.005). 3-year DFS was significantly better with G (34.0% vs 27.0%; p= 0.013). The number of overall survival events was 76 (34.2%). In the subgroup analysis of patients treated with G, lymph node status (pN1/N2) demonstrated significant correlation with DFS ($p<$ 0.05). Grade 3 or higher adverse events were less common with G than with VP (12.3% vs 48.3%; $p<$ 0.001). No interstitial lung disease was observed with G. **Conclusions:** Adjuvant G significantly prolonged DFS compared with VP in pts with resected stage II-IIIA (N1-N2) NSCLC with *EGFR*-activating mutation. Adjuvant gefitinib should be considered as an important option for stage II-IIIA lung cancer pts with *EGFR* mutation. Clinical trial information: NCT01405079.

8501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Salvage guideline for local-regional failure after stereotactic ablative radiotherapy for early-stage non-small cell lung cancer. *First Author: Eric Brooks, MD Anderson Cancer Center, Houston, TX*

Background: Up to 1 in 7 patients receiving stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer (NSCLC) will develop local-regional recurrence. While SABR is the pillar of treatment for medically inoperable patients, little is known about outcomes and management for this potentially curable, local-regionally recurrent patient group. **Methods:** We present the first long-term results for the largest group of salvaged patients with local-regional recurrence after SABR. 772 patients with clinically early-stage I-II NSCLC were treated with SABR (50 Gy in 4 or 70 Gy in 10 fractions) between 2004-2014 at our center. Patients with isolated local recurrence (LR, n = 34) or regional recurrence (RR, n = 41) were analyzed and compared to patients with no recurrence (NR, n = 569). **Results:** Median time to LR or RR after SABR was 14 months. Salvage was performed in 79.4% of LR and 92.7% of RR patients. Salvage consisted of surgery (20% LR, 2% RR), re-irradiation (24% LR, 17% RR), radiofrequency ablation (15% LR), chemotherapy (15% LR, 26% RR), and chemoradiation (6% LR, 44% RR) based on a standard multi-disciplinary decision approach (Figure 1). 5-year OS was 37.1% for LR and 39.1% for RR patients. Of LR and RR patients, those receiving salvage had significantly better 5-year OS compared to those not receiving salvage (45.2% LR, 42.9% RR, 0% no salvage; p = 0.009). 5-year OS for salvaged patients was not statistically different from patients with NR (53.5% NR, p = 0.466). 5-year lung-cancer specific survival was 51% for LR and 55.1% for RR patients. Subsequent DM occurred in 20.5% of LR and 29.3% of RR patients at a median of 8.4-10.3 months. No salvaged patient experienced grade 5 toxicity. **Conclusions:** Patients with local or regional recurrence after SABR have excellent outcomes with salvage therapy, with no statistical difference in 5- year OS between LR and RR patients salvaged after SABR, and patients with no recurrence. Because a standard multidisciplinary approach was applied to any LR or RR patient after SABR, a novel treatment algorithm is generated. We offer a much needed management guide for thoracic oncologists treating patients who local-regionally recur after SABR.

8502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Prophylactic cranial irradiation (PCI) versus observation in radically treated stage III non-small cell lung cancer (NSCLC): A randomized phase III NVALT11 study. *First Author: Harry J.M. Groen, University of Groningen, University Medical Center Groningen, Groningen, Netherlands*

Background: Brain metastases are one of the major sites of tumor failure in patients (pts) with radically treated stage III NSCLC. The value of PCI in these pts remains unsettled. This study is designed to investigate whether PCI reduces the incidence of symptomatic brain metastases (sBM). **Methods:** Pts were randomized between observation and PCI after concurrent or sequential chemo-RT with or without surgery. PCI dose was left to the physician(36 Gy/18F, 30 Gy/12F, 30 Gy/10F). Pts were registered before randomization, those progressing after chemo-RT were not randomized. Pts were followed for sBM (defined as increased intracranial pressure, headache, nausea, vomiting, cognitive, affective disturbances, seizures, focal neurological symptoms andMRI/CT), side effects, survival, quality of life (QLQ-C30, EuroQol 5D). The primary endpoint is the proportion of patients developing sBM. Randomizing 300 pts the study has 90% (2-sided p = 0.05) power to detect 17% decrease in pts developing sBM at 24 months (mo). **Results:** Between 2009 and 2015, 195 pts were registered, 175 were randomized, 87 received PCI and 88 pts were in the observation arm. In 2013 due to slow accrual, it was decided to reduce the number of randomized pts to 175 pts. With 75 events a 2-sided log-rank test would have 80% power to detect HR 0.52 and alpha 0.05. One pt in PCI arm was withdrawn after randomization. Pts characteristics were male (n = 114, 66%); adeno/squa/other 72 (41%), 62 (36%), 40 (23%); PS 0/1/2 66 (38%), 99 (57%), 9 (5%); stage IIIA/B 93 (53%), 80 (46%), unknown 1 (1%). Median follow up was 48.5 mo (95% CI, 39 - 54). Proportion of pts with sBM was 4/86 (4.6%) in PCI and 25/88 (28.4 %) in observation (p < 0.00001). Seven (8.1%) pts in PCI and 26 (29.7%) pts in observation arm had BM on imaging (p < 0.001). Median time to sBM was not reached in either arm. Median OS was 24.2 mo in PCI and 21.9 mo in observation arm (p = 0.52). Global QoL at 3 mo was worse in PCI arm (p = 0.02) but not afterwards. **Conclusions:** PCI significantly decreases the proportion of patients developing both symptomatic BM without influencing overall survival. PCI decreases 3 months global quality of life measures but not beyond. Clinical trial information: NTR 1601.

8503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032. *First Author: Matthew David Hellmann, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients (pts) with advanced SCLC after first-line platinum-based chemotherapy (PLT-CT) have a poor prognosis and limited treatment options. CheckMate 032 is a phase I/II trial evaluating multiple regimens of nivo ± ipi in solid tumors, including advanced SCLC. Tolerability and efficacy of nivo ± ipi were demonstrated in early results from the initial treatment arms (Antonia, *Lancet Oncol* 2016), prompting long-term follow-up and the addition of a randomized expansion cohort to further evaluate nivo ± ipi in advanced SCLC. **Methods:** In the initial treatment arms, pts with advanced SCLC and disease progression after prior PLT-CT were assigned to nivo (3 mg/kg Q2W; n = 98) or nivo 1 + ipi 3 (1 mg/kg and 3 mg/kg Q3W x 4, then nivo 3 Q2W; n = 61); safety/efficacy was assessed with a follow-up of ~18 mo. In the subsequent SCLC expansion cohort, pts were randomized 3:2 to nivo vs nivo 1 + ipi 3 and stratified by number of prior therapies. The primary endpoint was objective response rate (ORR). **Results:** Updated efficacy/safety results from the initial (non-randomized) nivo and nivo 1 + ipi 3 arms are summarized in the table. Responses were durable and occurred regardless of PD-L1 expression or PLT-sensitivity; safety was consistent with prior nivo ± ipi studies. In the expansion cohort, 247 pts were randomized to nivo or nivo 1 + ipi 3. The presentation will contain the first report of efficacy/safety results and subgroup analyses from this randomized expansion cohort. **Conclusions:** Durable responses are observed with nivo and nivo + ipi in pts with previously treated SCLC. The expansion cohort represents the first randomized evaluation of combined immune checkpoint blockade in SCLC. Clinical trial information: NCT01928394.

Updated results from initial CheckMate 032 SCLC treatment arms.

	Nivo n = 98	Nivo 1 + Ipi 3 n = 61
ORR, %	11	25
PLT-sensitive, % (n/N)	13 (7/56)	25 (7/28)
PLT-resistant, % (n/N)	8 (3/37)	24 (6/25)
Disease control rate, %	36	49
Median duration of response, mo	Not reached	11.7
Median overall survival (OS), mo	4.1	7.9
1-yr OS, %	30	42
2-yr OS,[a] %	17	30
Median follow-up, mo	15.7	21.0
Treatment-related (TR) adverse events, %		
Any grade	60	82
Grade 3–4	14	33
TR discontinuation rate, %	5	11

[a]Estimated

8504 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Phase II study of maintenance pembrolizumab (pembro) in extensive stage small cell lung cancer (ES-SCLC) patients (pts). *First Author: Shirish M. Gadgeel, Karmanos Cancer Institute, Detroit, MI*

Background: The median progression free survival (PFS) and overall survival (OS) following initial chemotherapy in ES-SCLC pts are 2 and 7 months, respectively (Ready N, J Clin Oncol 2015). We evaluated the benefits of maintenance pembro in ES-SCLC pts who had response/stable disease after 4-6 cycles of platinum/etoposide. **Methods:** Pts were required to begin pembro within 8 weeks of completion of chemotherapy, with restaging scans no more than 3 weeks prior to start of pembro. Prophylactic cranial radiation was permitted. Pts were treated with pembro 200 mg I.V. every 3 weeks for a maximum of 2 years. Disease assessment was done every 2 cycles for the first 6 cycles and then as per investigator discretion. Primary end point of the study was PFS. PFS according to immune related response criteria (irPFS) and OS were also assessed. Tumor tissue was analyzed for PD-L1 expression by the DAKO 22C3 antibody. Any level of expression was considered as positive for PDL1. Blood for circulating tumor cells (CTCs) was collected prior to first, second and third cycle of pembro. **Results:** Of the 45 pts enrolled, 55% were males and 22% had brain metastases. Median age was 66 years. The median time from end of chemotherapy to start of pembro was 5 weeks. Median number of pembro cycles was 4 (1-20 cycles). 35 pts had measurable disease at study entry. The disease control rate with pembro was 42% (1 CR, 3 PR, 15 SD). At a median follow up of 6 months, the median PFS was 1.4 months (90% CI-1.3-4.0) and the irPFS was 4.7 months (90% CI- 1.8-6.7). The median OS was 9.2 months (90% CI-6.1-15.2). 11 pts are still on therapy (3-20 cycles). The median CTC prior to pembro was 1 (0-256, n=37 pts). Each unit increase in baseline CTC correlated with worse PFS ($p = 0.052$; adjusted for brain mets, age and sex). PDL1 could be assessed in 35 pts and was positive in 1 pt. Most common adverse events were fatigue, nausea, cough and dyspnea. One pt developed atrio-ventricular conduction block and 1 pt type 1 diabetes. **Conclusions:** Maintenance pembro did not improve PFS in these patients but favorable OS suggests that some SCLC patients can benefit from maintenance pembro. Biomarkers to identify patients most likely to benefit from pembro need to be defined. Clinical trial information: NCT02359019.

8505 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Randomized trial of cisplatin and etoposide in combination with veliparib or placebo for extensive stage small cell lung cancer: ECOG-ACRIN 2511 study. *First Author: Taofeek Kunle Owonikoko, Emory University, Atlanta, GA*

Background: Veliparib, a potent inhibitor of Poly (ADP) ribose polymerase (PARP) enzyme potentiates standard chemotherapy against small cell lung cancer (SCLC) in preclinical studies. We evaluated the combination of veliparib (V) with cisplatin/etoposide (CE) doublet for first-line therapy of extensive stage SCLC (ES-SCLC). **Methods:** Patients with ES-SCLC stratified by gender and serum LDH levels, were randomized to receive four 3-wk cycles of CE (75mg/m^2 and 100 mg/m^2) along with V (100mg bid on d1-7) or placebo (P). The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS). Using an overall one-sided 0.10 level logrank test, this study had 88% power to detect a 37.5% reduction in the PFS hazard rate. **Results:** 128 eligible pts were enrolled across 33 US sites. Median age, 66 yrs; men, 52%; PS 0/1 (29%/71%). The estimated median PFS was 6.1 m vs. 5.5 m [unstratified HR: 0.75; 1-sided $p = 0.06$) favoring CE+V. The median OS was 10.3 m vs. 8.9 m respectively for CE+V and CE+P [stratified HR: 0.83 (80% CI 0.64-1.07); 1-sided $p = 0.17$]. There was a significant treatment by strata interaction in PFS: male pts with high LDH derived benefit [PFS HR of 0.34 (80% CI: 0.22-0.51)]; among pts not in this strata: PFS HR = 0.81 (80% CI: 0.60-1.09). The best objective response rate was 71.9% vs. 65.6% (2-sided $p = 0.57$). Salient grade ≥3 adverse events occurring in 5% of patients are summarized in the table below. Analysis of tumor samples for predictive biomarkers is planned. **Conclusions:** The addition of veliparib to doublet chemotherapy was associated with improved PFS in patients with extensive stage SCLC. Clinical trial information: NCT01642251.

	CE + Veliparib			CE + Placebo		
	Grade (%)			Grade (%)		
Toxicity Type	**3**	**4**	**5**	**3**	**4**	**5**
Anemia	17	2	-	12	-	-
Febrile Neutropenia	5	-	-	3	-	2
Fatigue	3	-	-	5	-	-
Neutropenia	20	29	-	14	18	-
Thrombocytopenia	8	2	-	2	3	-
Leukopenia	8	11	-	12	2	-
Acute kidney injury	5			2	2	

8506 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Mature overall survival (OS) results from the LUME-Meso study of nintedanib (N) + pemetrexed/cisplatin (PEM/CIS) vs placebo (P) + PEM/CIS in chemo-naïve patients (pts) with malignant pleural mesothelioma (MPM). *First Author: Anna K. Nowak, School of Medicine, Faculty of Medicine and Health Sciences, University of Western Australia, Crawley, Australia*

Background: LUME-Meso is a Phase (Ph) II/III, double-blind, randomized study. N targets MPM by inhibiting VEGFR 1–3, PDGFR α/β, FGFR 1–3, Src and Abl kinases. Primary analysis of the Ph II data demonstrated improved progression-free survival (PFS; hazard ratio [HR]=0.56; 95% confidence interval [CI] 0.34–0.91; p=0.017). Mature Ph 2 OS and updated PFS results are reported here. **Methods:** Pts with unresectable MPM (ECOG PS 0–1) were stratified by histology (epithelioid/biphasic) and randomized 1:1 to receive ≤6 cycles PEM (500 mg/m^2)/CIS (75 mg/m^2) Day 1 + N or P (200 mg bid, Days 2–21), followed by N or P monotherapy until progression or toxicity. The primary endpoint was PFS. The primary OS analysis and updated PFS analysis were performed as predefined. **Results:** 87 pts were randomly assigned (N=44, P=43). OS benefit favored N over P treatment (HR=0.77; 95% CI 0.46–1.29; p=0.319; 62 [71%] OS events) and was greatest in epithelioid pts (HR=0.70; 95% CI 0.40–1.21; p=0.197) with a median (m) OS gain of 5.4 months (mOS [95% CI]: 20.6 [16.2–28.8] N vs 15.2 [12.2–23.6] P). Updated PFS results (HR=0.54; 95% CI 0.33–0.87; p=0.010) also showed greatest benefit for epithelioid pts (HR=0.49; 95% CI 0.30–0.82; p=0.006) with a mPFS gain of 4.0 months (mPFS [95% CI]: 9.7 [7.2–12.4] N vs 5.7 [5.5–7.0] P). Improved forced vital capacity, objective response rates and duration of response were also observed with N treatment. Drug-related adverse events (AEs) in N- vs P-treated pts were 97.7% vs 97.6%. Grade ≥3 AEs of note included neutropenia (27.3% vs 4.9%), ALT (11.4% vs 0) and GGT (6.8% vs 0) elevations, and diarrhea (6.8% vs 0). AEs led to trial discontinuation in only 3 (6.8%) N vs 7 (17.1%) P pts. **Conclusions:** Mature Ph II OS data show that adding N to standard 1st-line treatment gives a strong signal towards improved OS. Updated PFS confirmed the primary analysis; AEs were manageable. The greatest clinical benefit was observed in pts with epithelioid histology. Median survival of 20.6 months in epithelioid pts treated with N is unprecedented in advanced MPM trials. Ph III is actively recruiting in this pt population. Clinical trial information: NCT01907100.

LBA8507 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase II trial. *First Author: Arnaud Scherpereel, University Hospital of Lille, Lille, France*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 5, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

8508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Neoadjuvant nivolumab in early-stage, resectable non-small cell lung cancers. *First Author: Jamie E. Chaft, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Anti-PD-1 therapy produces objective and often durable responses in ~20% of unselected patients (pts) with metastatic non-small cell lung cancer (NSCLC). However, the role of PD-1 blockade in treating resectable NSCLC is unknown. This is the first study to test nivolumab in the neoadjuvant setting. This trial design provides an opportunity to examine anti-PD-1 mechanism of action and immunologic correlates of outcomes. **Methods:** Patients with Stage IB - IIIA NSCLC received 2 doses of nivolumab 3mg/kg over 4 weeks before surgery. The primary endpoint was safety in 20 patients with resected NSCLC. Efficacy was explored using objective pathologic response criteria. Correlative studies of the tumor immune microenvironment, tumor mutation and predicted neoantigen loads, and changes in T cell receptor (TCR) clonality in tumor and blood pre and post treatment were conducted. **Results:** 22 pts were treated. Nivolumab was well-tolerated and no surgeries were delayed. 1 pt withdrew from study preop without progression or toxicity. Among the 21 attempted resections, 1 tumor was unresectable. 9/21 (43%, 95% CI 24-63%) had a major pathologic response ($<$ 10% viable tumor cells in resection specimen). With a median postop follow-up of 9 months, 18 pts (86%) remain alive and recurrence free. Pre-treatment tumor exome sequencing showed a correlation between both tumor mutation and predicted neoantigen loads with pathologic response. Multiplex immunohistochemistry of pre- and post-treatment tumors showed an influx of PD-1+CD8+ T cells into responding tumors. TCR sequencing demonstrated that expanded peripheral T cell clones after treatment match clones found in the tumor. **Conclusions:** Neoadjuvant nivolumab in resectable NSCLC did not delay surgery. Major pathologic response rate was encouraging and compares favorably to outcomes with cisplatin-based neoadjuvant chemotherapy. Genomic analyses suggest that higher mutational and neoantigen burden could result in deeper pathologic response. Immunologic analyses support the detection of intra-tumoral T cell clones in the blood after treatment with nivolumab and may provide further insight into the molecular and immunologic features of response and non-response to PD-1 blockade. Clinical trial information: NCT02259621.

8513 Poster Discussion Session; Displayed in Poster Session (Board #249), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Trabectedin (T) as second line treatment option for patients with epithelioid malignant pleural mesothelioma (MPM) in progression following pemetrexed/platin-derivates chemotherapy: ATREUS trial. *First Author: Diego Luigi Cortinovis, Azienda Ospedaliera San Gerardo, Monza, Italy*

Background: Systemic chemotherapy in MPM is inevitably followed by relapse, and response rates to second line treatment are limited. T is an antineoplastic agent targeting both the malignant cells and the tumor microenvironment with demonstrated activity against a range of tumors. We aimed to study the activity and safety of T in advanced MPM. **Methods:** ATREUS, an Italian multicenter single arm phase II trial, assessed the activity T in MPM evaluating the proportion of patients responding to treatment and achieving progression free survival for 12 weeks (PFS12w). Pre-treated epithelioid and naive or pre-treated biphasic/sarcomatoid pts were treated until progression or unacceptable toxicity. Initial dose was 1.3 mg/m^2, over 3 hours every 21 days, later reduced to 1.1 mg/m^{2}to improve tolerability. In the epithelioid cohort, sample size was based on a Simon's Optimal Two-Stage Design. The study was set to reject, at an alpha error of 10% the hypothesis that PFS12w was $\leq$25% and to demonstrate, with a power of 85% the hypothesis that PFS12w was $\geq$40%. At least 20 out of 62 pts with assessed disease, no major protocol violations, either receiving $\geq$12 weeks of treatment or interrupting before for progression or death (per protocol – PP analysis) were to reach PFS12w in order to consider T effective. **Results:** 71 pts were enrolled and evaluable. Average age was 65.8 $\pm$ 8.75 years. 71.8% were male and 82.5% presented stage III or IV disease. 42.4% (25/59) of pts included in the PP analysis obtained PFS12w (95% CI: 29.6% - 55.9%). In a second, more conservative analysis, including pts withdrawn prematurely for toxicity or intercurrent illness as failures, PFS12w rate reached 38.5% (25/65 pts). The most frequent grade $\geq$3 treatment-related toxicities werehepatic toxicity (60.5%), non-febrile neutropenia (21.1%), and fatigue (6.6%). Five pts (7%) interrupted treatment for toxicities (2 liver, 1 multi-organ failure, 1 thrombocytopenia, 1 T intolerance). **Conclusions:** In pts with advanced epithelioid MPM, second line treatment with T showed an elevated rate of disease stabilization. Safety data is promising but require further evaluation. Clinical trial information: NCT02194231.

8514 Poster Discussion Session; Displayed in Poster Session (Board #250), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Outcomes of anti-PD-1 therapy in mesothelioma and correlation with PD-L1 expression. *First Author: Gareth Rivalland, Olivia Newton-John Cancer Wellness and Research Centre, Melbourne, Australia*

Background: Early phase trials of anti-programmed death 1 (PD-1) antibodies have demonstrated important responses in malignant mesothelioma (MM). Expression of the ligand, PD-L1, is a potential biomarker for PD-1 directed therapy use and is expressed in a significant proportion of MM. We present results for a cohort treated with PD-1 inhibitory antibodies and assessed for PD-L1 expression. **Methods:** Patients (pts) with unresectable pleural or peritoneal mm treated with anti-PD-1 antibodies were included. Data was collected retrospectively. Radiological response was assessed using RECIST 1.1. Overall survival (OS) and progression-free survival (PFS) were evaluated. PD-L1 expression was assessed with IHC clone E1L3N (Cell Signaling Technology). PD-L1 positivity was defined as membranous expression on tumour cells: $>$ 5% for PD-L1+ and $>$ 50% for PD-L1^{hi}. **Results:** Forty-six pts were treated between July 2015 and January 2017. Median age was 66.5 years, ECOG PS was 0/1 in 3/46 (7%) and 35/46 (76%) respectively. Most were male (83%), and 43/46 (93%) had $\geq$1 prior therapy, with a median of 2 (range 0 - 5). The predominant histology was epithelioid (n = 32/46; 70%). Pembrolizumab was used in 45/46 and BGB-A317 (a PD-L1 antibody) in 1 pt. Of the 46 pts, the overall response rate (ORR) was 15% (7 PR) with 15/46 (33%) achieving stable disease, giving a DCR of 44%. Progression was seen in 24/46 (52%). Median OS for the entire cohort was 8.0 months (95% CI: 2.3 – 11.9). Median duration of response was not yet reached (range 1.5 -19.8). PD-L1 testing was performed in 14 samples, with PD-L1+ in 5 (36%) and PD-L1^{hi} in 4 (29%). The ORR was 40% (2 PR, 3 SD) with PD-L1+, 50% (2 PR, 2 SD) with PD-L1^{hi} and 22% (2/9 patients) with negative expression. PFS and OS were greater with both PD-L1+ (PFS HR: 0.26, 95% CI 0.05 – 1.32, p = 0.10) and PD-L1^{hi} (PFS HR: 0.17, 95% CI 0.02 – 1.47, p = 0.11). PD-L1+ positivity remained a borderline predictor of improved survival on multivariate analysis (p = 0.06). Complete PD-L1 analysis will be presented at the meeting. **Conclusions:** PD-1 targeted therapy demonstrated a clinically significant response rate in this cohort of mm patients. Initial analysis suggests PD-L1 expression is correlated with improved response and survival.

8515 Poster Discussion Session; Displayed in Poster Session (Board #251), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Immune microenvironment in mesothelioma: Looking beyond PD-L1. *First Author: Bibhusal Thapa, Olivia Newton-John Cancer Research Institute, Melbourne, Australia*

Background: Studies using immune checkpoint inhibitors in mesothelioma (MM) have shown promise. Differences in response to PD-L1 and PD-1 inhibitors (10% vs 25%) have been reported. Also, expression of PD-L1 alone appears to be a limited predictor. As the roles of the multiple check point receptors and their ligands become defined, an understanding of their expression and interplay in the mm tumour microenvironment, which could affect suitability for checkpoint inhibition therapy, has become necessary. **Methods:** Tissue microarrays were constructed and stained with PD-L2, LAG3 and TIM3 antibodies. Tumour infiltrating lymphocytes (TILs) were assessed in the stroma and expressed as a % of stromal area within invasive tumour. These data were combined with PD-L1 expression, CD4+ and CD8+ infiltration in the same cohort reported previously. To quantify the immunosuppressive milieu, we combined our assessment of PD-L1, PD-L2 and TIM3 expression to derive an "Immune checkpoint score (ICS)" and explored its correlation with the tumour microenvironment and clinicopathological covariates. We are also exploring its predictive value in an independent cohort of mm patients who have received anti-PD-1 treatment. **Results:** Amongst 329 patients evaluated, PD-L1 was positive (+) in 41.7% and PD-L2+ in 24.5%. TIM3+ lymphocytes were found in 99.4% but LAG3+ lymphocytes in only 0.2%. 28/173 (16%) of PD-L1- patients were PD-L2+ and 31/136 (22%) PD-L1 and PD-L2 negative patients had high infiltration with TIM3+ lymphocytes. High ICS was associated with non-epithelioid histology, increased TILs and poorer survival. On multivariate analysis, high TILs, non-epithelioid histology and poor physiological status remained significantly associated with poorer survival. Data on the predictive role of ICS score will also be reported. **Conclusions:** While co-expression of PD-L1, PD-L2 and TIM3 can occur, their expression is mutually exclusive in a large proportion of patients. The expression of PD-L2 may explain differences in responses seen between PD-1 compared to PD-L1 inhibitors. A comprehensive assessment of these multiple immunosuppressive pathways may be necessary to truly gauge the immunosuppressive environment and tailor immunotherapy for individual cases.

8516 Poster Discussion Session; Displayed in Poster Session (Board #252), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Prevalence and clinical correlation of programmed cell death 1 ligand (PD-L1) expression in patients with resected non-small cell lung cancer (NSCLC): Results from the European Thoracic Oncology Platform (ETOP) Lungscape cohort. *First Author: Keith Kerr, Aberdeen Royal Infirmary, Aberdeen, United Kingdom*

Background: Conflicting data exists on the potential prognostic impact of PD-L1 expression in NSCLC. The Lungscape project, a fully annotated large biobank of resected stage I-III NSCLC, allows detailed analysis of this issue. **Methods:** Prevalence of PD-L1 positivity and its association with clinicopathological characteristics and patient outcome - Relapse-free Survival (RFS), Time-to-Relapse (TTR) and Overall Survival (OS) - was explored in the ETOP Lungscape cohort. PD-L1 expression was assessed on tissue microarrays (TMAs) using the DAKO 28-8 immunohistochemistry assay. Positivity cut-off points of ≥1%, 5% and 50% for neoplastic cell membrane staining were considered. **Results:** PD-L1 data were available for 2182 patients, from 15 ETOP centers, with median follow-up 4.8 years; 1191 patients still alive; median age 66 years; 64% male, 32/54/11% for current/former/never smokers; 49/29/22% for stages I/II/III; 51/42/4/3% adenocarcinomas (AC)/squamous cell (SCC) /large cell and sarcomatoid (LCS)/other. Median RFS/TTR/OS were 53/99/69 months (AC: 52/84/72, SCC: 54/not reached/64; and LSC 52/103/74). PD-L1 prevalence with 1% cut-off was, overall: 43%, 95% confidence interval (95%CI): 41-46; (AC: 42%, 95%CI: 39-46; SCC: 44%, 95%CI: 40-47; and LCS: 53%, 95%CI: 42-65), while for 5% threshold, prevalence was 34%, 95%CI: 32-36. PD-L1 1% positivity was a significant predictor only for AC: $HR_{RFS: + vs -} = 0.82$; 95%CI: 0.69-0.97, $HR_{TTR: + vs -} = 0.83$; 95%CI: 0.68-1.01, $HR_{OS: + vs -} = 0.83$; 95%CI: 0.69-1.01 (adjusted p = 0.024, 0.064, 0.063 respectively). This effect is found also for the 5% cut-off, and preserved in the overall model including all histologies. Using the 50% cut-off, PD-L1 positivity was detected in 17% of patients; 95%CI: 15-18, but was no longer a significant predictor of outcome, overall and by histology type. **Conclusions:** PD-L1 positivity (1% and 5% cut-offs) was present in more than one third of resected NSCLC and was associated with a better prognosis for AC patients.

8517 Poster Discussion Session; Displayed in Poster Session (Board #253), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Genomic alterations (GA) and tumor mutational burden (TMB) in large cell neuroendocrine carcinoma of lung (L-LCNEC) as compared to small cell lung carcinoma (SCLC) as assessed via comprehensive genomic profiling (CGP). *First Author: Young Kwang Chae, Northwestern Medicine Developmental Therapeutics Institute, Chicago, IL*

Background: SCLC and L-LCNEC are aggressive neoplasms that are both associated with smoking history and are thought to overlap in clinical, histogenetic, and genomic features. We reviewed the genomic profiles of >1187 patients to assess the genomic similarities of these diseases. **Methods:** Comprehensive genomic profiling (CGP) of tumors from 300 L-LCNEC and 887 SCLC patients in the course of clinical care was performed to suggest pathways to benefit from therapy. **Results:** Commonly altered genes in both diseases included *TP53, RB1, MYC/MYCL1, MLL2, LRP1B* and *PTEN;* alterations in other genes occurred at somewhat differing frequencies (table). For both diseases, *RB1* mutation significantly co-occurred with *TP53* mutations (p<0.001), but occurred in a mutually exclusive fashion to *STK11* and *CDKN2A* (p<0.001). *RB1* was mutually exclusive with *KRAS* for L-LCNEC but not for SCLC. The interquartile range for SCLC and L-LCNEC TMB is 7.9 and 12.6 with the 75% quartile being 14.4 and 17.1 respectively. Cases of both diseases will be presented with radiographic response to genomically matched targeted therapy and immunotherapy, particularly in cases of high TMB. **Conclusions:** Given the similar overall genomic profiles and clinical behavior of a subset of these diseases, they could be conceived of as a single disease to be further classified by genomically defined classes such as SCLC-type (*TP53*/*RB1*mutated) and NSCLC-like (wild type for one or both). By analogy to NSLC and melanoma, benefit from immunotherapy appears most likely for only the upper quartile of cases in TMB.

Gene	L-LCNEC Frequency (% altered)	SCLC
TP53	72.3	90.9
RB1	37.7	69.5
CDKN2A	15.0	3.3
MYC	14.7	6.0
Percentile	TMB (mutations/Mb)	
25th percentile	4.5	6.3
Median	9.9	9.9
75th percentile	17.1	14.4

8518 Poster Discussion Session; Displayed in Poster Session (Board #254), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A nationwide genomic screening project for small cell lung cancer in Japan (LC-SCRUM-Japan). *First Author: Haruyasu Murakami, Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

Background: Recent genomic studies of small-cell lung cancer (SCLC) have identified promising therapeutic strategies for this highly lethal form of cancer. Thus, we established a nationwide lung cancer genomic screening project in Japan (LC-SCRUM-Japan) to identify SCLC patients harboring targetable genomic alterations for the development of novel targeted therapies. **Methods:** The samples were subjected to a next-generation sequencing (NGS) system, Oncomine™ Comprehensive Assay, enabling the simultaneous analysis of 143 cancer-related genes. **Results:** As of December 2016, 133 institutions were participating and 295 patients had been enrolled. The median age was 69 years (range, 14-90 years). Two hundred seventeen (74%) were male and most patients (93%) were smokers. Among 268 samples completed analysis, we identified high prevalence of inactivating TP53/RB1 mutations in 198 (74%) /82 (31) of cases, respectively. MYC/MYCL1/MYCN amplifications were detected in 10 (4%) /13 (5) /4 (1) of cases, respectively. The NGS analysis also showed that 62 (23%) of cases had at least one targetable genomic alterations, including 7 EGFR activating mutations (3%), 6 KRAS activating mutations (2%), and 8 FGFR1 copy number gains (3%). No case was positive for ALK or ROS1 fusions. Never-smokers (71% vs. 5%, p<0.001) were significantly frequent in the EGFR type compared to the others. The KRAS type showed significantly poor progression free survival (PFS) of the first-line chemotherapy compared to the others (median PFS 1.2 vs. 6.1 months, respectively; p<0.001). Mutations in the PI3K/AKT/mTOR pathway were detected in 22 (8%) of the tumors: 10 PIK3CA mutations (4%), 9 PTEN inactivating mutations (3%) and 3 TSC2 inactivating mutations (1%). Among them, a case with PTEN mutation was enrolled in the investigator initiated phase II study of gedatolisib named "EAGLE-PAT" (UMIN 000020585). **Conclusions:** We identified a series of targetable genomic alterations in SCLC. This nationwide screening system is helpful for identifying targetable genomic alterations and their clinical features, contributing to the development of novel targeted therapies for this disease. Updated screening results will be presented at the 2017 ASCO Annual Meeting.

8519 Poster Discussion Session; Displayed in Poster Session (Board #255), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Analysis of circulating tumor DNA in localized lung cancer for detection of molecular residual disease and personalization of adjuvant strategies. *First Author: Aadel Chaudhuri, Stanford Cancer Institute, Stanford, CA*

Background: Identifying localized non-small cell lung cancer (NSCLC) patients with residual disease following curative intent therapy is difficult due to normal tissue changes caused by surgery or radiation and an inability to detect microscopic disease. Analysis of circulating tumor DNA (ctDNA) might enable identification of molecular residual disease (MRD) and personalization of adjuvant treatment approaches but has not been explored in lung cancer. **Methods:** We applied CAPP-Seq, an ultra-sensitive next-generation sequencing based ctDNA quantitation method, to pre- and post-treatment blood samples from a cohort of 41 patients treated with chemoradiation, radiotherapy or surgery for stage I-III primary lung cancer. Detection of ctDNA at a single MRD time-point within 4 months of treatment completion was compared with surveillance by cross-sectional imaging. Furthermore, we developed an approach for identification of tumor mutation burden based on mutations detected in plasma, leveraging whole exome sequencing data from 1,177 NSCLCs sequenced by TCGA. **Results:** Median follow-up time was 35 months. Pre-treatment ctDNA was detected in 38 (93%) patients and 19 (46%) had detectable post-treatment ctDNA MRD. MRD+ patients displayed significantly inferior 3-year freedom from progression (0% vs. 92%; HR 38; P < 0.0001) and 3-year overall survival (8% vs. 75%; HR 12; P < 0.0001) than MRD- patients. Detection of ctDNA MRD had positive and negative predictive values for disease progression of 100% and 93%, respectively. Furthermore, we non-invasively identified activating EGFR mutations or high mutational burden (≥5 CAPP-Seq non-synonymous mutations, corresponding to > 200 non-synonymous mutations per exome or > 4 single nucleotide variants per megabase of exome) in 47% of patients with detectable ctDNA MRD, suggesting potentially favorable responses to TKIs and immune checkpoint inhibitors, respectively. **Conclusions:** Our results indicate that ctDNA analysis accurately detects MRD in localized lung cancer patients and could facilitate personalized adjuvant treatment at early time-points when disease burden is minimal.

8520 Poster Discussion Session; Displayed in Poster Session (Board #256), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Molecular analysis of thymic epithelial tumors (TETs): A report by The Cancer Genome Atlas (TCGA) research network. *First Author: Patrick J. Loehrer, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Thymoma (T) and thymic carcinoma (TC) are the most common malignancies of the anterior mediastinum. Additionally, thymoma has an unique association with autoimmune disorders, notably myasthenia gravis (MG). Histologic classification of TETs has been largely based on the gross description of the epithelial cell appearance and the relative abundance of associated lymphocytes. A comprehensive molecular analysis of TETs has not heretofore been conducted. **Methods:** The TCGA Research Network conducted multi-platform analyses of 117 TETs (T = 105; TC = 10 and micronodular T = 2), which included whole-exome, transcriptome, methylome and targeted proteome analysis. Patient characteristics: median age = 60 years (range 17-84); M:F (%) = 52:48; Masaoka Stage (I-36, IIA-39, IIB-19; III-15; IVA-1; IVB-5); mg was present in 32 patients. No patient had prior therapy for metastatic disease, but 14 had prior chemotherapy and 39 had prior radiation therapy in adjuvant setting. WHO histologic classification (blinded review) revealed A = 10; A/B = 48, B1 = 12, B2 = 25, B3 = 10, micronodular T = 2 and TC = 10. **Results:** T has one of the lowest mutational loads of any tumor in the TCGA. A unique transcription factor, GTF2I, was the most commonly observed mutation in WHO Types A and A/B. All GTF2I mutations were exclusively at the amino acid 424 locus. This is the only tumor with this specific mutation within the entire TCGA database. HRAS, NRAS and TP53 mutations were less commonly noted among all TETs. Four distinct molecular-driven subtypes of TETs were identified that strongly correlated with the current WHO histologic classification. Increased aneuploidy and overexpression of muscle autoantigens were associated with mg phenotype. **Conclusions:** Based on molecular analysis, four clusters were identified that correlated strongly with the current WHO Histologic Classification. Also identified was a unique mutation in GTF2I, which was associated with WHO Type A and A/B thymoma. This international effort represents the largest and most comprehensive molecular analysis of TETs conducted to date is expected to have important clinical and translational implications for this rare disease.

8521 Poster Discussion Session; Displayed in Poster Session (Board #257), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A phase II study of pembrolizumab for patients with previously treated advanced thymic epithelial tumor. *First Author: Jinhyun Cho, Inha University Hospital, Incheon, Republic of Korea*

Background: No standard treatment exists for patients with thymic epithelial tumor (TET) who progress after platinum-containing chemotherapy. We conducted a phase II study of pembrolizumab in patients with TET to evaluate the efficacy and safety. **Methods:** Between March 2016 and December 2016, patients with histologically confirmed TET who progressed after platinum-containing chemotherapy were eligible. Patients were excluded if they had an active autoimmune disease requiring systemic treatment within the past one year. Patients received 200mg of pembrolizumab intravenously every 3 weeks until tumor progression or unacceptable toxicity. The trial was registered with ClinicalTrials.gov, number NCT02607631. **Results:** 33 patients were enrolled, 26 with thymic carcinoma (TC) and 7 with thymoma (T). 19 (57.3%) patients received ≥ 2 prior lines of systemic chemotherapy. Median number of cycles was 8 (ranges, 1-13) and median follow up was 6.3 months (ranges, 1.4-9.9). Of 33 patients, 8 (24.2%) achieved partial responses, 17 (51.5%) stable disease, and 8 (24.2%) progressive disease as best response, resulting in overall response rate of 24.2% (7 confirmed PR). The median progression-free survival was not reached for 7 T and 6.2 months for 26 TC. The most common adverse events of any grade include dyspnea (33.3%), chest wall pain (30.3%), anorexia (21.2%) and fatigue (21.2%). Treatment-related adverse events ≥ grade 3 associated with immune related adverse events (irAE) include hepatitis (12.1%), myocarditis (9.1%), myasthenia gravis (6.1%), thyroiditis (3.0%), ANCA-associated rapidly progressive glomerulonephritis (3.0%), colitis (3.0%), and subacute myoclonus (3.0%) except anemia (3.0%). 8 (24.2%) patients (5 T, 3 TC) discontinued study treatment due to irAE, which were manageable with immediate administration of high dose corticosteroid and other immunosuppressive agents in most of patients (87.5%). **Conclusions:** Pembrolizumab showed promising antitumor activity in refractory or relapsed TET. Given the relatively high incidence of irAEs, early detection and management of autoimmune toxicity is essential to ensure feasibility of pembrolizumab treatment in patients with TET. Clinical trial information: NCT02607631.

8522 Poster Discussion Session; Displayed in Poster Session (Board #258), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Treatment of lung cancer patients in multidisciplinary (MDC) and serial care (SC) clinics. *First Author: Meredith Ray, University of Memphis, Memphis, TN*

Background: MDC may improve the quality of care for complex diseases. We compared the use of stage-appropriate treatment for lung cancer patients in a co-located MDC to serially-referred (SC) patients within the same healthcare system. **Methods:** Prospective cohort study of newly-diagnosed lung cancer patients enrolled before onset of treatment from MDC or the standard clinics (SC). Eligible pts had ECOG PS 0-2. Stage-appropriate treatment selection was determined using National Comprehensive Cancer Network (NCCN) guidelines based on clinical stage just before treatment onset. Differences in stage-based treatment rates were calculated using Chi-squared tests. **Results:** 162 had MDC and 317 SC. Compared to serial care patients, MDC patients were more likely black (37% v 30%) female (51% vs 48%), older (median 69 vs median 66) and less likely commercially insured (36% v 43%). Surgical resection was more frequently used for early stage patients in MDC: 72% v 58% for stage IA/IB (p = 0.2259); 58% v 31% for stage IIA/B and IIIA (T3N1M0) (p = 0.0375). MDC patients also had trends towards higher rates of recommended concurrent chemoradiation therapy for stage IIIA (T4N0-1M0) (75% vs 53%) (p = 0.5835), IIIB (T1-3N3, T4N2) (78% v 68%), but equal rates of concurrent chemoradiation therapy for stage IIIA (T1-3N2M0) (68% vs 68%). Stage IV patientss were more likely to receive chemotherapy or targeted therapy in MDC v SC (87% vs 80%) (p = 0.3795). **Conclusions:** Lung cancer patients in the MDC model are more likely to receive recommended stage-appropriate treatment than those in the usual serial care model, despite relatively adverse demographic characteristics. Clinical trial information: NCT02123797.

8523 Poster Discussion Session; Displayed in Poster Session (Board #259), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Safety and feasibility of consolidation pembrolizumab following concurrent chemoradiation for unresectable stage III non-small cell lung cancer: Hoosier Cancer Research Network LUN14-179. *First Author: Greg Andrew Durm, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: The standard of care for unresectable stage III NSCLC is concurrent chemorad. Following treatment, the risk of radiation pneumonitis is greatest at 1-3 mo. Pneumonitis risk increases with consolidation chemotherapy. A previous trial by our group (Hanna et al, JCO 2008) of consolidation docetaxel showed 80.8% completed 3 planned cycles of chemo with a grade 3-5 pneumonitis rate of 9.6% and 1 death. PD-1 inhibitors are also associated with an increased risk of pneumonitis in the metastatic setting. We conducted a phase II trial of consolidation pembro initiated 1-2 mo after concurrent chemorad, a period during which pts are at high risk of developing pneumonitis. **Methods:** Pts with stage III NSCLC who completed chemorad with either carbo/paclitaxel, cis/etop, or cis/pemetrexed plus 59-66.6 Gy of radiation and had no PD received pembro 200mg IV q3wk for up to 1 yr. Primary endpoint is time to metastatic disease. The objective of the study is to evaluate both safety and efficacy, and here we report preliminary safety and feasibility results. Evaluable pts for this analysis had ≥3 mo of f/u or went off study due to PD, toxicity, or death < 3 mos after initiation of pembro. **Results:** 93 pts enrolled. Median age 67 (range 46-84), 59 (63.4%) were male. 87 (93.5%) were former or current smokers. 68 (73.1%) received carbo/pac, 24 (25.8%) received cis/etop, and 1 received cis/pemetrexed. SqCC (n = 41), non-SqCC (n = 43), NSCLC NOS (n = 8), mixed (n = 1). IIIA (n = 56), IIIB (n = 37). At the time of analysis, 83 of 93 pts were evaluable. 66 of 83 (79.5%) received ≥ 3 mo of pembro. 17 (20.5%) pts developed any grade pneumonitis with 14 of 17 occurring in the first 12 wks (median 9 wks). Only 3 (3.6%) pts developed grade 3-5 pneumonitis related to pembro. There was 1 pneumonitis-related death and a second death from respiratory failure possibly related to pembro. **Conclusions:** This early report indicates that most patients can safely receive consolidation pembro within 1-2 mo of completing chemorad. The incidence of serious pneumonitis during the first 3 mo of treatment appears low. Updated safety data on all 93 pts will be presented at the ASCO meeting. Clinical trial information: NCT02343952.

8524 Poster Discussion Session; Displayed in Poster Session (Board #260), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Temporal trend in the use of surgery in the management of stage IIIa non-small cell lung cancer (NSCLC) between 2000-2013: A SEER analysis. *First Author: Veena Iyer, University Of Toledo, Toledo, OH*

Background: The optimal treatment of patients with Stage IIIA NSCLC, a heterogeneous group comprised of T1-T4, N0-N2 disease, is controversial. Lack of clear data and guidelines allows several options for treatment, and hence there has been significant variability in clinical practice. The purpose of this study was to evaluate the nationwide trends in rates of surgery for Stage IIIA lung cancer diagnosed between 2000-2013. **Methods:** The study included patients with Stage IIIA NSCLC, 18 years and older diagnosed between 2000 and 2013. We used Z-tests in SEER*Stat to compare relative survival rates for patients diagnosed between 2000-2010. **Results:** Among the 27,697 patients with Stage IIIA NSCLC, 45% were females and median age was 67. 35% were treated with surgery. Multivariate analysis demonstrated that year of diagnosis, race, marital status, geographic region, tumor size, tumor grade, nodal status all were significantly associated with the use of surgery. Relative survival at 24 months (RS_{24}) was 62% for patients who had surgery and 29% for patients without surgery (z = -47.3). The proportion of patients receiving surgery decreased from 55.6% in 2000 to 32.6% in 2010 and 29.7 in 2013 ($p < 0.0001$) while the relative survival at 24 months (RS_{24}) from 2000 to 2010 rose from 34.7% to 43.2% (z = -4.89). The RS_{24} for patients who received surgery rose from 55.3% in 2000 to 77.6 % in 2010 (z = -3.58). Change in RS_{24} for patients who did not have surgery also improved from 19.6% to 31.2%. The median RS of the surgical cohort changed from 28 m to 44 m. **Conclusions:** Based upon reporting within the SEER database, the proportion of stage IIIA NSCLC patients undergoing surgery has decreased over the study time period. However, the relative survival rates have improved significantly for both the overall group and those having surgery, suggesting that significant strides have been made both in selecting the group of patients who would benefit from surgical resection and in the overall management of this group of patients.

8525 Poster Session (Board #261), Sat, 8:00 AM-11:30 AM

Survival benefit of systemic chemotherapy given as adjuvant (ACT) after thoracic surgery for N0-1 non-small cell lung cancer (NSCLC) patients (pts) with synchronous brain metastasis (SBM). *First Author: Sarah Shin, University at Buffalo, Buffalo, NY*

Background: Pts with solitary SBM and otherwise early-stage NSCLC demonstrate prolonged survival with surgical resection of both primary and metastatic disease. The role of "ACT" after thoracic surgery in this circumstance is not well-defined. We seek to determine the effect on overall survival(OS) of ACT after resection of primary tumor in pts with surgically resectable primary NSCLC and SBM. **Methods:** The National Cancer Database (NCDB) was queried to identify pts who underwent resection of NSCLC as the primary cancer (without other malignancies) from years 2010-2014 (n = 90,518). We then focused on pts who also were diagnosed with SBM (n = 807). Only patients with pathologically confirmed N stage 0 (n = 419) or 1 (n = 101) status were included in the final analysis. Patients who received platinum-based ACT within 3 months after surgery were considered to have received ACT. Associations between treatment groups were analyzed using the Chi-square test for categorical variables and Wilcoxon Rank Sum test for continuous variables. Univariate and multivariate proportional hazards modeling results were used to assess the effect of treatment and the confounding variables on OS. Relative prognosis was summarized using estimates and 95% confidence interval(CI) for the hazard ratio (HR). Unadjusted differences in OS between the treatments are shown using Kaplan-Meier methods. All analyses were performed using SAS version 9.4. **Results:** There is no imbalance in terms of gender, race, income, nodal status, histology between groups. Non-ACT pts were older (n = 181, median 64 vs 58 years in ACT group, $p < 0.001$). Age, nodal status, ACT, and histology were associated with OS in both univariate and multivariate analysis, with OS HR 0.51 (95% CI 0.39-0.66) in favor of ACT (n = 339). One- and 5-year survival in ACT group versus non-ACT group was 83% (95% CI 78%-87%) and 33% (25%-40%), versus 57%(95% CI 48%-65%) and 18% (95% CI 11%-26%), respectively. **Conclusions:** ACT after thoracic surgery for N0-1 NSCLC with SBM is associated with improved OS in this analysis.

8526 Poster Session (Board #262), Sat, 8:00 AM-11:30 AM

The role of adjuvant chemotherapy in stage IB non-small cell lung cancer: A decision, effectiveness, and cost-effectiveness analysis. *First Author: Jessica Lynn Hudson, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Despite complete surgical resection (SR), half of stage I non-small cell lung cancer (NSCLC) patients die from systemic relapse. An independent risk factor for systemic progression is pathologic stage IB subtype (T2aN0M0, AJCC 7). The role of adjuvant chemotherapy (AC) in stage IB NSCLC is controversial. We studied the effectiveness and cost-effectiveness of AC after SR in stage IB NSCLC. **Methods:** Propensity score matching was performed on the National Cancer Database (2004-2011). The Kaplan-Meier method generated conditional probabilistic incremental 1- to 5-year survival after SR stratified by receipt of AC. Medicare allowable charges for SR, AC, and their respective complications were used. Decision analysis modeling and microsimulation were performed to account for proportions of chemotherapeutic agents administered in real-world settings. The incremental cost-effectiveness ratio (ICER) was calculated over a 5-year horizon. Probabilistic and two-way sensitivity analyses were performed. **Results:** 3662 of 18709 patient (19.6%) who met inclusion criteria received AC for SR stage IB NSCLC, with usage ranging from 15-27% annually. After propensity score matching, an overall survival benefit of AC was conferred over SR alone (at 5 years: 68.9% vs 60.4%, $p < 0.001$). The incremental cost of AC over SR alone was $11,541. The incremental effectiveness of AC was 0.28 life-years, with an ICER of $41,218. In two-way sensitivity analysis, AC plus SR dominated for the entire range of cost and survival estimates. In probabilistic sensitivity analysis, AC plus SR dominated the model above a willing-to-pay threshold of $16,000. AC costs could nearly double and the ICER remained under conventional thresholds. However, only 3 of the 4 common AC regimens were cost effective. **Conclusions:** In stage IB NSCLC, surgery is insufficient to render a cure. The addition of AC to SR extends life-expectancy and is cost-effective compared to SR alone. These conclusions are valid over a range of clinically meaningful variations in cost and treatment outcomes, though a cost-conscious approach is needed when selecting an AC regimen. This represents a novel change in the treatment of stage IB NSCLC.

8527 Poster Session (Board #263), Sat, 8:00 AM-11:30 AM

Early experience with IBM Watson for Oncology (WFO) cognitive computing system for lung and colorectal cancer treatment. *First Author: S.P. Somashekhar, Manipal Comprehensive Cancer Center, Bangalore, India*

Background: IBM Watson for Oncology is an artificial intelligence cognitive computing system that provides confidence-ranked, evidence-based treatment recommendations for cancer. In the present study, we examine the level of agreement for lung and colorectal cancer therapy between the multidisciplinary tumour board from Manipal Comprehensive Cancer Centre in Bangalore, India, and Watson for Oncology. **Methods:** Watson for Oncology is a Memorial Sloan Kettering Cancer Center (New York, USA) trained cognitive computing system that uses natural language processing and machine learning to provide treatment recommendations. It processes structured and unstructured data from medical literature, treatment guidelines, medical records, imaging, lab and pathology reports, and the expertise of Memorial Sloan Kettering experts to formulate therapeutic recommendations. Treatment recommendations are provided in three categories: recommended, for consideration and not recommended. In this report we provide the results of the independent and blinded evaluation by the multidisciplinary tumour board and Watson for Oncology of 362 total cancer cases comprised of 112 lung, 126 colon and 124 rectal cancers seen at the Centre within the last three years. The recommendations of the two agents were compared for agreement and considered concordant when the tumour board recommendation was included in the recommended or for consideration categories of the treatment advisor. **Results:** Overall, treatment recommendations were concordant in 96.4% of lung, 81.0% of colon and 92.7% of rectal cancer cases. By tumour stage, treatment recommendations were concordant in 88.9% of localized and 97.9% of metastatic lung cancer, 85.5% of localized and 76.6% of metastatic colon cancer, and 96.8% of localized and 80.6% of metastatic rectal cancer. **Conclusions:** Treatment recommendations made by the Manipal multidisciplinary tumour board and Watson for Oncology were highly concordant in the cancers examined. This cognitive computing technology holds much promise in helping oncologists make information intensive, evidence based treatment decisions.

8528 Poster Session (Board #264), Sat, 8:00 AM-11:30 AM

Typical bronchial NETs as a misleading biology. *First Author: Dalvinder Mandair, Royal Free Hospital Neuroendocrine Tumour Unit, London, United Kingdom*

Background: Bronchial Neuroendocrine tumours (NETs) are rare with an incidence of between 0.2 – 2 per 100,000 population. There has been an increase in prevalence due to increased awareness, enhanced immunohistochemistry and greater use of Computed tomography (CT). Bronchial NETs are classified according to the WHO guidelines developed in 2004 where they are graded by histological classification into 'typical', 'atypical' NETs or small and large neuroendocrine carcinoma's (NECs). Typical NETs are regarded as being low-grade malignant however metastatic disease can still develop. Aims: We sought to determine the incidence of metastatic typical bronchial NETs, their survival and investigate the imaging and treatment used in their management. **Methods:** We performed a retrospective analysis of all bronchial NETs managed at our centre from 2001 to 2016. From those identified as typical NETs, we analysed clinical records in those with advanced disease (Stage IV). **Results:** From a total of 251 bronchial NETs, there were 147 'Typical' NETs, 30(20%) of whom had advanced disease compared to 82 'Atypical' bronchial NETs of whom 55 had advanced disease (67%). The median age at diagnosis was 58 (range 24-77). In the 'Typical' NETs, 24/30 had liver metastases, 19/30 skeletal metastases, and 16 had carcinoid syndrome (CS). Functional imaging with FDG PET scan was positive in 7/10 patients and somatostatin receptor scintigraphy (SRS) positive in 16/20 and in 4/11 there was avidity with both. 20 patients were treated with somatostatin analogues predominantly for CS symptoms. 11 patients treated with peptide radiolabelled receptor targeted therapy (PRRT) with a median Time-To-Progression (TTP) of 27 months. 11 patients received chemotherapy with median TTP of 16 months with 4 patients demonstrating partial response. **Conclusions:** Typical bronchial NETs can lead to advanced disease in up to 20% of patients. Their behavior can be aggressive and is not predictable by histology alone. Functional imaging with both FDG and SRS may help determine the most appropriate treatment. Both PRRT and chemotherapy can be considered in progressive disease.

8529 Poster Session (Board #265), Sat, 8:00 AM-11:30 AM

The role of adjuvant therapy in the management of resected large cell neuroendocrine carcinoma (LCNEC) of the lung: A National Cancer Database (NCDB) analysis. *First Author: Lara Ann Kujtan, University of Missouri at Kansas City Medical School, Kansas City, MO*

Background: Large cell neuroendocrine carcinoma (LCNEC) is characterized by aggressive behavior and poor outcomes compared with other non-small cell lung cancers (ONSCLC). **Methods:** The National Cancer Database (NCDB) was used to identify patients diagnosed with early stage NSCLC (pathologic stage I, II, IIIA) from 2004-2012 who underwent surgical resection. Patients were divided into two groups: LCNEC and ONSCLC. One-way ANOVA was used to compare continuous variables, and chi-squared testing was used to compare categorical variables. Multivariate logistic regression analyses were used to obtain hazard ratios. **Results:** We identified 1672 patients with resected LCNEC and 134139 with resected ONSCLC. A higher proportion of patients with ONSCLC had a Charlson-Deyo co-morbidity score of 0 compared to LCNEC patients (50.6% vs. 43.8%; $p < 0.001$). No other significant differences in clinical and demographic characteristics were identified. Overall survival was lower for LCNEC patients across all stages when compared to patients with resected ONSCLC (46 months versus 74 months; 5-year survival 45% versus 57%; $p < 0.001$). Multivariate analysis confirmed the survival benefit for adjuvant chemotherapy in resected LCNEC across all stages, including stage IA, although it did not reach statistical significance (hazard ratio 0.72 (0.51-1.02), $p = 0.64$; Table). **Conclusions:** Adjuvant chemotherapy significantly improves survival for stage IB, II and IIIA LCNEC compared to surgery alone. Patients with stage IA LCNEC appear to benefit from adjuvant chemotherapy although it did not reach statistical significance. The overall magnitude of benefit from adjuvant chemotherapy appears to be higher for patients with LCNEC compared to ONSCLC.

Pathologic Stage	5-Year Survival		*p*-value	Adjusted HR	Adjusted *p*-value
	Surgical resection	Surgical resection + chemotherapy			
IA	49%	58%	0.009	0.72 (0.51,1.02)	0.064
IB	42%	67%	<0.001	0.47 (0.34,0.66)	<0.001
IIA	31%	52%	0.019	0.52 (0.29,0.96)	0.036
IIB	30%	50%	<0.001	0.57 (0.35,0.92)	0.021
IIIA	12%	28%	<0.001	0.41 (0.25,0.67)	<0.001

8530 Poster Session (Board #266), Sat, 8:00 AM-11:30 AM

Phase 1/2 study of veliparib (V) combined with carboplatin (Cb) and etoposide (E) in patients (pts) with extensive-stage disease (ED) small cell lung cancer (SCLC) and other solid tumors: Phase 1 results. *First Author: Florence Atrafi, Erasmus Medisch Centrum, Rotterdam, Netherlands*

Background: The majority of SCLC cases are diagnosed as ED, for which there is a poor prognosis and no curative treatment (Tx). V, a potent PARP inhibitor, has been shown in preclinical studies to enhance the antitumor activity of platinum-based agents and E against SCLC. The presented phase 1 dose-escalation (NCT02289690) evaluated V combined with Cb/E. **Methods:** Pts (≥18 years) with ED SCLC or other advanced/metastatic solid tumors with ≤1 line of prior cytotoxic therapy and ECOG performance score 0/1 were included. This study followed a 3+3 design. V starting dose and schedule were 80 mg BID PO administered on days (D) –2 to 5 in combination with Cb AUC 5 mg/mL • min administered on D 1 and E 100 mg/m^2 administered on D 1 to 3 via intravenous infusion in 21-D cycles. V schedules of D –2 to 12 and continuous dosing were also explored. Primary objectives were to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for V combined with Cb/E, and to evaluate the pharmacokinetic (PK) interaction between V and E. **Results:** Thirty-nine pts (n = 24 ED SCLC; n = 15 other solid tumors) with median age of 62 years (range 43–79) received study Tx. Most common adverse events (AEs; ≥40%) were nausea (54%), fatigue (51%), alopecia (46%), and anemia (44%); grade 3/4 AEs (≥30%) were decreased neutrophil count, neutropenia (31% each), and anemia (26%). Dose-limiting toxicity occurred in 1 pt (n = 1 grade 3 fatigue) at V 240 mg BID D –2 to 5. The MTD was not reached; RP2D for V was set at 240 mg BID on D –2 to 12 based on long-term tolerability. Continuous dosing of V 240 mg BID with Cb/E resulted in unacceptable Cb/E dose delays due to hematologic toxicity. Coadministration of V (80 to 240 mg BID) with Cb/E exhibited dose-proportional kinetics with no impact on the E PK. Confirmed responses: ED SCLC 63% (15/24 pts) across all dose levels and in 83% (5/6) at RP2D; other tumor types: 13% (2/15) across all dose levels. **Conclusions:** V + Cb/E had an acceptable safety profile in pts with ED SCLC, with an RP2D of 240 mg BID D –2 to 12. Coadministration of V with Cb/E had no effect on E PK. Responses were seen across all dose levels. A phase 2 study of V with Cb/E in ED SCLC is ongoing. Clinical trial information: NCT02289690.

8531 Poster Session (Board #267), Sat, 8:00 AM-11:30 AM

A multicenter, randomized, open-label, phase II trial of erlotinib versus etoposide plus cisplatin with concurrent radiotherapy in unresectable stage III non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutation. *First Author: Ligang Xing, Shandong Cancer Hospital, Jinan, China*

Background: Concurrent chemoradiotherapy is the standard treatment for patients(pts) with unresectable stage IIIA/IIIB NSCLC. In EGFR mutant pts, tyrosine kinase inhibitor(TKI) exhibits clinical benefits over chemotherapy regimens in terms of efficacy and safety as well as specific enhancement of radiation effects. This multicenter, randomized, open-label, phase II trial aimed to compare the erlotinib and etoposide/cisplatin with concurrent radiotherapy (RT) in pts with EGFR-mutant. **Methods:** Histopathology/cytology confirmed stage IIIA/B unresectable NSCLC pts (age 18-75) with ECOG PS 0-1 and EGFR exon 19 or 21 mutation were included and randomized (1:1) into two arms: erlotinib (E) and etoposide/cisplatin (EP). E arm was treated with oral erlotinib (150mg/day for 2 years or till either disease progression or intolerable toxicities) and RT (200cGy/day, 5 days/week for 6 weeks from first day erlotinib). EP arm was treated with sequential etoposide (50 mg/m^2 IV days 1-5, 29-33) and cisplatin (50mg/m^{2}IV day 1,8, 29,36) and RT (from first day drug). Primary endpoint is progress free survival (PFS). Secondary endpoints are objective response rate(ORR), local control rate(LCR), overall survival(OS), quality of life(QoL) and safety. **Results:** 252 pts were screened, and 41 were enrolled into E(n=20) and EP (n=21) arms. Characteristics of age, sex, histologic type, N2, EGFR 19 and 21 mutation were well balanced in each arm. Comparing with EP, median PFS of E arm was significantly improved (27.86 vs 6.41 months; HR 0.053, 95% CI: 0.006-0.463; $P<0.001$). ORR and DCR were 60.0% vs. 38.1% ($P=0.217$), and 65% vs. 47.6%($P=0.350$), respectively. Two arms had same incidence of adverse effects (CTCAE Grade≥1, 86.7%[13/15]), and most common sAE(Grade≥3) was rash (20%, 3/15) and hematological toxicity(26.7%, 4/15), respectively. **Conclusions:** In unresectable stage III EGFR mutant NSCLC pts, concurrent erlotinib/RT provides a statistically significant PFS improvement with well tolerability. These results warrant a phase III study to confirm. (RECEL, NCT01714908). Clinical trial information: NCT01714908.

8532 Poster Session (Board #268), Sat, 8:00 AM-11:30 AM

Randomized trial of thoracic radiotherapy with or without concurrent daily low-dose carboplatin in elderly patients with locally advanced non-small cell lung cancer (NSCLC): Long-term follow-up of Japan Clinical Oncology Group (JCOG) Study JCOG0301. *First Author: Shinji Atagi, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan*

Background: In the phase III JCOG0301 trial, concurrent chemoradiotherapy (CRT) was compared with radiotherapy (RT), demonstrating clinically significant survival benefits in elderly patients with locally advanced NSCLC after a median follow-up of 19.4 months. However, the long-term patterns and cumulative incidences of toxicity associated with CRT and RT are poorly understood for elderly patients. We report long-term survival data and late toxicities after a minimum follow-up of 6.4 years. **Methods:** Eligible patients were older than 70 years and had unresectable stage III NSCLC. They were randomly assigned to RT alone (RT arm: irradiation with 60 Gy in 30 fractions) or CRT (CRT arm: the same RT with additional concurrent use of carboplatin 30 mg/m^2 per fraction up to the first 20 fractions). The primary endpoint was overall survival (OS). Prognosis and adverse events data were collected beyond those in the initial report of this trial. Kaplan-Meier survival curves and 3- and 5-year survival proportions were calculated. Late toxicities were defined as occurring later than 90 days after RT initiation. **Results:** From September 2003 to May 2010, 200 patients (RT arm, n = 100; CRT arm, n = 100) were enrolled. Consistent with the initial report, the CRT arm had better OS than the RT arm (HR = 0.743, 95% CI = 0.552 – 0.998, one-sided p = 0.0239 by stratified log-rank test). In the RT and CRT arms, median OS was 16.5 and 21.7 months, 3-year survival was 16.3% and 34.3%, and 5-year survival was 9.2% and 15.2%, respectively. %Grade 3/4 late toxicities were 7.4% (heart 2.1%, lung 5.3%) in the RT arm (n = 94) and 7.5% (esophagus 1.1%, lung 6.5%) in the CRT arm (n = 93). No additional cases of late toxicity (Grade 3/4) were seen since the initial report. There were 7 treatment-related deaths, all of which were recorded in the initial report: 4 (4.0%) in the RT arm and 3 (3.0%) in the CRT arm. **Conclusions:** Long-term follow-up confirms the survival benefits of CRT for elderly patients with locally advanced NSCLC. There was no observed increase in late toxicity with CRT, as compared with RT alone. Clinical trial information: 00132665.

8533 Poster Session (Board #269), Sat, 8:00 AM-11:30 AM

Impact of adjuvant chemotherapy in non-metastatic node positive bronchial neuroendocrine tumors (BNET). *First Author: Gustavo Figueiredo Marcondes Westin, Mayo Clinic, Rochester, MN*

Background: BNET are a rare and frequently indolent group of neoplasms. Lobectomy is frequently done for patients with non-metastatic disease, and the role of adjuvant chemotherapy for patients with node positive disease (N+) is debated. **Methods:** Utilizing the National Cancer Database from 2004-2012 we identified 1682 patients with N+ non-metastatic BNET. All patients underwent primary resection, had pathologically confirmed diagnosis, complete follow up data, and were alive > 30 days following surgery. Overall survival (OS) was analyzed utilizing Kaplan-Meier curves, and log-rank tests were used to compare 2 groups of patients that differed based on receiving or not adjuvant chemotherapy. Subgroup analyses were performed based on histologic subtypes. Cox proportional hazards was performed to control for age, sex, race, grade, surgical margins, type of surgery, year of diagnosis, Charlson/Deyo Score, insurance, facility type, and location. **Results:** 651 patients with typical carcinoid (CT), 239 atypical carcinoid (ACT), 426 large cell neuroendocrine carcinoma (LCNEC), and 366 neuroendocrine carcinoma (NEC) were analyzed. The cohort median age was 61, and the female:male ratio was 1.8 for CT, ACT and NEC, and 1 for LCNEC 90% of patients were White and there were no significant differences amongst histologic subtypes. 6% of patients with CT received ADJ-CT, compared to 40% ACT, 42% NEC, and 70% LCNEC. In a multivariate analysis, only increasing age was associated with worse prognosis across all histologic subtypes, and non-academic facility for CT, and male sex for NEC. ADJ-CT was not associated with OS benefit for patients with ACT (HR 1.1; 95% CI 0.68-1.78; p:0.6), was associated with inferior OS in CT (HR: 3.8 (95% CI 1.9-7.0; p = 0.004) and NEC (HR: 2.15; 95% CI 1.5-3.0; p < 0.001), and may provide benefit for LCNEC (HR: 0.67; 95% CI 0.5-0.9; p = 0.009). **Conclusions:** Adjuvant chemotherapy was not associated with survival benefit for patients with node positive and non-metastatic BNET except for LCNEC, and may be harmful for patients with CT and NEC.

8534 Poster Session (Board #270), Sat, 8:00 AM-11:30 AM

Randomized phase II trial of S-1 plus cisplatin or docetaxel plus cisplatin with concurrent thoracic radiotherapy for inoperable stage III non-small cell lung cancer (TORG1018). *First Author: Kaoru Kubota, Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan*

Background: Concurrent chemoradiotherapy (CCRT) is standard of care in patients with inoperable stage III non-small cell lung cancer (NSCLC), however the best chemotherapy regimen has not been identified. The study was conducted to evaluate cisplatin plus S-1 (SP) or cisplatin plus docetaxel (DP) both with concurrent thoracic radiotherapy in patients with inoperable stage III NSCLC. **Methods:** Patients with inoperable stage III NSCLC were randomized to SP (S-1 40 mg/m^2 twice a day on days 1-14 and 29-42 plus cisplatin 60 mg/m^2 on days 1 and 29) or DP (docetaxel 50 mg/m^2 and cisplatin 80 mg/m^2 on days 1 and 29), stratified by institution, gender, histology, and stage. In both arms, concurrent radiotherapy began on day 1 (60 Gy/30 fr). After CCRT, patients in each group received two additional cycles of the consolidation chemotherapy. Primary endpoint was 2-year overall survival (OS), and secondary endpoints were OS, progression-free survival (PFS), toxicity profile, dose intensity and objective response rate (ORR). **Results:** From May 2011 to August 2014, 110 patients were enrolled from 19 institutions. Four patients (one in SP and 3 in DP) were ineligible, and 106 patients (53 in each arm) were evaluable for efficacy and safety. Patient characteristics were: male/female 83/23; median age 65 (range 42-74); performance status 0/1 59/47; IIIA/IIIB 59/47. With a median follow-up of 39.3 months, 2-year survival and median OS were 79% (95% CI: 66-88%) and 55.2 months in the SP arm and 69% (95% CI: 55-80%) and 50.8 months in the DP arm, respectively. ORR and median PFS in SP arm were 71.7% and 11.6 months, and ones in the DP arm were 67.9% and 19.9 months. Grade 3/4 leukopenia (62.3/34.0%) and neutropenia (56.6/28.3%) were significantly more frequent in DP arm than SP arm. Incidences of non-hematological toxicities including febrile neutropenia, anorexia, nausea, diarrhea, radiation pneumonitis and esophagitis tended to be higher in DP arm. No treatment-related death occurred. **Conclusions:** The 2-year OS favored for SP arm with less toxicity. We choose SP with concurrent thoracic radiotherapy as a future reference regimen. Clinical trial information: UMIN000005993.

8535 Poster Session (Board #271), Sat, 8:00 AM-11:30 AM

Feasibility of endobronchial ultrasound fine-needle aspiration for massively parallel next-generation sequencing in cancer patients. *First Author: Simon R. Turner, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Next generation sequencing (NGS) is an important emerging tool in precision oncology, allowing identification of a growing number of clinically validated and investigational therapeutic molecular targets. A potential limitation is that some NGS assays require more DNA input than more limited molecular assays. Endobronchial ultrasound fine-needle aspiration (EBUS-FNA) is a minimally invasive procedure for sampling mediastinal and pulmonary lesions, but it is unknown if it provides adequate material for NGS. **Methods:** An IRB approved, retrospective review was performed of patients undergoing EBUS-FNA by thoracic surgeons at our institution 3/1/14 - 9/28/16. NGS was performed using an assay developed at our institution that detects mutations in up to 410 genes (MSK-IMPACT). Samples diagnostic for malignancy and with MSK-IMPACT requested were identified. Pathology and clinical data were drawn from the medical record and MSK-IMPACT results were examined. **Results:** 784 EBUS-FNA were done in the study period. MSK-IMPACT was requested on 115 positive samples. MSK-IMPACT was successful in 99 samples (86.1%), identifying an average of 12.7 mutations at a mean coverage depth of 806X. In 17 (17.2%) samples, tumor content was suboptimal (< 20% of nucleated cells), with fewer identified mutations than in cases with higher tumor content (6.8 vs 13.9, p = 0.01). NGS was performed on paraffin-embedded cell blocks in 93 cases (93.9%), and in 6 cases DNA extraction was performed from residual cytological material isolated from supernatant including cell-free DNA. Failures were attributable to low cell content (7), high contamination by benign cells (4) or both (1) and processing issues (4). No difference in surgical or radiologic parameters were identified for failed or suboptimal samples. **Conclusions:** In our practice, EBUS-FNA has a high rate of success for obtaining adequate tissue for NGS. Ability to utilize cell-free DNA for molecular studies – a new process in our lab – allows increased success of molecular testing in scant samples. Further studies may identify factors contributing to NGS failure and to improving success for samples with minimal cellularity.

8536 Poster Session (Board #272), Sat, 8:00 AM-11:30 AM

Retrospective analysis of clinical outcomes of early stage ALK-positive (ALK+) non-small cell lung cancer (NSCLC). *First Author: Ibiayi Dagogo-Jack, Massachusetts General Hospital, Boston, MA*

Background: ALK rearrangements are important oncogenic drivers in NSCLC. However, the prognostic implications of these rearrangements are unclear due to 1) conflicting results from small series of patients (pts) with early-stage ALK+ NSCLC, and 2) use of highly effective ALK tyrosine kinase inhibitors (TKI) in the metastatic setting. To assess the prognostic significance of ALK rearrangements in resected NSCLC, we performed a retrospective analysis of survival outcomes among pts with resected ALK+, EGFR+, or KRAS+ NSCLC treated at two institutions. **Methods:** We reviewed charts of pts that underwent resection for stage 1-3 NSCLC at Massachusetts General Hospital or Memorial Sloan Kettering Cancer Center between 1/2009 and 12/2012. Recurrence-free survival (RFS) was estimated for each genotype. **Results:** Among 764 pts (480 KRAS+, 255 EGFR+, 29 ALK+), we identified 555 (73%), 101 (13%), and 108 (14%) pts with stage I, 2, and 3 NSCLC, respectively. ALK+ pts were distributed across all stages: 10 (34%) stage I, 6 (21%) stage 2, and 13 (45%) stage 3 NSCLCs. Chemotherapy was administered to 14 ALK+ (0% stage 1, 67% stage 2, 77% stage 3), 45 EGFR+ (3% stage 1, 44% stage 2, 81% stage 3), and 96 KRAS+ pts (4% stage 1, 56% stage 2, 71% stage 3), respectively, for early-stage NSCLC. Thirteen (7%) stage 1 EGFR+ patients received adjuvant EGFR TKI. Although median RFS was not reached for EGFR+ pts, it was 24.3 months (95%CI 11.4 to 65.3) for ALK+ pts and 72.9 months (95%CI 59.7 to undefined) for KRAS+ pts. RFS for ALK+ NSCLC was significantly shorter than the other groups (HR 2.9, 95%CI: 1.75-4.89 vs. EGFR and HR 1.8, 95%CI: 1.12-2.93 vs. KRAS). When adjusted for stage, ALK+ NSCLC remained associated with worse RFS compared to EGFR+ NSCLC (HR 1.8, 95%CI: 1.09-3.12), but not when compared to KRAS+ NSCLC (HR 1.30, 95%CI: 0.79-2.12). **Conclusions:** Early stage ALK+ NSCLC is associated with shorter RFS than EGFR+ NSCLC. The propensity for relapse and the significant anti-tumor activity of ALK TKIs in pts with metastatic NSCLC suggest that enrollment of patients on trials of adjuvant ALK TKIs should be prioritized.

8537 Poster Session (Board #273), Sat, 8:00 AM-11:30 AM

Multi-modality therapy for stage IIIa N2 non-small cell lung cancer: Does the answer lie in the components? *First Author: Jonathan David Spicer, McGill University Health Centre, Montréal, QC, Canada*

Background: Neoadjuvant chemoradiation prior to surgery offers excellent locoregional control, while neoadjuvant chemotherapy I meant to offer improved systemic therapy in stage IIIA N2 non-small cell lung cancer (NSCLC). Data are lacking to select the optimal regimen. We compared oncologic outcomes for stage IIIA N2 NSCLC utilizing granular data from three experienced lung cancer treatment centers. **Methods:** This collaborative retrospective study unites 3 major thoracic centers with differing approaches to IIIA N2 NSCLC. Patients undergoing surgical resection post-neoadjuvant chemotherapy (CxT) or concurrent chemoradiation (CxRT) were included. Primary outcomes were overall and disease- free survival (OS and DFS). **Results:** Demographic data and outcome data are in Table 1. There were no differences in 5-year OS (CxT 40% vs CxRT 42%, p=0.265) nor in DFS (CxT 30% vs 31%, p=0.275). Recurrence rates (CxT47%vsCxRT48%,p=0.799) and patterns were identical (Local: CxT 10% vs CxRT 8%; and Distant: CxT 30% vsCxRT29%,p=0.764). There was no difference in peri-operative mortality. To address potential bias from differing staging strategies, we excluded patients without invasive mediastinal staging and there were still no differences in OS (CxT 40% vs CxRT 42%, p=0.364) and DFS (CxT 30% vs CxRT 31%, p=0.332) Multivariable analysis identified pnemonectomy (HR1.66,p<0.001) and ypN2 (HR1.84, p<0.001) to be associated with overall survival. **Conclusions:** Both treatment strategies produce equivalent and better than expected outcomes compared to historical controls for IIIA N2 NSCLC.

Demographic and outcome data.

	Preoperative chemotherapy only (N=662)	Preoperative chemo-radiation (N=109)	P value
Age, years; Mean(Range)	64(31-86)	62(43-80)	0.050
Sex(Male)	316(47.7)	53(48.6)	0.863
Pack years, Mean(Median)	39(35)	32(30)	0.097
Recurrence patterns			
None	353(53.3)	53(53.5)	0.764
Local	65(9.8)	8(8.1)	
Distant	201(30.4)	29(29.3)	
Both	43(6.5)	9(9.1)	
90-day mortality	24(3.6)	5(4.6)	0.588

8538 Poster Session (Board #274), Sat, 8:00 AM-11:30 AM

Interplay between immune infiltration and tumor progression and survival in non-small cell lung cancer: An analysis of institutional and public data. *First Author: Ali Jalali, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In many types of cancer, infiltration of tumor by immune cells, as a reflection of the immune response against the tumor, is thought to play a critical role in clinical outcome. Tumors, however, tend to evade the immune response as they progress. In this study, we characterize the interplay between immune infiltration and tumor progression and survival in non-small cell lung cancer (NSCLC). **Methods:** We performed histologic immune profiling and microarray expression analysis on primary tumor specimens from 275 NSCLC patients (PR: PROSPECT trial) as well as RNA-Seq expression analysis on biopsy specimens from 50 patients with advanced NSCLC (B2: BATTLE-2 trial). RNA-Seq data from the TCGA lung cancer project was also analyzed. Immune Infiltration Score (IIS) was computed from the expression data using the Estimate package in R. Immune Suppression Score (ISS) was defined as the difference between the mean of CD3, CD4, CD8, FOXP3, and PD1 counts in the periphery and core of the tumor. **Results:** Tumor IIS is correlated (all $p < 0.0005$) with tumor immune infiltration as measured by inflammatory cell count on frozen tumor or several immune marker counts in tumor core. IIS is positively associated with survival ($p = 0.04$) independently of age ($p = 0.008$) and stage ($p = 8e\text{-}10$). IIS in the top half is associated with higher median survival vs. bottom half (10.2 vs 2.2 months, $p < 0.0001$) in B2. In TCGA lung adenocarcinoma samples, IIS is higher in stage I/II disease vs stage III/IV ($p = 0.003$). For all immune markers in PR samples, periphery of the tumor on average has higher counts vs tumor core ($p < 0.0011$), and this difference (suppression score) is higher in stage III/IV samples vs stage I/II for CD3, CD4, and CD8 (all $p < 0.04$) and for FOXP3 and PD1 ($p < 0.1$). ISS is negatively associated with survival ($p = 0.02$) independently of age ($p = 0.06$) and stage ($p < 0.0001$). **Conclusions:** As NSCLC tumors progress, immune infiltration in the periphery of the tumor increases while infiltration in the core decreases, reflecting increasing immune suppression. Tumor immune infiltration and suppression, as measured by IIS and ISS, are significant predictors of survival, independently of age and stage.

8539 Poster Session (Board #275), Sat, 8:00 AM-11:30 AM

Risk factors associated with brain metastases in ECOG-ACRIN E1505, a phase III randomized trial of adjuvant chemotherapy with or without bevacizumab for patients with completely resected stage IB (>/= 4 cm) - IIIA non-small cell lung cancer (NSCLC). *First Author: John M. Varlotto, University of Massachusetts Memorial Medical Center, Worcester, MA*

Background: ECOG-ACRIN E1505 was a phase III randomized trial of adjuvant chemotherapy with or without bevacizumab for patients with completely-resected Stage IB (>4CM) – IIIA non-small cell lung cancer. Prior studies have shown that the risk of brain recurrence in patients after definitive surgical resection is approximately 10%; however, covariates associated with development of brain recurrence have varied across these studies. We sought to estimate the incidence of and risk factors for brain recurrence. **Methods:** Among the 1501 patients enrolled to ECOG-ACRIN E1505, 121 patients developed brain metastases as their first site of recurrence and are the subject of this investigation. All 1501 patients underwent a pneumonectomy (N = 192) or (bi) lobectomy and had an R0 resection. The cumulative incidence of brain recurrence was estimated after adjusting for recurrence at other sites and death as competing events. A multivariable regression model was fitted using the methodology of Fine and Gray to evaluate the effect of covariates on the subdistribution of brain recurrence. **Results:** With a median follow-up of 50.3 months, a total of 121 brain metastases had been reported as the first site of recurrence. The incidence of brain recurrence at 12 months post-randomization was 3.7% (95% CI: 2.8% – 4.7%), and it increased to 8.5% (95% CI: 7.0% - 10.0%) at 3 years, and to 9.9% (95% CI: 8.0% - 11.7%) at 6 years. Risk factors for brain metastases included pneumonectomy (HR=1.8; p=0.01), and nonsquamous histology(HR=2.04; p=0.003), but bevacizumab(HR=0.64; p=0.02) was associated with potentially protective effect. **Conclusions:** The cumulative incidence of brain recurrence increased over time to 9.9% at 6 years in this population of patients with surgically-resected non-small cell lung cancer. Treatment, tumor histology, and type of resection appear to be associated with the risk of brain recurrence. Clinical trial information: NCT00324805.

8540 Poster Session (Board #276), Sat, 8:00 AM-11:30 AM

A nomogram for predicting post-operative cancer specific survival in AJCC 8th edition stage I NSCLC patients. *First Author: Wenhua Liang, Department of Thoracic Surgery/Oncology, the First Affiliated Hospital of Guangzhou Medical University, China State Key Laboratory and National Clinical Research Center for Respiratory Disease, Guangzhou, China*

Background: The AJCC 8th edition staging system has moved 4-5 cm 7th edition stage Ib NSCLC to current stage IIa, thus theoretically all current stage I patients are not considered candidates for adjuvant therapy (ad-Tx). This study was to develop a clinical nomogram for predicting cancer specific survival (CSS) of the current stage I resected NSCLC to identify those with higher risk for cancer-related deaths and potentially benefiting from ad-Tx. **Methods:** NSCLC cases between 1998 and 2013 was extracted from the SEER database and were randomly divided into training (n = 23,496) and validation (n = 7,915) cohorts. We identified and integrated the recurrence-associated factors to build a nomogram. The model was subjected to bootstrap internal validation and independent validation. The predictive accuracy and discriminative ability were illustrated by calibration plots and concordance index (C-index). We determined the cut-off for high-risk group by matching the nomogram-predicted 5-year CSS with that of the current 4-5 cm stage IIa cases. **Results:** In multivariate analysis, independent factors for CSS were examined lymph node count (< 16 vs. $>= 16$), tumor size, resection scope (lobectomy/segmentectomy/wedge resection), differentiation grade, histology (squamous vs. non-squamous vs. former BAC with majority being AIS/MIA) and visceral pleural invasion, which were then integrated into the model (sex and age were not included due to lack of direction to ad-Tx selection). The calibration curves showed excellent agreement between nomogram prediction and actual observation. The C-index of the nomogram was higher than that of staging system (Ia1, Ia2, Ia3, Ib) (training set, 0.60 vs. 0.56, $P < 0.01$; validation set, 0.60 vs. 0.57, $P < 0.01$). Specifically, 21.5% stage Ib patients (8.8% of all stage I) were categorized into high risk group (score > 29.5) and had inferior CSS compared with 4-5 cm stage IIa patients. **Conclusions:** We established a nomogram that can individually predict CSS for 8th edition stage I NSCLC. By this model, we identified a subset of patients with relatively high risk for recurrence. Further study to determine the impact of postoperative ad-Tx on these high risk patients is undergoing.

8541 Poster Session (Board #277), Sat, 8:00 AM-11:30 AM

Comprehensive molecular and immune profiling of non-small cell lung cancer and matched distant metastases to suggest distinct molecular mechanisms underlying metastasis. *First Author: Won-Chul Lee, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite complete resection, many non-small cell lung cancer (NSCLC) patients still develop and succumb to distant metastases. Previous studies suggested distant metastasis may be due to genomic evolution and/or suppressed immune surveillance. However, the relationship between specific genomic alterations and immune surveillance has not been systemically studied. **Methods:** We performed whole exome sequencing, RNA-Seq, methylation microarray, immunohistochemistry using multiple immune markers, and T cell receptor sequencing on 7 pairs of NSCLC primary tumors and matched metastases including 6 metachronous brain and 1 synchronous liver metastases. **Results:** On average, 84% of all somatic mutations (54% to 97%) and all 28 canonical cancer gene mutations were shared between primary tumors and paired distant metastases. Metastases also resembled paired primary tumors closely in regard to somatic copy number aberration profiles, methylation profiles. Subclonal analysis showed almost identical clonal architectures in 4 of 7 pairs of primary tumor and metastasis comparable to the similarity observed between different regions within the same tumors. The other 3 pairs, however, displayed clear evidence of clonal evolution. We validated these findings in a published dataset consisting of 38 pairs of primary NSCLC tumors and matched distant metastases. The RNA-Seq data showed that 25 of the top 35 significantly down-regulated signaling pathways in metastases relative to primary tumors were related to immune activation, which was validated in an independent cohort of 41 primary NSCLC tumors and distant metastases using NanoString's PanCancer Immune Profiling Panel. **Conclusions:** Our data suggest that molecular mechanisms underlying postsurgical distant metastasis may be variable among NSCLC patients. While genomic evolution may play a role in development of metastasis in some patients, distant metastasis may be early event during carcinogenesis without further genomic evolution in a substantial proportion of NSCLC patients. Furthermore, immune suppression may be a characteristic of cancer cells of metastatic capacity.

8542 Poster Session (Board #278), Sat, 8:00 AM-11:30 AM

Results of stereotactic body radiation therapy (SBRT) for T2 lung cancer: Outcomes of longer term follow-up. *First Author: Stephen Shamp, University Hospitals, Cleveland, OH*

Background: SBRT is a well-established, highly efficacious treatment for T1N0 non-small cell lung carcinoma (NSCLC). Its efficacy in T2N0 cancers is less clear. This is a review of our institutional experience with long-term follow-up. **Methods:** 45 patients with medically inoperable T2 N0/Nx M0 NSCLC who were treated with definitive SBRT between 2009 and 2013 were analyzed retrospectively. All patients underwent PET/CT staging and fiducial marker placement for image guided therapy with the Cyberknife platform. Radiation dose was 50 Gray in 5 fractions (N = 24), 50 Gray in 4 fractions (N = 11) or 54-60 Gray in 3 fractions (N = 10) delivered over 7 to 14 days. We analyzed overall survival from the date of start of SBRT, and we performed analyses actuarially using Cox regression analysis and Kaplan-Meier survival analysis for comparisons of hazard ratio (HR) among subgroups. **Results:** 45 patients were studied (median age 74). The 5-year actuarial overall survival was 18.7% (39.3% at 2 years), with most patients dying from lung cancer recurrence/progression outside of the treatment field. Subgroup analyses showed no statistically significant differences with respect to age, gender, histology, nominal radiation prescription dose, tumor diameter or PTV target volume (median PTV 87cc). There was statistically significantly better survival associated with increased maximum biologically effective dose (BED10) of radiation at the center of the tumor ($p = 0.03$). **Conclusions:** Unlike the outcomes for T1 NSCLC, our results in T2 NSCLC were disappointing, with a high rate of out-of-field failure and death from lung cancer. We stress the importance of diagnosis and treatment of NSCLC at the T1N0 stage. We suggest that patients with T2N0/Nx NSCLC be considered for SBRT dose intensification and/or combined modality therapy protocols.

8543 Poster Session (Board #279), Sat, 8:00 AM-11:30 AM

Detailed pathologic evaluation of low dose CT (LDCT) detected stage I/0 lung adenocarcinomas (ADCA). *First Author: Eric Burks, Lahey Hospital and Medical Center, Burlington, MA*

Background: Although LDCT lung screening improves survival, some worry that indolent BAC-like ADCA may be over-detected/treated. Comprehensive histologic subtyping has recently been adopted to improve grading and thus risk stratification in lung ADCA. We report a detailed pathologic comparison of stage I/0 lung ADCAs detected by LDCT screening vs. incidentally discovered ADCAs stratified by NCCN risk criteria. **Methods:** We performed comprehensive histologic subtyping on 35 consecutive stage I/0 LDCT screen detected ADCAs in patients meeting NCCN group 1/2 high risk (HR) criteria and compared to incidentally detected stage I/0 ADCAs meeting HR (n = 41) or low-risk (LR, n = 28) criteria. **Results:** Screen detected and incidentally detected ADCAs from HR groups show an equally low-rate of indolent, non-invasive/minimally invasive ADCAs (9%) compared to LR patients (36%). Aggressive solid predominant ADCAs were equally more frequent in HR patients from screen and incidentally detected patients (19%) compared to LR patients (6%). The rate of angiolymphatic invasion (59%) and air space invasion (32-34%) were similarly elevated in HR screen and incidental patients compared to LR patients (39% & 17% respectively). A collection of lepidic predominant (BAC-like) ADCAs associated with aggressive non-predominant cribriform and/or solid patterns, elevated mitotic rates, and high proportion of lymphatic invasion were uniquely observed in the screen-detected group (12%). Subgroup analysis of screen detected NCCN group 1 vs. 2 shows group 2 tumors exhibit histologic features which are at least as aggressive as group 1 tumors, albeit at smaller invasive sizes (1.2 cm vs. 1.5 cm) and lower stage (IA 75% vs. 61%). **Conclusions:** This is the first detailed pathologic comparison of LDCT screen detected vs incidentally discovered stage I/0 ADCA. Tumors from HR patients are pathologically more aggressive than LR tumors. Not all BAC-like tumors in LDCT screen detected patients should be presumed indolent given that approximately half of these bear histologic features of aggressive ADCAs while still in a lepidic predominant phase. NCCN group 2 tumors are similar to group 1 and should be further studied.

8544 Poster Session (Board #280), Sat, 8:00 AM-11:30 AM

Short- and long-term outcomes of early stage non-small cell lung cancer (NSCLC) surgery. *First Author: Michael J. Kelley, Durham VA Medical Center, Durham, NC*

Background: The goal of this study was to determine patient factors associated with short- vs long-term survival after surgery for stage I/II NSCLC and assess the distribution of causes of death over time. **Methods:** Using the VA Central Cancer Registry, we identified patients diagnosed 2001-2005 with stage I/II NSCLC who had surgery and survived 30 days after resection. We used multivariate logistic regression models to determine the impact of patient characteristics on 1 year (1Y), 5 year (5Y), and 10 year (10Y) mortality. We compared causes of death at 1Y versus 5Y after diagnosis. **Results:** The analysis included 4,693 patients. Among these patients, the 1Y, 5Y, and 10Y overall survival (OS) rates were 87%, 45%, and 22%, respectively. 50% of patients alive at 5 year survived to 10 years. For each survival time period, highest survival rates were among patients who were younger ($\leq$65), had stage I disease, had lobectomy, and had fewer comorbidities (all $p < 0.0001$). Significant differences in 1Y and 10Y OS were noted for histology, with highest 1Y OS among adenocarcinoma (88%) and squamous cell (87%) and highest 10Y OS among large cell (28%) and adenocarcinoma (25%). Racial differences were only observed in 10Y OS (whites 22%, blacks 26%, $p = 0.01$). In multivariate analyses, age $>$ 65, stage II disease, surgery other than lobectomy, and $\geq$3 comorbidities were associated with increased likelihood of 1Y, 5Y, and 10Y mortality. Large cell and other histology were the only additional significant predictors of 1Y mortality [OR: 1.94 (1.33-2.84) and OR:1.36 (1.05-1.77), respectively], and squamous cell histology was a significant predictor of 10Y mortality [OR: 1.19 (1.02-1.40)] relative to adenocarcinoma. Among patients who died within 1 year of diagnosis (n = 616), the primary causes of death were lung cancer (63%), cardiovascular disease (10%), other cancer (8%), respiratory disease (3%), and other causes (15). The contribution of these causes of 5Y mortality (n = 2602) were 60%, 11%, 10%, 4%, and 12%, respectively. **Conclusions:** Half of patients alive at 5Y after resection of stage I/II NSCLC were alive at 10Y. 10Y survival is associated with younger age, earlier stage, non-squamous histology, lobectomy, and fewer comorbidities, but not race.

8545 Poster Session (Board #281), Sat, 8:00 AM-11:30 AM

Intratumor heterogeneity of stage IA lung adenocarcinoma by multiregion whole exome sequencing and association with survival. *First Author: Kelly Quek, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Our previous study has suggested that complex genomic intratumor heterogeneity (gITH) was associated with an increased risk of relapse in patients with localized lung adenocarcinomas (LUAD). We have launched a study to investigate molecular and immune profile ITH of Stage IA NSCLC (a patient population with no optimal biomarker to guide postsurgical therapy) to understand the molecular evolution during early carcinogenesis and to identify biomarkers for early detection and intervention. Here, we report the preliminary analysis on gITH. **Methods:** We performed multiregion whole exome sequencing on 30 Stage IA LUAD and matched normal lung tissue to a median sequencing depth of 494x. 15 patients have relapsed within 3 years postsurgery (cases) and 15 patients have not relapsed with a minimum of 5-year postsurgical follow up (controls). Cases and controls are 1:1 matched for the key prognostic factors including tumor size, smoking status, age, gender, ethnicity and lobectomy or wedge resection. Shannon diversity index (SDI) was used to quantify ITH in each individual tumor. Kaplan-Meier method was used to evaluate the relationship between ITH and disease-free survival (DFS) as well as overall survival (OS). **Results:** Consistent with our previous study, 108 of 110 (98.2%) canonical cancer gene mutations were shared events by all regions of individual tumor. Compared to non-relapsed controls, tumors from relapsed cases demonstrated significantly higher degree of ITH (SDI of 1.78 in cases vs 1.58 for controls, $p = 0.016$). Higher degree of gITH was associated with shorter DFS ($p = 0.008$) and shorter OS ($p = 0.0153$). Significantly higher mutation burden was observed in tumors from relapsed patients (median of 10.86 mutations per MB in cases vs 7.45 mutations per MB in controls, $p = 0.03$). Analysis of gITH on a larger cohort and on predicted neoantigen, methylation, gene expression and immune profiles are in progress. **Conclusions:** Majority of cancer gene mutations are clonal events during early carcinogenesis of LUAD. Complex gITH may be associated with more aggressive biology and inferior clinical outcome in patients with Stage IA LUAD, therefore, may be evaluated as a potential biomarker.

8546 Poster Session (Board #282), Sat, 8:00 AM-11:30 AM

Tolerability of veliparib (V) in combination with carboplatin (C)/paclitaxel (P): Based chemoradiotherapy (CRT) in subjects with stage III non-small cell lung cancer (NSCLC). *First Author: David E. Kozono, Dana-Farber Cancer Institute, Boston, MA*

Background: CRT is a standard for patients with Stage III NSCLC. V is a potent, orally bioavailable PARP1/2 inhibitor that can delay DNA repair following chemotherapy or radiation induced damage. A Phase 2 study indicated favorable efficacy of V vs placebo when added to C/P in advanced NSCLC (Ramalingam et al. *Clin Cancer Res.* 2016). Based on these results, a Phase 1/2 trial was initiated to study the safety and efficacy of V/C/P-based CRT in the treatment of Stage III NSCLC. **Methods:** Subjects without prior NSCLC therapy suitable for definitive CRT received V plus C AUC 2 + P 45 mg/m^2 weekly + 60 Gy over 6-9 weeks. V was escalated from 60 mg BID to a maximum planned dose based on prior studies of 240 mg BID via 3+3 design with allowed over-enrollment followed by consolidation therapy of V 120 mg BID + C AUC 6 + P 200 mg/m^2 for up to two 21-day cycles. **Results:** Thirty-one subjects (median age 64; 10 male) have been enrolled to date into dosing cohorts at 60 mg (7), 80 mg (9), 120 mg (7) and 200 mg (8). PK of V was dose proportional. CRT or V required dose reduction for 0 or 1 subject, respectively. Four (13%) subjects discontinued study during CRT. No DLTs have been observed and an MTD has not yet been identified. The most common any grade AEs were fatigue (16), esophagitis (15), nausea (13), neutropenia (12), thrombocytopenia (12), constipation (10) and decreased appetite (10). 21 SAEs were observed including 8 with reasonable attribution to V but outside the DLT window including G3/4 febrile neutropenia (2), G3 dehydration (1), G3 vomiting (1), G3 radiation esophagitis (1), G3 esophageal stricture (1), G3 intractable N/V (1) and G5 sepsis during consolidation (1). Of 21 subjects evaluable for tumor assessment, best response was CR (1), PR (11), SD (6), and PD (3). **Conclusions:** V/C/P-based CRT followed by V/C/P consolidation therapy is a tractable regimen for the treatment of Stage III NSCLC. A randomized placebo-controlled Phase 2 extension of this study is planned. Clinical trial information: NCT02412371.

8547 Poster Session (Board #283), Sat, 8:00 AM-11:30 AM

Phase Ib study of tepotinib in EGFR-mutant/c-Met-positive NSCLC: Final data and long-term responders. *First Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: Patients (pts) with NSCLC that is initially responsive to EGFR tyrosine kinase inhibitors (EGFR TKI) typically develop resistance, often associated with aberrant c-Met activity. Dual inhibition of EGFR and c-Met is therefore a rational option to treat c-Met+ EGFR TKI-resistant NSCLC. Tepotinib is a highly selective c-Met inhibitor with good tolerability and promising activity against solid tumors. We report final data from a phase Ib trial of tepotinib + gefitinib in pts with c-Met+/EGFR-mutant NSCLC conducted in Asia. **Methods:** Eligible pts were adults with locally advanced/metastatic NSCLC and ECOG PS 0–1. Tumors had to express EGFR with an activating mutation be resistant to EGFR TKI therapy and be c-Met+ by IHC. Pts received tepotinib 300 or 500 mg QD combined with gefitinib 250 mg QD (T300G250 or T500G250). The primary objective was to determine the recommended phase II dose (RP2D) of tepotinib in combination with gefitinib; secondary objectives included pharmacokinetics (PK), safety, and antitumor activity. **Results:** 18 pts were enrolled (median age 65 [41–78]; 8 male); 6 received T300G250, 12 T500G250. No dose-limiting toxicities were observed, and tepotinib 500 mg QD was confirmed as the RP2D. 17 pts experienced treatment-related treatment-emergent adverse events (TRTEAEs), mostly grade $\leq$2 and most commonly diarrhea (12), rash (8), and amylase increase (6). Grade $\geq$3 TRTEAEs were increased amylase (n = 4), increased lipase (3), neutropenia (1), and hyperglycemia (1). The best overall response was partial response in 6 pts; 4/7 pts with IHC 3+ tumors responded (all treated with T500G250) vs 2/11 with IHC 2+ tumors. Response durations of pts with PR were 4.2–12.5 months. 4/18 pts (IHC 2+, n = 3) had stable disease. 8 pts experienced progression free survival $>$ 5 months, 3 pts $>$ 10 months. PK were as expected from previous studies. **Conclusions:** Tepotinib in combination with gefitinib was well tolerated. The RP2D of tepotinib for use in combination with gefitinib in NSCLC is 500 mg QD. T500G250 showed signs of activity against c-Met+ tumors. A phase II trial is randomizing $\approx$156 pts with c-Met+/T790M– tumors who have failed first-line EFGR TKI 2:1 to tepotinib + gefitinib or pemetrexed + cisplatin/carboplatin. Clinical trial information: NCT02864992.

8548 Poster Session (Board #284), Sat, 8:00 AM-11:30 AM

Prognostic impact of PD-L1 expression in correlation with HLA class I expression status in stage I adenocarcinoma of the lung. *First Author: Kazue Yoneda, University of Occupational and Environmental Health, Kitakyushu, Japan*

Background: Programmed death-ligand 1 (PD-L1) and human leukocyte antigen (HLA) class-I, expressed on tumor cells (TCs), are important regulators in cancer immunity. The current study was conducted to assess prognostic impact of PD-L1 status in correlation with HLA class-I status in lung adenocarcinoma. **Methods:** A total of 94 patients with completely resected pathologic stage I lung adenocarcinoma were retrospectively reviewed. PD-L1 expression on TCs was evaluated with immunohistochemistry, in correlation with several clinicopathological and molecular features including HLA class-I expression on tumor TCs. **Results:** Seventeen patients (18.1%) had tumor with positive PD-L1 expression (percentage of TCs expressing PD-L1, $\geq$ 5%), and the incidence was higher in smokers with higher smoking index and in poorly differentiated tumor. There was no significant correlation between HLA class-I expression and PD-L1 expression. PD-L1-positivity was a significant factor to predict a poor survival (5-year survival rate, 66.7% versus 85.9%; P = 0.048), which was enhanced in tumor with normal HLA class-I expression (p = 0.029) but disappeared in tumor with reduced HLA class-I expression. **Conclusions:** The prognostic impact of PD-L1 expression on TCs in early-stage resectable lung adenocarcinoma was distinct according to HLA class-I expression on TCs.

8549 Poster Session (Board #285), Sat, 8:00 AM-11:30 AM

Lobectomy with mediastinal nodal dissection versus partial lobectomy in patients with bronchial carcinoid tumors: A NCDB analysis. *First Author: Gustavo Figueiredo Marcondes Westin, Mayo Clinic, Rochester, MN*

Background: Bronchial carcinoid tumors are a rare group of neoplasms that usually have an indolent clinical behavior. Surgical resection is the main treatment modality for patients with early stage disease, however it is unclear if lobectomy with mediastinal lymph node dissection (L) is superior compared to partial lobectomy (PL). **Methods:** Utilizing the National Cancer Database from 2004-2012, 1551 patients diagnosed with T1N0 or T2N0 typical carcinoid tumors (CT), and 167 atypical carcinoid tumors (ACT), who underwent L or PL (segmental or wedge resection) as initial treatment strategy, and did not receive chemotherapy or radiation were identified. All patients had pathologically confirmed diagnosis, negative surgical margins, and complete follow up data. Overall survival (OS) was analyzed utilizing Kaplan-Meier curves, and log-rank tests were used for statistical comparisons. Cox proportional hazards were performed to control for age, sex, race, grade, year of diagnosis, Charlson/Deyo Score, insurance, income, and facility type. T-test was used to compare post-surgical hospital stay. **Results:** The entire cohort median age was 61 years (range 18-90), and male to female ratio was 0.43. 75% of patients with CT and 78% of ATC underwent L. The 90 day mortality following surgery was $<$ 1 % in both surgical groups. Patients who underwent L had longer post-operative hospitalization stay (mean 5.3 vs. 4.3 days; $p < 0.001$). The 5 year survival for patients with CT was 95% in the L versus 93% in the PL group (p = 0.62), and for ACT 89% in the L versus 81% PL group (p = 0.28). In a multivariate analysis increasing age was the only prognostic factor, and was associated with inferior survival. The HR for death comparing PL to L was 1.09 (95% CI: 0.65-1.78; p = 0.71) for CT and 1.25 (95% CI: 0.45-3.23; p = 0.65) for ACT. **Conclusions:** Patients with localized node-negative CT and ACT have excellent 5 year survival. Performing a lobectomy with mediastinal node dissection may not provide additional benefit compared to partial lobectomy, but this may increase the length of hospital stay.

8550 Poster Session (Board #286), Sat, 8:00 AM-11:30 AM

The correlation between mutation burden and disease free survival in patients with lung adenocarcinomas. *First Author: Changzheng Wang, BGI Education Center, University of Chinese Academy of Sciences, Shenzhen, China*

Background: Lung cancer is one of the leading causes of cancerous deaths globally. High mutation burden is a special character in lung adenocarcinoma patients. Mutation burden is usually based on the number of non-synonymous mutations implying the instability of genome. We hypothesize genome-wide mutation burden indicates mutation degree and is correlated with prognostic in lung adenocarcinoma. **Methods:** Whole-exome sequencing was performed on 98 Chinese lung adenocarcinoma patients with tumor and normal tissue to a mean depth of 49.6x. The total number of non-synonymous somatic mutations was calculated from the sequencing data of each patient. Patients were divided into high mutation burden and low mutation burden groups in accordance with the mean mutation burden and Kaplan-Meier analysis was performed for survival analysis between these two groups. The association between mutation burden and age or smoking status was analyzed by Wilcoxon rank-sum test. **Results:** Among these 98 patients, the values of mutation burden varied from 5 to 1121 with mean value 161.8, 36 (36.7%) patients with smoking history and 34 (34.7%) patients were older than 65 years; the numbers of patients in I, II, III stage were 19 (19.4%), 16 (16.3%) and 63 (64.3%) respectively. 32 patients were classified into high mutation burden group, the other 66 patients classified into low mutation burden group. Survival analysis showed a significantly longer disease free survival (DFS) in low mutation burden group (p-value = 0.0133).Mutation burden was significantly associated with age ($<$ 65 vs $\geq$65, p-value = 0.0208) and smoking status (p-value = 8.67×10^{-4}). **Conclusions:** The association between mutation burden and age or smoking status suggested the high risk for mutation burden accumulation. The significant difference of DFS between high mutation burden and low mutation burden groups reveals the potential of mutation burden as one of the prognostic factors in patients with lung adenocarcinomas.

8551 Poster Session (Board #287), Sat, 8:00 AM-11:30 AM

Differential expression of immune inhibitory markers in association with HLA class I and the immune microenvironment in resected lung adenocarcinomas. *First Author: Mingjuan Lisa Zhang, Massachusetts General Hospital, Boston, MA*

Background: Similar to programed death ligand 1 (PD-L1), indoleamine 2,3-Dioxygenase 1 (IDO1) is known to exert immunosuppressive effects and be variably expressed in human lung cancer. However, IDO1 expression has not been well-studied in lung adenocarcinoma (ADC). **Methods:** PD-L1 and IDO1 expression were evaluated in 261 resected ADC using tissue microarrays and H-scores (cutoff 5). We compared IDO1 with PD-L1 expression in association with clinical features, tumor-infiltrating lymphocytes (TILs), HLA class I (β-2 microglobulin; B2M) expression, molecular alterations, and patient outcomes. **Results:** There was expression of PD-L1 in 89 (34.1%) and IDO1 in 74 (28.5%) cases, with co-expression in 49 (18.8%). Both PD-L1 and IDO1 were significantly associated with smoking, aggressive pathologic features, and abundant CD8+ and T-bet+ (Th1 marker) TILs. PD-L1 expression and abundant CD8+ were inversely associated with a loss of B2M membranous expression (p = 0.0019 and $p < 0.001$, respectively). Compared to PD-L1+/IDO1+ and PD-L1+ only cases, significantly fewer IDO1+ only cases had abundant CD8+ and T-bet+ TILs ($p < 0.001$, respectively). PD-L1 expression was significantly associated with *EGFR* wild-type ($p < 0.001$) and *KRAS* mutants (p = 0.021), whereas there was no difference in IDO1 expression between different molecular alterations. As for survival, PD-L1 was significantly associated with decreased progression-free (PFS) and overall survival (OS), while IDO1 was associated only with decreased OS. Interestingly, there was a significant difference in the 5-year PFS and OS (p = 0.004 and 0.038, respectively), where cases without PD-L1 or IDO1 expression had the longest survival, and those with PD-L1 alone had the shortest survival. **Conclusions:** While PD-L1 +/- IDO1 expression is observed in association with B2M expression, CTL/Th1 microenvironments, *EGFR* wild-type, and *KRAS* mutations, isolated IDO1 expression does not demonstrate these associations, suggesting that IDO1 may serve a distinct immunosuppressive role in ADC. Thus, blockade of IDO1 may represent an alternative and/or complementary therapeutic strategy to reactivate anti-tumor immunity.

8553 Poster Session (Board #289), Sat, 8:00 AM-11:30 AM

Expansion study of ADI-PEG 20, pemetrexed and cisplatin in patients with ASS1-deficient malignant pleural mesothelioma (TRAP). *First Author: Melissa Phillips, St Bartholomew's Hospital, London, United Kingdom*

Background: Argininosuccinate synthetase 1 (ASS1)-deficient malignant pleural mesothelioma (MPM) cells are sensitive to arginine deprivation with pegylated arginine deiminase (ADI-PEG20), which also potentiates the cytotoxic effect of pemetrexed (PEM). In the phase I dose-escalation TRAP study (NCT02029690) we showed that ADI-PEG20 with first-line PEM and cisplatin (CIS) chemotherapy (ADIPEMCIS) produced a 100% disease control rate (DCR) in patients (pts; n = 9) with ASS1-deficient thoracic cancers, with no additional toxicity (Beddowes et al 2017). Here, we present the TRAP expansion cohort experience in MPM. **Methods:** Good performance (ECOG 0-1) MPM pts with non-resectable disease and measurable by modified RECIST, were enrolled in a phase I TRAP expansion cohort at the maximum tolerated dose (MTD) of ADIPEMCIS, using tumoral ASS1 loss as a selection biomarker. PEM (500mg/m2) and CIS (75mg/m2) were given every 3 weeks with weekly IM ADI-PEG20 (36mg/m2) for a maximum of 6 cycles with maintenance ADI-PEG20 in responding pts. Primary endpoint was tumor response rate (modified RECIST), with secondary endpoints including progression-free survival (PFS), overall survival (OS), and toxicity. We measured plasma arginine and citrulline concentrations, ADI-PEG20 antibodies, and biopsied patients on progression to explore resistance mechanisms. **Results:** 31 ASS1-deficient MPM pts (median age 67) were enrolled (11 epithelioid, 10 biphasic and 10 sarcomatoid) out of 92 screened pts. Plasma arginine decreased with a reciprocal increase in plasma citrulline. The partial response rate was 35.5% (95% CI 19.2%-54.6%) with a DCR of 93.5% (95% CI 78.6%-99.2%). Median PFS was 5.6 months (95% CI 4-6) and median OS was 10.1 months (95% CI 6.7-17.7). 10/31 pts (32.3%) experienced grade 3/4 treatment-related toxicities, the most common being neutropenia (16.1%). Upregulation of ASS1 expression was observed in 2/3 biopsies on progression. **Conclusions:** The ADIPEMCIS regimen is active in ASS1-deficient MPM pts, including non-epithelioid disease. Based on these data the ATOMIC-meso phase 2/3 trial has opened comparing ADIPEMCIS versus PEMCISPlacebo, focusing on pts with non-epithelioid MPM. Clinical trial information: NCT02029690.

8554 Poster Session (Board #290), Sat, 8:00 AM-11:30 AM

Patterns of comorbidity, treatment, resource utilization, and referral in malignant pleural mesothelioma patients in the US. *First Author: Marjorie Glass Zauderer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Malignant pleural mesothelioma (MPM) is a rare but aggressive cancer, which may be challenging to diagnose. The standard of care for MPM is cisplatin plus pemetrexed. In the recent phase III MAPS trial, addition of bevacizumab provided a significant survival benefit. There is limited data on real-world MPM treatment patterns to provide context to trial results. Consequently, the present study was conducted to evaluate treatment and referral patterns, co-morbidities and resource use in patients with MPM in the U.S. **Methods:** Patients ≥18 years old with a diagnosis of MPM between Jan 2004 and September 2015 were identified from the MarketScan claims database. Patients were required to have data for 12 months prior, and at least 3 months post, the diagnosis index date. Patients with other (non-MPM) cancers, malignant mesothelioma of non-pleural origin and those enrolled in clinical trials were excluded from the analysis. Treatment and resource utilization were identified by their corresponding HCPCS and DRG codes. Referral patterns were estimated starting from the first lung-related visit during the year preceding MPM diagnosis. **Results:** In the cohort of 1,869 patients, the median age was 71 years (range 61–79) and 65% were male. 4.1% of patients underwent radical surgery and of the remaining 96%, 15.6% had first-line chemotherapy, 33.2% had first-line chemotherapy plus radiotherapy, 11.7% received radiotherapy, and 39.5% received no chemotherapy or radiotherapy. The most common diagnosis on the first lung-related visit was pleural effusion (16.5%), followed by chest pain (10.7%), shortness of breath (9.6%) and cough (8.5%). The median time from first lung-related visit to MPM diagnosis was 77 days (mean 134 days, IQR 23–258). **Conclusions:** This real-world analysis showed that only a small proportion of MPM patients (~4%) received radical surgery and a large number of patients did not receive any treatment at all, indicating a large unmet need for effective treatments in this disease area. Additionally, the pathway to MPM diagnosis may be challenging in this population with a poor prognosis, often involving multiple healthcare contacts over an extended period of time.

8555 Poster Session (Board #291), Sat, 8:00 AM-11:30 AM

Effect of FAK inhibitor defactinib on tumor immune changes and tumor reductions in a phase II window of opportunity study in malignant pleural mesothelioma (MPM). *First Author: Raphael Bueno, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

Background: Defactinib is an oral Focal Adhesion Kinase (FAK) inhibitor with preclinical activity in MPM. We assessed responses to defactinib treatment prior to planned surgical resection in naive patients with MPM. **Methods:** Three cohorts of 10 participants each received defactinib 400mg BID for 12, 35 and 21 days. Pre- and post-treatment blood, tumor biopsies and imaging were obtained for biomarker, immune cell and tumor response (modified RECIST, Tumor volume and SUV max) assessment. Toxicity was monitored for 30 days post treatment. **Results:** Between 12/2013 and 12/2017, 31 participants were registered at our center; 1 withdrew prior to intervention. Among 30 treated, 24 (80%) were male; median age 70 (47-83) years; surgery was EPP 7%, complete pleurectomy decortication (PD) 10%, extended PD 60%, partial PD 10%, unresectable 13%; MPM subtype was epithelioid 67%, biphasic 17%, sarcomatoid 17%. Expected complications of FAK inhibition, diagnostic/staging/operative procedures occurred in 83% (grade 1, 30%; grade 2, 43%; grade 3, 10%). Unexpected adverse events occurred in 77% (grade 1, 63%; grade 2, 20%; grade 3, 17% [wound-infection, prolonged QT interval, and hyperglycemia in 3% each; increased INR in 7%]; grade 5, 7% [due to progressive disease in 3%, intraoperative anaphylactoid reaction unrelated to the drug in 3%]). Objective partial response was observed in 13%, stable disease in 67%, progression in 17%. Tumor volume decreased 3-72% in 47% patients and increased 1-82% in 53%. SUV max decreased 3-69% in 50% and increased 1-61% in 50%. Biological correlates of treatment included target inhibition (75% pFAK reduction); tumor immune microenvironment changes: increased naïve (CD45RA+PD-1+CD69+) CD4 and CD8 T cells, reduced myeloid and Treg immuno-suppressive cells, reduced exhausted T cells (PD-1+CD69+), reduced peripheral MDSCs; and histological subtype change (pleomorphic or biphasic to epithelioid) in 13% of cases. **Conclusions:** Brief preoperative defactinib exposure was well tolerated, did not alter resectability or mortality compared to prior series, and showed evidence of therapeutic and immunomodulatory effects. Clinical trial information: NCT02004028.

8556 Poster Session (Board #292), Sat, 8:00 AM-11:30 AM

Patterns of metastases in malignant pleural mesothelioma in the modern era: Redefining the spread of an old disease. *First Author: Dearbhaile Catherine Collins, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: Malignant pleural mesothelioma (MPM) has been historically documented as a locally infiltrative disease in large series from the early 1980s. With the changing landscape of cancer diagnosis and treatment, increased areas of unusual metastases have been published as case reports. With no standard second-line therapies for MPM, referral to early phase trial units is common. We report the metastatic patterns of a large cohort of MPM patients treated at the Royal Marsden Drug Development Unit (DDU). **Methods:** Clinical data was gathered for MPM patients referred to the DDU from 1992 to 2016. Radiographic details were collected from CT, bone scan and FDG PET imaging. Prior treatment, response, somatic mutations, clinical trial and survival data was obtained from medical records. **Results:** From the database, 165 evaluable patients with MPM were identified. Median age at diagnosis was 64 years (range 37–90) and 76% were male. Epithelioid MPM comprised 81% and 65% were right sided. Bone metastases were reported in 20%, with the majority lytic in nature (*Table*). Peritoneal and omental disease was evident in 24% with ascites in 16%. In 11% of cases lung metastases presented as diffuse miliary-type pattern. Visceral metastases (15%) were predominantly liver (78%), but also occurred in adrenals, spleen and kidneys. Symptomatic brain metastases were recorded in 3%. Median overall survival was 24.2 months (95% CI: 20.8 - 29.2). **Conclusions:** This large study documents the metastatic patterns of advanced MPM in the 21st century and highlights an increased frequency of traditionally unexpected sites of metastases. Higher than expected incidence of lytic bone metastases (20%) suggests consideration of bone imaging in advanced MPM clinical workflow and trial protocols.

Local spread		Distant spread	
Nodal disease	65%	Parenchymal lung metastasis	27%
Pleural effusion	64%	Peritoneal/omental disease	24%
Chest wall involvement	43%	Bone metastasis	20%
Contralateral lung disease	36%	Subcutaneous metastatic nodules	19%
Pericardial infiltration	29%	Visceral metastasis	15%
Pericardial effusion	12%	Intramuscular metastasis	4%
		Brain metastasis	3%

8557 Poster Session (Board #293), Sat, 8:00 AM-11:30 AM

Biomarkers of pembrolizumab (P) activity in mesothelioma (MM): Results from a phase II trial. *First Author: Hedy L. Kindler, University of Chicago, Chicago, IL*

Background: PD-L1 expression and the Interferon-Gamma gene expression profile (IFN-G GEP) are predictive of response to checkpoint blockade in several solid tumors. Relevant biomarkers in mm pts treated with these agents have not been determined; these were evaluated in a phase 2 trial of P in mm (NCT02399371). **Methods:** Eligible pts had histologically confirmed MM, PS 0-1, disease progression on 1-2 prior regimens. P 200 mg was given Q21 days. Part A (N = 35) determined the response rate (RR) of P in PD-L1 unselected mm pts and assessed an optimal PD-L1 threshold (22C3 IHC assay). If ≥3 responses, the study proceeded to Part B (N = 30), using a biomarker enrichment strategy if a threshold was found. Nanostring nCounter was used to assess IFN-G GEP (6 gene). **Results:** 35 pts enrolled in Part A 5/15-2/16; 1 withdrew. Median age 66 (range 26-85); PS 0: 62%; male: 82%; epithelial/sarcomatoid/biphasic/NOS: 74%/21%/3%/3%; pleural/peritoneal: 85%/15%; 2nd-line: 59%. Partial response (PR): 7 (21%), stable disease (SD): 20 (59%). Median response duration: not reached. Median progression-free survival (PFS): 6.2 months (95% CI: 3.2, 8.2). Median overall survival: 11.9 months (95% CI: 6.4, –). Toxicity ≥ grade 3: adrenal insufficiency, fatigue, pneumonitis 6%; colitis, confusion, hepatitis, hyponatremia, neutropenia, rash 3%. PD-L1 expression by tumor proportion score (N = 32): none (53%); 1-49%: (22%); ≥50%: (25%). PD-L1 IHC (ROC area 0.63; 95% CI: 0.37, 0.89), CD274 mRNA expression, and IFN-G GEP did not correlate statistically with response. Responses occurred in GEP low, non-inflamed tumors, and in PD-L1- tumors. RR was numerically higher in PD-L1+ (27%) than in PD-L1- pts (12%); there was a trend towards longer PFS and OS in PD-L1+ pts. **Conclusions:** P has clinically meaningful single-agent activity in PD-L1 unselected, previously treated mm pts, achieving a 21% RR and a disease control rate of 80%. Biomarkers established in other cancers, such as PD-L1 IHC and IFN-G GEP, may not be as useful in MM. Novel biomarkers including MM-specific gene signatures may be necessary and are being evaluated. Part B of the study is ongoing with no PD-L1 pre-selection (19/30 pts enrolled), and will be used as a biomarker validation cohort. Funded by a MARF grant. Clinical trial information: NCT02399371.

8558 Poster Session (Board #294), Sat, 8:00 AM-11:30 AM

Tremelimumab in combination with durvalumab in first or second-line mesothelioma patients: Safety analysis from the phase II NIBIT-MESO-1 study. *First Author: Luana Calabro, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy*

Background: The anti-CTLA-4 tremelimumab at two different dose-schedules of administration showed promising activity in second-line malignant mesothelioma (MM) patients (Calabrò et *al.*, *Lancet Oncol*, 2013; Calabrò et *al.*, *Lancet Respir Med*, 2015). These initial results and the efficacy of targeting the PD-1/PD-L1 axis in different tumor types, prompted the NIBIT-MESO-1 study aimed at investigating the efficacy and safety of tremelimumab combined with the anti-PD-L1 durvalumab in mm patients. We report the safety analysis from the fully-enrolled NIBIT-MESO-1 study. **Methods:** The NIBIT-MESO-1 is a phase II, open-label, single Center study. Forty mm patients received tremelimumab at 1 mg/Kg i.v. every 4 weeks (Q4W) for 4 doses, and durvalumab at 20 mg/Kg i.v. Q4W for 13 doses. Primary objective is immune-related (ir)-objective response rate; secondary are safey, ir-disease control rate, ir-progression free survival, and overall survival. Tumor assessment *per* ir-modified RECIST or ir-RECIST 1.1 for pleural or peritoneal MM, respectively, was performed at baseline and q12 weeks. Adverse events (AEs) were recorded according to CTC v4.0. (ClinicalTrials.gov Id: NCT02588131). **Results:** From October 2015 to October 2016, 40 mm patients (38 pleural and 2 peritoneal), median age 64 years (range 41-80), ECOG performance status 0 (n = 19) or 1 (n = 21) were enrolled in the study. mm histology was epithelioid (n = 32), biphasic (n = 5), sarcomatoid (n = 2) or undefined (n = 1). As of January 2017, 12 first or 28 second-line mm patients received a median of 5.5 doses of therapy (range = 1-13). Twenty-four patients (60%) experienced any grade irAEs: 5 patients (12.5%) had grade 3-4 AEs, the most frequent being hepatotoxicity (7.5%). AEs were generally manageable and reversible per protocol guidelines. Three patients (7.5%) were discontinued due to treatment-related AEs (1 trombocytopenia, 1 limbic encephalitis, 1 liver toxicity). **Conclusions:** The combination of tremelimumab and durvalumab is safe and manageable in mm patients. Clinical trial information: NCT02588131.

8559 Poster Session (Board #295), Sat, 8:00 AM-11:30 AM

Systemic therapy use and outcomes after relapse from accelerated hemithoracic radiation and surgery for malignant pleural mesothelioma (MPM). *First Author: Sara V. Soldera, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: The prognosis of patients (pts) with MPM remains poor. Accelerated hemithoracic radiation followed by extrapleural pneumonectomy and adjuvant chemotherapy in ypN2 disease (SMART) provides encouraging results. The ability to administer systemic therapy (Tx) and response rate (RR) after recurrence remains unclear. We therefore examined subsequent lines of Tx and outcomes following relapse after SMART. **Methods:** A retrospective analysis of pts diagnosed with recurrent MPM following SMART was conducted at a single institution. OS was determined from date of relapse to death and was estimated using the Kaplan-Meier method. Potential prognostic variables were tested utilizing the log-rank test. **Results:** Out of 86 pts undergoing SMART from 2008 to 2016, 53 (62%) developed recurrent disease of which 36% had pathological confirmation. Two cases with initial epithelial subtype on surgical specimen relapsed with different histology (sarcomatoid and small cell). In 48% of pts, relapse was unclear at first imaging (n = 42) and a median of 98 days (range 6-966) lapsed between first suspicion and final diagnosis. The median age at relapse was 66 years (range 45-79), 47% had a performance status (PS) ≥2 (n = 45) and 64% were of epithelial subtype. After a median follow up of 7.6 mo, the median OS was 5.2 mo. PS ≥2 was associated with worse OS (2.8 vs 10.7 mo, $p < 0.001$). Of 42 pts followed after relapse, 36% received any Tx (19% 1 line; 12% 2 lines; 5% ≥3 lines). Tx was omitted in 62% of pts due to poor PS (26/42). First line Tx consisted of platinum doublet in 93% of pts (n = 15). Of 13 pts with response evaluable disease, RR was 15% (0 CR, 15% PR). Of note, 0/13 pts had neoadjuvant Tx and 3/13 pts had adjuvant Tx (10, 13 and 38 mo lapsed between end of adjuvant Tx and start of Tx in the relapsed setting). 6/15 pts discontinued Tx due to toxicity, 5/15 due to progression and median number of cycles was 4. **Conclusions:** Pts with relapsed MPM following SMART have poor prognosis and low RR to first line Tx. Poor performance status at relapse is a poor prognostic factor. Earlier detection, novel diagnostic markers of relapse and consideration of maintenance strategies should be investigated in future studies.

8560 Poster Session (Board #296), Sat, 8:00 AM-11:30 AM

Malignant mesothelioma in 91 danish women: The environmental asbestos exposure. *First Author: Vasiliki Panou, Department of Respiratory Diseases and Clinical Cancer Research Center, Aalborg University Hospital, Aalborg, Denmark*

Background: Malignant Mesothelioma (MM) is an asbestos-related malignancy that presents mainly in the pleura (MPM) and peritoneum (MAM). In a densely populated area of Aalborg city in North Jutland, Denmark, a large Eternit asbestos factory that was active for 60 years until 1986 and two shipyards were situated. The Region of North Jutland, Denmark has a high mm incidence in women of 1.0/100,000. **Methods:** From 1974-2015, 101 histological and cytological samples of women diagnosed with mm in Aalborg University Hospital were identified re-evaluated by modern immunohistochemistry. Patient information regarding asbestos exposure was retrieved from medical records and selected Danish registries. Asbestos exposure was classified as *primary* for asbestos workers; *domestic,* for women living with an asbestos worker; *environmental,* when living or working within 10.000 meters from an asbestos emitting location; *unknown,* where no source of asbestos exposure could be identified. **Results:** Clinical and histopathological mm diagnosis was certain for 91 women. Potential asbestos exposure is summarized in Table 1. The employment of the women and their relatives include work at the asbestos cement factory, shipyard, construction, laboratory, pipe factory, electrician and insulator. The women with domestic and combined domestic and environmental (secondary) exposure to asbestos were most prone to develop MPM rather than MAM while women primary exposed to asbestos developed MAM rather than MPM (p=0.016). **Conclusions:** This study showed that the vast majority (64%) of the women diagnosed with mm had documented non-occupational asbestos exposure and almost 1/5 had a sole environmental exposure, by living in proximity to asbestos industry. Environmental asbestos exposure is a serious risk factor for mm in women. Primary asbestos exposure, inferring more intense exposure through occupation, may predispose to peritoneal mesothelioma in women.

Types of asbestos exposure	Number of patients (%)
Primary	8 (9%)
Domestic	14 (15%)
Environmental	18 (19%)
Combined domestic and environmental	26 (29%)
Unknown	25 (27%)

8561 Poster Session (Board #297), Sat, 8:00 AM-11:30 AM

A nonrandomized confirmatory phase III study of sublobar surgical resection for peripheral ground glass opacity dominant lung cancer defined with thoracic thin-section computed tomography (JCOG0804/WJOG4507L). *First Author: Kenji Suzuki, Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan*

Background: The optimal mode of surgery for peripheral ground glass opacity (GGO) dominant lung cancer (LC) defined with thoracic thin-section computed tomography (TSCT) remains unknown. **Methods:** We conducted multi-institutional confirmatory phase III trial to evaluate the efficacy and safety of sublobar resection for peripheral GGO dominant LC. Mode of surgery is basically wedge resection, and segmentectomy is allowed when surgical margin is insufficient ($<$ 5 mm) or histological invasiveness. LC with maximum tumor diameter (MTD) $\leq$ 2.0 cm and with consolidation tumor ratio $\leq$ 0.25 based on TSCT were registered. The primary endpoint was 5-year relapse-free survival (RFS). The planned sample size was 330, with the expected 5-year RFS of 98%, threshold of 95%, one-sided α of 5% and power of 90%. Survival analyses were performed using the Kaplan-Meier method and their confidence intervals were estimated by Greenwood's formula. **Results:** Between May 2009 and April 2011, 333 pts were enrolled from 51 institutions. The primary endpoint, RFS was estimated on 314 pts who underwent sublobar resection. Median age was 62 (range 24 - 79) and 104 were smokers. Median MTD on lung window was 1.20 cm (0.53 - 2.00). Median MTD of consolidation was 0 (0.00 - 0.48). Operative modes were 258 wedge resection and 56 segmentectomy. Histological diagnosis were 310 adenocarcinomas, 27 pre-cancerous lesions, and 14 non-neoplastic lesions. Median pathological surgical margin was 15 mm (0 - 55). Grade 2 or higher postoperative complications based on CTCAE v3.0 were observed in 119 (37.9%), and Grade 3 in 17 (5.4%), without any Grade 4 or 5. The 5-year RFS was 99.7% (95% CI, 97.7 - 100.0%), which met the primary endpoint. There was no local relapse. The ratio of FEV1.0 change between preoperative and one year after surgery over preoperative value ranged -37% to +49% with a median of -5%. **Conclusions:** Sublobar resection, mainly wedge resection, offered sufficient local control and RFS for peripheral GGO dominant LC on TSCT. Sublobar resection should be the first choice of mode of surgery if surgical margin is enough preserved. Clinical trial information: 000002008.

8562 Poster Session (Board #298), Sat, 8:00 AM-11:30 AM

Optimal thoracic radiation dose in limited stage small cell lung cancer. *First Author: Madhusmita Behera, Winship Cancer Institute, Acworth, GA*

Background: Several studies have demonstrated improved overall survival in limited stage small cell lung cancer (LS-SCLC) patients (pts) with the addition of thoracic radiation therapy (RT) to chemotherapy. However, the optimal dose of thoracic RT when given daily, which is the most common practice pattern in the US, is yet to be firmly established. We analyzed outcomes associated with once-daily low dose (LD) RT relative to once-daily high dose (HD) RT for LS-SCLC in the National Cancer Data Base (NCDB). **Methods:** The NCDB was queried to capture pts with LS-SCLC treated with thoracic RT from 2004-2013. The cohort of pts that received 60 Gy (LD) was compared with the cohort that received RT $\geq$70 Gy (HD). The univariate (UV) association of overall survival (OS) was assessed using Cox proportional hazards models and log-rank tests. A multivariable (MV) Cox proportional hazard model and Kaplan-Meier (KM) analyses were performed to compare the LD vs. HD cohorts. Propensity score matching method was also implemented to reduce treatment selection bias. All analyses were performed using SAS Version 9.4. **Results:** A total of 5,159 pts (LD-3441; HD- 1718) were included in the analysis. Pt characteristics (LD/HD): median age 65/64 yrs; males 44/46%; whites 89/88%, academic centers 28/31%, Charlson-Deyo comorbidity score 0- 61%/64%; government insured 61/57%. 96% of pts in LD and 95% in HD cohorts had received chemotherapy. On MV analysis, no differences were found in OS between HD and LD RT(HR 0.98, p = 0.5), which was confirmed by KM analysis with 5-yr survival of 21% in LD vs 21.5% in HD (p = 0.8). On MV analysis of OS stratified by comorbidity score, LD was associated with significantly better survival compared to HD in pts with a comorbidity score of 1 and above (HR 0.87, p = 0.02). The LD group also had a better 5-yr survival than HD group in pts with higher comorbidity score (19% vs 14%, p = 0.01). No difference in survival was noted between the two cohorts for pts with no recorded comorbidities (HR 1.03, p = 0.6). **Conclusions:** In LS SCLC pts, survival was similar in pts who received daily RT of 60 Gy compared to those that received 70 Gy and above. In pts with worse performance status, those who received LD RT of 60 Gy had better survival.

8563 Poster Session (Board #299), Sat, 8:00 AM-11:30 AM

Disparities in the management of stage I small cell lung carcinoma (SCLC): A National Cancer Database (NCDB) analysis. *First Author: Zaheer Ahmed, Department of Medicine, University of Missouri, Kansas City, MO*

Background: Effective treatment of stage I SCLC requires both surgical resection and chemotherapy. We analyzed the National Cancer Database (NCDB) for the treatment patterns and disparities in the management of stage I SCLC. **Methods:** We identified patients with clinical stage I SCLC from the NCDB. Median and 5-year survival were calculated using Kaplan Meier analysis. Multivariable logistic regression model was used to determine the factors that can predict surgical resection. **Results:** We identified 4,849 patients with clinical stage I SCLC diagnosed between 2004 and 2012. We divided them into 4 treatment groups; surgical resection with chemotherapy (n = 774, 15.9%), surgical resection without chemotherapy (n = 423, 8.7%), non-surgical treatment (n = 2,978, 61.4%) and no treatment (n = 674, 13.9%). 5-year survival for each group was 47%, 36%, 22% and 11% respectively, (p-value $<$ 0.001). Among patients who underwent surgical resection, lobectomy (67.1%) was the most common procedure followed by sublobar resection (28.8%) and pneumonectomy (2.8%) with 5-year survival of 48%, 34% and 33% respectively, (p-value $<$ 0.001). Multivariate analysis identified that elderly (age $\geq$ 70) patients, African-Americans, patients with low income and Medicaid are less likely to undergo surgery, (p-value $<$ 0.001). Patients receiving treatment at academic cancer centers, right sided tumors and Charlson score $\geq$ 1 are more likely to receive surgery, (p-value $<$ 0.001). **Conclusions:** Despite better outcomes only 25% of patients undergo surgery for stage I SCLC. Over the years there has been only a modest increase in the proportion of patients undergoing resection. We have identified significant disparities in the treatment of patients with stage I SCLC. Our data clearly show the need to educate physicians on appropriate delivery of care for patients with stage I SCLC.

8564 Poster Session (Board #300), Sat, 8:00 AM-11:30 AM

Association of PD-L1 expression with tumor infiltrating immune cells and mutation burden in the high grade neuroendocrine carcinoma of the lung. *First Author: Hye Sook Kim, Myongji Hospital, Goyang, Republic of Korea*

Background: Large cell neuroendocrine carcinoma (LCNEC) and small cell lung cancer (SCLC) are recognized as high grade neuroendocrine carcinoma of the lung and remain among the most fatal malignancies. Programmed death-ligand 1 (PD-L1) is expressed in a group of cancers that may be suitable for specific immunotherapy. We retrospectively investigated PD-L1 expression in tumor cells (TC) and tumor infiltrating immune cells (IC) and correlated this with mutation burden and clinical outcome. **Methods:** A total of 192 patients with LCNEC (n = 72) and SCLC (n = 120) were explored. PD-L1 expression was scored by immunohistochemistry in TC and IC. We used the Ion AmpliSeq Comprehensive Cancer Panel to identify mutation in all exons in 409 cancer-related genes. **Results:** The overall prevalence of PD-L1 expression on TC was 15.1 % (29/192). No significant difference was observed between LCNEC and SCLC (16.7% vs. 14.2%, p = 0.365). Tumor-infiltrating IC and PD-L1 positive immune cells (IC) were observed in 34.4% (66/192) and 31.3% (60/192), respectively. The prevalence of tumor-infiltrating IC and PD-L1 expression on IC were significantly higher in LCNEC compared to SCLC (57.6% vs. 23.3%, p $<$ .001; 45.8% vs. 22.5%, p = .001, respectively). Tumor-infiltrating IC and PD-L1 expression on IC were correlated with higher nonsynonymous mutational load (p = 0.048 and 0.038, respectively). Tumor-infiltrating immune cells (median 11.3 vs. 6.8 months, p = 0.005), and its correlated PD-L1 expression on IC (median 11.3 vs. 7.0 months, p = 0.024) were related with better progression free survival. There was no relevance between biomarker status and overall survival. **Conclusions:** These findings suggest that the PD-1/PD-L1 pathway is activated in a fraction of HGNEC of lung with correlating higher mutational burden. Further studies are needed to determine the PD-L1 expression and correlated clinical features to refine role of anti-PD1 treatments in these patient population.

8565 Poster Session (Board #301), Sat, 8:00 AM-11:30 AM

Survival outcomes in extensive stage small cell lung cancer patients treated with thoracic radiation. *First Author: Kristin Ann Higgins, Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, GA*

Background: The benefit of consolidation thoracic radiation in extensive stage small cell lung cancer (E-SCLC) remains unclear. This study utilized the National Cancer Database (NCDB) to evaluate overall survival outcome (OS) for patients receiving chemotherapy (CT) alone for E-SCLC versus CT + thoracic radiation (TRT). **Methods:** The NCDB was queried to capture patients (pts) with stage E-SCLC from 2010-2013. Patients with brain metastases at diagnosis were excluded, as were patients receiving radiation prior to initiation of chemotherapy. Univariate association of OS was assessed using Cox proportional hazards models and log-rank tests. A multivariable Cox proportional hazard model and Kaplan-Meier analyses were performed to compare treatment with CT only to CT + TRT. Propensity score matching method was also implemented to reduce treatment selection bias. All analyses were performed using SAS Version 9.4. **Results:** A total of 14,367 (12,019 received CT, 2,348 received CT + TRT) pts were included in the analysis. Patient characteristics included a median age of 66 years; 66 years for pts receiving CT, and 63 for pts receiving CT + TRT ($p < 0.001$). Male gender comprised 51% of pts; 52% in CT group versus 49% in CT + TRT ($p < 0.001$). Charlson-Deyo comorbidity score was zero in 53% of all patients; 52% in the CT group versus 57% of CT + TRT group ($p < 0.001$). In the CT + TRT group, the median total thoracic radiation dose was 45 Gy. On multivariate analysis, CT only was associated with an increased risk of death relative to CT+ TRT (HR 1.74 [1.65 – 1.84], $p < 0.001$). 5 year OS was 7% vs. 2% for CT + TRT versus CT alone ($p < 0.001$). On propensity matched analysis, CT + TRT was associated with better 5-year OS compared to CT alone (8% vs. 2%; $p < 0.001$). On multivariate analysis of propensity matched samples, chemotherapy alone continued to be associated with worse survival (HR 1.76 [1.62 – 1.91], $p < 0.001$). **Conclusions:** For E-SCLC, CT alone as standard of care is associated with worse survival relative to CT + TRT.

8566 Poster Session (Board #302), Sat, 8:00 AM-11:30 AM

Comparing treatment strategies for stage I small cell lung cancer: A National Cancer Database study. *First Author: Peter Alexander Paximadis, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI*

Background: Concurrent chemoradiotherapy is the standard of care for limited stage small cell lung cancer (SCLC). The ideal treatment strategy for stage I SCLC, however, is less clear. The purpose of this study is to compare outcomes for patients receiving definitive surgery, stereotactic body radiation therapy (SBRT), or external beam radiation therapy (EBRT) for stage I SCLC using the National Cancer DataBase (NCDB). **Methods:** Patients with a first primary diagnosis of stage I (T1-2 N0 M0) SCLC treated between 2004 and 2013 were identified in the NCDB. Patients were defined as having a first course of treatment of either definitive surgery, EBRT (45-74 Gy in 15-40 fractions) or SBRT (40-60 Gy in $\leq$5 fractions). Other recorded information included age, gender, race, T stage, Charlson-Deyo score, and use of chemotherapy. Overall survival (OS) was determined using the Kaplan-Meier method and Cox proportional hazards regression methods were used to estimate risk of overall mortality. **Results:** A total of 5944 patients with stage I SCLC were identified; of those, 2681 fit the study criteria. The median age of patients in the cohort was 68 years and median follow up was 26.6 months. Definitive surgery was performed in 944 (35%), EBRT in 1597 (60%), SBRT in 140 (5%), and chemotherapy was delivered in 2067 (77%). The 2- and 3-yr OS for the whole cohort was 62% and 50%; 72% and 62% for surgery, 56% and 44% for EBRT, and 56% and 40% for SBRT. Patient age, female gender, Charlson-Deyo score < 2, tumor size $\leq$3 cm, receipt of surgery and receipt of chemotherapy were all associated with improved OS. Comparing treatment strategies in a multivariate model, surgical resection demonstrated improved OS over EBRT (HR 2.0, $p < 0.001$) and SBRT (HR 1.66, $p < 0.001$). When excluding patients who underwent surgery, SBRT demonstrated improved OS compared with EBRT (HR 1.28, $p = 0.04$). In addition, receipt of chemotherapy resulted in improved OS (HR 0.66, $p < 0.001$). **Conclusions:** In this hospital-based registry study, definitive surgical resection and use of chemotherapy resulted in improved survival outcomes for patients with stage I SCLC. For patients who are not candidates for surgery, SBRT may offer a survival benefit compared with standard EBRT.

8567 Poster Session (Board #303), Sat, 8:00 AM-11:30 AM

Using circulating tumor DNA analysis to depict genomic profiles and predict survival outcomes in patients with small-cell lung cancer. *First Author: Jinghui Wang, Department of Medical Oncology, Beijing Chest Hospital, Capital Medicine University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China*

Background: Small-cell lung cancer (SCLC) accounts for approximately 15% of lung cancers. Most patients have extensive-stage disease with widespread metastases and poor survival. Understanding the molecular mutation profile of each SCLC patient would allow precision treatment and improved clinical outcome. However, tumor tissues from surgery are not available for most SCLC patients and biopsy specimens are often have limited quantities. Several studies have provided evidence of circulating tumor DNA (ctDNA) in detecting somatic variants of multiple solid tumors. This study evaluated utility of ctDNA to depict genomic profiles and predict survival outcomes in SCLC patients. **Methods:** 22 Plasma samples were obtained before initial treatment from 22 patients with SCLC enrolled between 2012 and 2016. Targeted-capture deep sequencing was performed to identify somatic variants in 465 cancer-related genes. Genomic mutation profiles were described and the clinical implications were further analyzed. **Results:** Tumor DNA can be detected in all 22 plasma samples collected from patients with SCLC. In total, 340 variants were identified, and the mean and median mutation rate were 6.3 and 6.6 per Mb. *TP53* and *RB1* are the most frequently mutated genes, detected in 90.9% (20/22) and 59.1% (13/22) patients, respectively. Further analysis showed that high ctDNA fraction in cell-free DNA (cfDNA) was associated with heavy tumor burden ($R = 0.7$, $p = 0.0017$). Moreover, patients with high ctDNA fractions (ctDNA fraction $>=$ 18.3%) had poor progression free survival (PFS) (HR, 17.2; $p = 0.0019$). The median PFS of patients with high versus low ctDNA fractions was 5.2 months (95% CI 4.6 to 5.8 months) versus 10.0 months (95% CI 9.3 to 10.7 months), respectively. **Conclusions:** In this study, ctDNA analysis offers a promising way to depict the molecular profile in patients with SCLC. Moreover, these findings highlight the potential clinical utility of ctDNA to predicate clinical outcome in SCLC.

8568 Poster Session (Board #304), Sat, 8:00 AM-11:30 AM

Trilaciclib (G1T28): A cyclin dependent kinase 4/6 inhibitor, in combination with etoposide and carboplatin (EP) for extensive stage small cell lung cancer (ES-SCLC)—Phase 1b results. *First Author: Caio Max S. Rocha Lima, Gibbs Cancer Center and Research Institute, Spartanburg, SC*

Background: Chemotherapy (chemo) has significant clinical utility, however consequent damage to hematopoietic stem and progenitor cells (HSPCs) and the immune system may limit activity. If chemo-mediated anti-tumor activity was maximized, while minimizing myelosuppression and immunosuppression, patient outcomes would be improved. Trilaciclib (T) is an intravenous CDK4/6 inhibitor in development to reduce myelosuppression and preserve immune system function during chemo. HSPCs are dependent on CDK4/6 for proliferation. Preclinical data demonstrated that transient T-induced G1 cell cycle arrest renders HSPCs resistant to chemo cytotoxicity, allowing faster hematopoietic recovery, preservation of long-term function, and enhancement of anti-tumor immunity and activity. **Methods:** Objectives of this ongoing multicenter Phase 1b/2a study are to assess dose limiting toxicities (DLTs), safety, tolerability, hematological profile, PK, and anti-tumor activity of T administered prior to EP. Phase 1b was open-label, dose-finding, and the ongoing Phase 2a is randomized (1:1), double-blind. Eligible pts had confirmed diagnosis of ES-SCLC, adequate organ function, ECOG PS 0-2, no prior chemo, and no symptomatic brain metastases. **Results:** 19 pts were enrolled in the Phase 1b: 10 pts received T 200 mg/m^2 + EP and 9 pts received T 240 mg/m^2 + EP. T + EP was well tolerated. 2 pts at T 200 mg/m^2 and 1 pt at T 240 mg/m^2 experienced asymptomatic DLTs in cycle 1. 2 pts (1 at each dose) had an ANC < 1500 on cycle 2 day 1, delaying the start of cycle 2, and 1 pt at the T 200 mg/m^{2}dose had grade 4 thrombocytopenia. There were no cases of febrile neutropenia or bleeding. PK analysis showed no drug interactions between T and EP. 17/19 pts were evaluable: 1 pt had CR, 14 had PR (confirmed ORR = 88%); 1 pt had SD (clinical benefit rate = 94%). **Conclusions:** In the Phase 1b part of the study, T + EP was well tolerated. Early activity results are promising with a confirmed objective response rate of 88%. This novel approach allowing the administration of chemotherapy while preserving HSPC and immune system function could potentially improve treatment outcomes for SCLC pts. Clinical trial information: NCT02499770.

8569 Poster Session (Board #305), Sat, 8:00 AM-11:30 AM

Small cell lung cancer: The immune microenvironment and prognostic impact of checkpoint expression. *First Author: Gareth Rivalland, Olivia Newton-John Cancer Wellness and Research Centre, Melbourne, Australia*

Background: To date, immunotherapy has had limited success in small cell lung cancer (SCLC), despite the tumor's high mutation load. Little is understood of the immune tumor microenvironment in SCLC due to a paucity of resected tumor. We present a SCLC cohort and describe the prognostic impact of checkpoint expression. **Methods:** SCLC tissue microarrays with triplicate cores from 105 SCLC specimens underwent IHC assessment for PD-L1, PD-L2, LAG3, TIM3, FoxP3, CD4 and CD8 on tumor and/or tumor infiltrating lymphocytes (TILs). Checkpoint positivity was defined $>$ 5% tumor expression or TIL expression in $>$ 5% of the total core area. Associations with clinicopathologic characteristics and survival were assessed. A Cox model was used for univariate and multivariate survival analysis. **Results:** Tumor expression of PD-L1 was positive (+) in 17/95 (18%), PD-L2+ in 2/96 (2%), and TIM3+ or LAG3+ in no cases. TILs expressed PD-L1+ in 64/95 (67%), PD-L2+ in 22/96 (22%), TIM3+ in 57/96 (59%) and LAG3+ in 43/96 (45%). FoxP3+ lymphocytes were found in all samples (range 0.02 – 2.98% of total core). TIL expression of PD-L1, PD-L2, TIM3 and LAG3 were all significantly correlated (p value $\leq$0.001 for all comparisons), and were associated with high FoxP3+ expression. All four checkpoints were expressed on TILs in 20/105 (19%) patients. PD-L1+ and PD-L2+, but not TIM3 or LAG3, on TILs were significantly higher in limited stage compared with extensive stage SCLC (76% v 52%, p 0.045 and 28% v 7%, p 0.02 respectively). There was no association between stage and tumor expression. TIL expression of PD-L1, PD-L2, TIM3 and LAG3 were all associated with improved prognosis. PD-L1+ median OS: 17.2 v 7.9 months (HR 0.36; 95%CI 0.22 – 0.6; p $<$ 0.001). Univariate analysis showed stage and TIL expression of PD-L1, PD-L2, TIM3 and LAG3 were associated with improved survival, but only stage and PD-L1+ TILs remained significant on multivariate analysis (p $<$ 0.01). **Conclusions:** Immune checkpoint molecules are frequently expressed in SCLC-associated TILs, but not the tumor itself. TIL expression of checkpoint molecules is associated with improved survival. Limited tumor expression of PD-L1 and an exhausted immune cell phenotype may contribute to immunotherapy failure.

8570 Poster Session (Board #306), Sat, 8:00 AM-11:30 AM

Histology determination of lung cancers: A report on genomic profiling of lung cancer of mixing histology. *First Author: Ming Tang, MD Anderson Cancer Center, Houston, TX*

Background: Histopathology, largely determined by morphology, plays a critical role in choosing appropriate treatment for lung cancer. The understanding of molecular determination of lung cancer histology is rudimentary. Our recently published data (Zhang, Science, 2014 and Liu, Nature Communications, 2016) have demonstrated that within the same patients with identical genetic background and identical exposure, tumor regions with different morphologic appearances may have very similar genomic profiles while tumors with the same morphology may have distinct genomic landscape. **Methods:** We collected 12 lung cancers of mixing histology with 2 to 4 histologic components within each tumor. In total, 26 tumor regions including 9 adenocarcinomas, 6 large-cell neuroendocrine carcinoma, 6 small cell carcinomas and 4 squamous cell carcinomas and one poorly differentiated lung carcinoma were microdissected and subjected to whole exome sequencing. **Results:** A substantial number of identical mutations were shared between different histologic components within the same tumor in all 12 patients. However, the proportion of shared mutations varies in different patients ranging from as little as 4% to as much as 99%. Mutation spectrum is also similar between different histologic components within the same tumors suggesting similar mutational process in place. Identical canonical cancer gene mutations including TP53, KRAS, PIK3CA, SOS1 and STK11 are generally shared between different histologic components within the same tumors. Canonical mutations in FBXW7 and MTHFR were detected in squamous component, but not small-cell component in one patient. **Conclusions:** Different histologic components of lung cancers of mixing histology are likely derived from the same progenitor cells, but the molecular timing of branch separation of subclones giving rise to different histologic components varies in different tumors. Although genomic aberrations may play a role in a subset of tumors, histologic features may not be determined at genomic level for most lung cancers. Gene expression and methylation analyses from these tumors are underway.

8571 Poster Session (Board #307), Sat, 8:00 AM-11:30 AM

Longitudinal monitoring of circulating tumor DNA and peripheral T cell repertoire in patients with small cell lung cancer. *First Author: Wade Thomas Iams, Northwestern University, Chicago, IL*

Background: Advances in the treatment of small cell lung cancer (SCLC), an aggressive disease with poor prognosis, will require the development of diagnostic methods during treatment that are more sensitive and descriptive than are currently available. The emergence of "liquid biopsy" technologies coupled with comprehensive genomic information about common mutations in SCLC prompted us to implement a blood-based assay for simultaneous sequencing of circulating, cell-free tumor DNA (cfDNA) and determination of the peripheral a and b T cell receptor repertoire in patients with SCLC. **Methods:** Our SCLC assay uses targeted hybrid capture and next generation sequencing of cfDNA extracted from patient plasma to detect somatic mutations in 14 frequently mutated genes in SCLC. We also sequenced rearranged T cell receptor α and β genes, each with 5000 unique α and β CDR3 open reading frames per microgram of gDNA. Over 26 months we followed 27 patients with SCLC (16 with extensive stage and 11 with limited stage disease) and examined cfDNA from 141 plasma samples and T cell repertoire from 41 samples. **Results:** We detected somatic, disease-associated mutations in 85% of patient samples (23/27) with allele frequencies of cfDNA ranging from $\leq$0.5% to $\geq$85%. The most commonly mutated genes were *TP53* (17/27 patients) and *RB1* (10/27 patients). We detected 87 unique genomic alterations in 12 different genes (in addition to *TP53* and *RB1* these included *PTEN*, *NOTCH1-4*, *MYC*, *MYCL1*, *PIK3CA*, *KIT*, and *BRAF*). The observed mutant allele frequencies in longitudinal samples tracked with treatment response, including cases in which cfDNA allele frequencies increased before clinical evidence of relapse. Longitudinal monitoring of T cell repertoire demonstrated both variability between patients and sequential changes during therapy, including one case of decreased T cell numbers accompanying disease relapse. **Conclusions:** As the field of immuno-oncology matures, we anticipate that coupled determination of T cell repertoire together with cfDNA monitoring will merge into a clinically useful "molecular image" of each patient's disease status and real-time host immune response.

8572 Poster Session (Board #308), Sat, 8:00 AM-11:30 AM

Postoperative radiation for tumor control and overall survival in thymic epithelial tumors (TET): A matched-pair analysis. *First Author: Feng Ming Kong, Indiana University Department of Radiation Oncology, Indianapolis, IN*

Background: Due to lack of randomized trials, the role of postoperative radiation therapy (PORT) in thymic epithelial tumors (TET) remains controversial. This study aimed to evaluate whether PORT improves tumor control and overall survival (OS) in patients with resected TET in a large single institution database. **Methods:** This is a retrospective study of all TETs seen at Indiana University between 1975 and 2016. Patients with resected thymoma (T) or thymic carcinoma (TC) were eligible disregarding their margin status or stage. Study endpoints were progression free survival (PFS) and OS. Age, gender, race, tumor size, stage, pathology, grade, completeness of resection and adjuvant treatment modality were analyzed for significance on PFS and OS. Multivariate Cox model was used to identify significant factors for propensity score matching. Differences between the PORT and surgery alone group were estimated using stratified log-rank test. **Results:** A total of 478 patients with previous surgical resection were eligible. Masaoka Stage was: I-86 (22%); II-87 (23%); III-107 (28%); and IV-106 (27%), respectively. Multivariate analysis demonstrated that gender (HR = 1.4, p = 0.03), stage (HR = 1.3, p = 3×10^{-3}), TC (HR = 1.6, p = 0.03) and PORT (HR = 1.6, p = 0.002) were significantly associated with PFS. Age (HR = 1.1, p = 4×10^{-7}), TC (HR = 3.2, p = 3×10^{-5}), stage (HR = 1.4, p = 0.003) were associated with OS. PORT was given to 126 (26%) patients. Propensity score matching based on independent prognostic factors identified 99 patients for PORT, matched to 285 patients without. The 5-/10-year intra-thoracic progression free rates were 77%/69% and 85%/68%, for patients with and without PORT (p = 0.009), respectively. The 5-/10-year PFS rates were 39%/18% and 61%/32%, for patients with and without PORT (p = 0.002), respectively. The median survival, 5-/10-year OS rates for patients treated with PORT were 150 (95%CI 111~277) months, 87%/57% and respectively, compared to 192 months (95%CI 167~279), 88%/69% for patients receiving surgery alone (p = 0.13). **Conclusions:** This matched-paired analysis from a single institution suggests that PORT does not impact the PFS or OS in a selected population of resected TET.

8573 Poster Session (Board #309), Sat, 8:00 AM-11:30 AM

Pembrolizumab in patients with recurrent thymic carcinoma: Results of a phase II study. *First Author: Giuseppe Giaccone, Georgetown University, Washington, DC*

Background: There are few treatment options for thymic carcinoma after chemotherapy. We completed a single institution phase II study of pembrolizumab (P) in patients with recurrent thymic carcinomas. **Methods:** Main eligibility criteria included: progression after ≥ 1 chemotherapy line, ECOG PS 0-2, no history of autoimmune disease, and adequate organ function. P was given at 200mg IV every 3 weeks. The primary objective of the study was response rate (RR) by RECIST v1.1 criteria; secondary objectives were PFS and OS, and safety. **Results:** From 3/2015 to 12/2016 we accrued 41 patients. Of 40 eligible patients, 29 were male, 19 Caucasians, median age was 57 years (range 25-80), 14 had squamous carcinoma histology, and 19 ECOG PS 0. Median number of cycles delivered was 6 (range 1-31). The most common side effects were mild fatigue (10), diarrhea (4) and rhinorrhea (4). Six patients developed multiple grade 3-4 immune-relates AEs (irAEs): myocarditis/myositis (1), myositis/myocarditis/hepatitis/myasthenia gravis (1), myositis/hepatitis (1), bullous pemphigoid (1), hepatitis (1), hepatitis/pancreatitis/diabetes mellitus type 1 (1). There were no treatment related deaths. The 2 patients who developed myocarditis required a pacemaker. Three patients interrupted treatment because of irAEs (all responders) and 3 because of progression around the time of the irAE. irAEs were more frequent in females (4/6; p = .026). Five patients developed hypothyroidism and 1 hyperthyroidism. RR assessed in all 40 eligible patients was 22.5%: 1 complete response, 8 partial responses (plus 1 unconfirmed), 20 stable disease and with 11 progressions. Two partial responses show minimal residual disease with no PET uptake. Two responders have progressed and 5 responses are beyond 12 months duration. Of 29 cases tested for PD-L1 staining (Dako 22C3), high PD-L1 (≥50% tumor cells positive) was seen in 8 (28%); 6/9 responders had high PD-L1 expression. Targeted NGS in 15 cases did not show correlation between mutational burden and response. **Conclusions:** P has activity in patients with thymic carcinoma. irAEs are more frequent than in other tumors. Further analysis of NGS, Nanostring and PD-L1 expression and updated survival will be presented. Clinical trial information: NCT02364076.

8574 Poster Session (Board #310), Sat, 8:00 AM-11:30 AM

Paraneoplastic syndrome and survival in thymic epithelial tumors (TET): The Indiana University experience. *First Author: Weili Wang, Department of Radiation Oncology, Simon Cancer Center, Indiana University School of Medicine, Indianapolis, IN*

Background: Paraneoplastic syndromes (PNS) are commonly associated with thymic epithelial tumors (TET), especially thymoma. The purpose of this analysis is to examine the clinical impact of PNS in TET. **Methods:** Patients with pathologically diagnosed TET at a single institution were reviewed retrospectively. The primary and second endpoints for this study were overall survival (OS) and recurrence rates. Clinical factors included age, gender, race, performance score, histology, WHO classification, Masaoka stage, post-operative status, tumor size and number of positive lymph nodes. Cox proportional hazards model was used to identify significant prognostic factors for OS between different PNS groups. **Results:** From 1975 to 2016, 733 patients with TET (thymoma (T) -71%, thymic carcinoma (TC) -26% and neuroendocrine tumor (NET)-3%) were seen at Indiana University. Of these, 203 (28%) had PNS including myasthenia gravis (n = 130), red cell aplasia (n = 20), hypogammaglobulinemia (n = 14), systemic lupus erythematosus (n = 12) or other PNS (n = 64). Among these, 37 (18%) had two or more types of PNS. PNS were seen in 35% (183/523) of T, 9% (16/187) of TC and 15% (3/20) of NET ($p < 0.001$), respectively. Recurrence rates and mortality at 5 year were 8% and 10% in PNS (+) group compared to 13% and 16% in PNS (-) group ($p < 0.05$). Intrathoracic recurrences were more common in PNS (+) patients (89% vs 77%; $p = 0.016$). In both groups, adverse factors for survival included: older age, advanced stage, number of positive lymph nodes and TC histology (all *p-values* < 0.05). However, post-operative R1/2 status was adverse prognostic factor only in the PNS (-) group ($p = 0.001$). **Conclusions:** PNS is common in TETs. Patients with PNS have lower risk of recurrence and mortality compared to patients without PNS, but may have a higher risk of intrathoracic recurrence.

TPS8575 Poster Session (Board #311a), Sat, 8:00 AM-11:30 AM

EA5142 adjuvant nivolumab in resected lung cancers (ANVIL): The newest study in the ALCHEMIST platform. *First Author: Jamie E. Chaft, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There have been no advances in the systemic treatment of resected lung cancers in the last decade. This is in contrast to advanced disease where molecularly targeted therapies for patients with oncogene-driven tumors have replaced and/or delayed chemotherapy and where immunotherapy drugs that target the programmed death receptor pathway (PD-1 or PD-L1) are now utilized in first and second line. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) is a National Cancer Institute (NCI) sponsored National Clinical Trials Network (NCTN) initiative to address the role of genomic testing and personalized therapies in the adjuvant treatment of non-small cell lung cancers. EA5142 is the newest of the ALCHEMIST studies, investigating adjuvant nivolumab in patients not eligible for the EGFR or ALK directed trials. **Methods:** ALCHEMIST is a clinical trial platform that consists of integrated protocols: ALCHEMIST Screening (A151216; NCT02194738), ALCHEMIST-EGFR (A081105; NCT02193282), ALCHEMIST-ALK (E4512; NCT02201992), and ALCHEMIST-nivo (EA5142; NCT02595944). In ALCHEMIST-Screening, up to 8,000 patients with pathologically confirmed stage IB (≥ 4 cm)-IIIA NSCLC will be enrolled either before or after surgical resection. Tumors that are non-squamous histology will be centrally genotyped for *EGFR* mutations and *ALK* rearrangements. Patients with *EGFR* or *ALK*-positive tumors are offered enrollment in trials evaluating adjuvant erlotinib or crizotinib, respectively. In the ~80% of patients enrolled with tumors that have wildtype *EGFR* and *ALK* or those with squamous histology central testing will be performed for PD-L1 utilizing immunohistochemistry (DAKO 28-8). Adjuvant therapy is allowed but not required. Patients are randomized to nivolumab 240 mg IV over 3 minutes every 2 weeks for up to 1 year versus standard of care observation, stratified by stage, histology, prior adjuvant treatment, and PD-L1 status (> / = 1% or < 1%). ANVIL has enrolled 52 of 714 planned patients to detect co-primary endpoints of a 30% improvement in overall survival and/or a 33% reduction in disease free survival favoring nivolumab. EA5142 is currently open at over 400 centers nationwide. Clinical trial information: NCT02595944.

TPS8576 Poster Session (Board #311b), Sat, 8:00 AM-11:30 AM

A phase III trial to compare atezolizumab (atezo) vs best supportive care (BSC) following adjuvant chemotherapy in patients (pts) with completely resected NSCLC: IMpower010. *First Author: Heather A. Wakelee, Stanford University School of Medicine, Stanford, CA*

Background: The anti–PD-L1 mAb atezo blocks the interaction between PD-L1 and its receptors PD-1 and B7.1 and restores anti-tumor immunity. In the OAK trial, pts with 2L/3L advanced NSCLC had improved mOS in the atezo arm (13.8 mo) vs the docetaxel (doc) arm (9.6 mo), with a survival benefit observed regardless of PD-L1 expression levels on tumor cells (TC) or tumor-infiltrating immune cells (IC). However, more effective treatment options are needed for pts with early-stage NSCLC. A global Phase III, randomized, open-label trial, IMpower010 (NCT02486718), is being conducted to evaluate the efficacy and safety of atezo vs BSC following adjuvant cisplatin (cis)–based chemotherapy (chemo) in pts with resected stage IB (tumors ≥ 4 cm)-IIIA NSCLC. **Methods:** Pts eligible for study must have complete tumor resection 4 to 12 weeks prior to enrollment for pathologic stage IB (tumors ≥ 4 cm)-IIIA NSCLC, be adequately recovered from surgery, be able to receive cis-based adjuvant chemo and have an ECOG PS 0-1. Pts with other malignancies, autoimmune disease, hormonal cancer or radiation therapy within 5 years and prior chemo or immunotherapy are excluded from study. Approximately 1127 pts will be enrolled regardless of PD-L1 status. Pts will receive up to four 21-d cycles of cis-based chemo (cis [75 mg/m^2 IV, d 1] + vinorelbine [30 mg/m^2 IV, d 1, 8], doc [75 mg/m^2 IV, d 1] or gemcitabine [1250 mg/m^2 IV, d 1, 8], or pemetrexed [500 mg/m^2 IV, d 1; only non-squamous NSCLC]). No adjuvant radiation therapy is permitted. After adjuvant chemo, eligible pts will be randomized 1:1 to receive 16 cycles of atezo 1200 mg q3w or BSC. Stratification factors include sex, histology (squamous vs non-squamous), disease stage (IB vs II vs IIA) and PD-L1 status by IHC (TC2/3 [≥ 5% expressing PD-L1] and any IC vs TC0/1 [< 5%] and IC2/3 vs TC0/1 and IC0/1 [< 5%]). The primary endpoint is disease-free survival; secondary endpoints include OS and safety. Exploratory biomarkers, including PD-L1 expression, immune- and tumor-related biomarkers before, during and after treatment with atezo and at radiographic disease recurrence, or confirmation of new primary NSCLC, will be evaluated. Clinical trial information: NCT02486718.

TPS8577 Poster Session (Board #312a), Sat, 8:00 AM-11:30 AM

Checkmate 816: A phase 3, randomized, open-label trial of nivolumab plus ipilimumab vs platinum-doublet chemotherapy as neoadjuvant treatment for early-stage NSCLC. *First Author: Patrick M. Forde, Johns Hopkins Kimmel Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy, Baltimore, MD*

Background: At initial diagnosis, 20% of patients (pts) with NSCLC present with early-stage disease. The 5-year overall survival (OS) rate after surgery for stage IB–IIIA NSCLC is 25%–60%. Addition of adjuvant chemotherapy to surgery only provides a 5% absolute OS benefit at 5 years. Neoadjuvant treatment with immune checkpoint inhibitors may extend OS in early-stage NSCLC by enhancing systemic immunity and eradicating micrometastatic disease. In contrast to the adjuvant setting, the neoadjuvant setting is associated with a higher tumor burden, the presence of abundant tumor antigens, and the consequent potential for tumor-associated neoantigen presentation to the immune system. In an ongoing feasibility trial in pts with stage IB–IIIA NSCLC, nivolumab (nivo; a fully human PD-1 immune checkpoint inhibitor antibody) given alone as neoadjuvant treatment induced a major pathological response (MPR; $<$ 10% residual viable tumor cells) rate of 39% (7/18), did not delay or interfere with surgery, and was not associated with new safety signals. In a phase 1 study in pts with stage IIIB/IV NSCLC, first-line nivo + ipilimumab (ipi; a CTLA-4 immune checkpoint inhibitor antibody) showed a greater radiologic objective response rate than nivo alone (39% vs 23%). These data provided the rationale for Checkmate 816 (NCT02998528), a phase 3 study evaluating nivo + ipi vs platinum-doublet chemotherapy as neoadjuvant treatment for early-stage NSCLC. **Methods:** Approximately 326 pts aged $\geq$18 years with resectable stage IB/II/IIIA NSCLC, ECOG performance status 0–1, pulmonary function capable of tolerating lung resection, and available lung tumor tissue will be enrolled in North America, South America, Europe, and Asia. Pts are ineligible if they have autoimmune disease or had received prior treatment with immune checkpoint inhibitors. Pts will be randomized to receive nivo + ipi or platinum-doublet chemotherapy. The primary endpoint is MPR rate. Secondary endpoints include event-free survival, OS, and complete pathological response. Start date is January 2017. The estimated primary completion date is July 2019. Clinical trial information: NCT02998528.

TPS8578 Poster Session (Board #312b), Sat, 8:00 AM-11:30 AM

eXalt3: A phase III study of ensartinib (X-396) in anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). *First Author: Leora Horn, Vanderbilt University Medical Center, Nashville, TN*

Background: Ensartinib is a novel, potent anaplastic lymphoma kinase (ALK) small molecule tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, Axl, EPHA2, LTK, ROS1 and SLK. Ensartinib has demonstrated activity in ALK treatment naïve and previously treated patients and has a generally well tolerated safety profile. **Methods:** eXalt3 (NCT02767804) is a global, randomized, open-label phase III study comparing the efficacy and safety of ensartinib to crizotinib in ALK- positive TKI naïve non-small cell lung cancer (NSCLC) patients. It is being conducted in $>$ 100 sites in North America, South America, Europe, and the Asia/Pacific region. Enrollment began in 2016. The primary efficacy endpoint is progression free survival (PFS) assessed by independent radiology review. Secondary efficacy endpoints include overall survival, response rates (overall and central nervous system [CNS]), PFS by investigator assessment, time to response, duration of response, and time to CNS progression. Approximately 270 patients with ALK+ NSCLC who have received no prior ALK TKI and up to one prior chemotherapy regimen will be randomized 1:1 to ensartinib 225 mg QD, or crizotinib 250 mg BID, with stratification based on prior chemotherapy, ECOG performance status (PS), CNS metastases and geographic region. Eligibility includes patients $\geq$ 18 years of age, stage IIIB or IV ALK+ NSCLC. Patients are required to have measurable disease per RECIST 1.1, adequate organ function, and an ECOG PS of $\leq$2. Adequate tumor tissue (archival or fresh biopsy) must be available for central testing. The study has $>$ 80% power to detect a superior effect of ensartinib over crizotinib in PFS at a 2-sided alpha level of 0.05. Clinical trial information: NCT02767804.

TPS8579 Poster Session (Board #313a), Sat, 8:00 AM-11:30 AM

Randomized phase III trial of concurrent chemoradiation followed by nivolumab or placebo for locally advanced non-small cell lung cancer (NSCLC) (RTOG 3505). *First Author: David E. Gerber, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Despite aggressive therapy with concurrent chemoradiation, fewer than 25% of patients with stage 3 NSCLC achieve 5-year survival and are presumably cured. To date, treatment modifications—including consolidation chemotherapy, maintenance therapy with molecularly targeted agents, concomitant administration of monoclonal antibodies, and escalation of radiation therapy (RT) dose—have not improved these outcomes. Immune checkpoint inhibitors represent an effective treatment for advanced NSCLC and may enhance RT-associated anti-tumor immunity. RTOG 3505 will test whether the addition of the anti-programmed death 1 (PD1) antibody nivolumab after chemoradiation improves overall survival (OS) and progression-free survival (PFS) in this population. **Methods:** Key eligibility criteria include surgically unresectable stage 3 NSCLC, ECOG 0-1, adequate organ function, available archival tissue, and absence of active autoimmune disease. Patients will receive thoracic RT to 60 Gy with concurrent cisplatin 50 mg/m^2 IV on Days 1, 8, 29, and 36, and etoposide 50 mg/m^2 IV on Days 1-5 and 29-33. This regimen was selected to (1) minimize risk of pulmonary toxicity and steroid requirements, and (2) optimize timing of immunotherapy. Between 4 and 12 weeks after completion of chemoradiation, eligible patients will be randomized to nivolumab 240 mg IV or placebo every 2 weeks for 1 year. Stratification factors include performance status, histology, and tumor PD-L1 status. Co-primary endpoints are OS and PFS, as determined by central radiology review. Secondary objectives include toxicity assessment, patient-reported outcomes and quality of life, and OS and PFS according to PD-L1 expression. Exploratory objectives include biomarkers to predict treatment efficacy and toxicity. A total of 660 patients will be enrolled to provide $\geq$90% power to detect (1) a hazard ratio (HR) of 0.7 for OS with two-sided type I error of 0.04, and (2) HR of 0.667 for PFS two-sided type I error of 0.01, allowing a 16.7% drop-out rate before randomization. Clinical trial information: NCT02768558.

TPS8580 Poster Session (Board #313b), Sat, 8:00 AM-11:30 AM

A phase II study of atezolizumab as neoadjuvant and adjuvant therapy in patients (pts) with resectable non-small cell lung cancer (NSCLC). *First Author: Dwight Hall Owen, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Trials of neoadjuvant and adjuvant chemotherapy have demonstrated an absolute survival benefit of 5% for patients with early stage disease. Atezolizumab is a humanized IgG1 monoclonal antibody that inhibits PD-L1 from binding to its receptors PD-1 and B7.1, thereby restoring anti-tumor immune response. In the OAK trial, a randomized phase III trial of patients with metastatic NSCLC who progressed on platinum based chemotherapy, atezolizumab improved overall survival in patients regardless of PD-L1 expression compared with docetaxel (13.8 months vs. 9.6 months, HR 0.73 [95% CI 0.62 – 0.87]) with a manageable safety profile. **Methods:** NCT02927301 is a phase II, open-label, single-arm study designed to evaluate the efficacy and safety of atezolizumab as a neoadjuvant and adjuvant therapy in patients with Stage IB, II, or IIIA NSCLC prior to curative-intent resection. Approximately 180 patients with NSCLC will be enrolled in this study at 15 academic medical centers in the United States. The study has two parts: the primary part will evaluate the ability of neoadjuvant atezolizumab to produce pathologic responses in patients with early stage NSCLC. Atezolizumab 1200 mg IV will be given every 3 weeks for two doses. Surgical resection of tumors following treatment will allow determination of pathologic response rates and potential predictive biomarkers. Part 2 is exploratory and will evaluate atezolizumab adjuvant therapy for up to 12 months in patients who demonstrate clinical benefit in Part 1. The primary endpoint is major pathologic response rate (defined as $\leq$ 10% of viable tumor tissue) based on surgical resection. Secondary end points include overall response rate by status of mutation load, neoantigen score and gene expression signatures. OS and DFS are exploratory end points. This trial presents a unique opportunity to evaluate exploratory biomarkers given the availability of pre- and post-treatment biopsy specimens for assessment of evolution of immune related markers associated with response. The study opened to accrual in January 2017. Clinical trial information: NCT02927301.

TPS8581 **Poster Session (Board #314a), Sat, 8:00 AM-11:30 AM**

Checkmate 743: A phase 3, randomized, open-label trial of nivolumab (nivo) plus ipilimumab (ipi) vs pemetrexed plus cisplatin or carboplatin as first-line therapy in unresectable pleural mesothelioma. *First Author: Gerard Zalcman, GH Bichat Claude Bernard, Paris, France*

Background: Malignant pleural mesothelioma (MPM) is an aggressive cancer with a 5-year overall survival (OS) rate of $< 10\%$. At diagnosis, most patients (pts) have unresectable disease. Combination chemotherapy of cisplatin (or carboplatin as an alternative) + pemetrexed is the approved first-line standard of care. Phase 1 and 2 data suggest that targeting immune checkpoint pathways (eg, programmed death [PD]-1/PD-ligand 1 [PD-L1] and/or cytotoxic T-lymphocyte antigen-4 [CTLA-4]) may provide benefit with acceptable safety in MPM. In pts with previously treated, malignant mesothelioma, single-agent tremelimumab (a CTLA-4 inhibitor antibody) was active but did not improve OS vs placebo. In a phase 2 study of nivo (a fully human PD-1 immune checkpoint inhibitor antibody) in 34 pts with MPM that progressed after first-line platinum-based chemotherapy, 12-week disease control rate (DCR) was 50%, 5 pts had partial response, and 12 pts had stable disease. Given the data with single-agent CTLA-4 and PD-1 inhibitors and that CTLA-4 inhibition can induce PD-L1 expression, there is reason to anticipate synergy when combining CTLA-4 and PD-1 inhibitors in MPM. A phase 2 study assessing nivo alone and nivo + ipi (a CTLA-4 inhibitor antibody) in MPM is ongoing. CheckMate 743 (NCT02899299) is a phase 3 study that will evaluate the efficacy and safety of first-line nivo + ipi vs chemotherapy for MPM. **Methods:** Approximately 600 adult pts with unresectable MPM and ECOG performance status 0–1 will be randomized. Pts are ineligible if they have primary peritoneal, pericardial, or tunica vaginalis testis mesotheliomas; have active, untreated CNS metastases; or had received prior systemic therapy for pleural mesothelioma or a prior PD-1/PD-L1 or CTLA-4 checkpoint inhibitor antibody. Pts are randomized 1:1 to receive nivo + ipi or pemetrexed + cisplatin/carboplatin. Primary endpoints are OS and progression-free survival (PFS), assessed by blinded independent central review. Secondary endpoints are objective response rate (ORR), DCR, and correlation of PD-L1 expression level and efficacy (ORR, PFS, and OS). Clinical trial information: NCT02899299.

TPS8582 **Poster Session (Board #314b), Sat, 8:00 AM-11:30 AM**

ATOMIC-Meso: A randomized phase 2/3 trial of ADI-PEG20 or placebo with pemetrexed and cisplatin in patients with argininosuccinate synthetase 1-deficient non-epithelioid mesothelioma. *First Author: Peter Wojciech Szlosarek, St Bartholomew's Hospital, London, United Kingdom*

Background: Argininosuccinate synthetase 1 (ASS1)-deficient malignant pleural mesothelioma (MPM) is sensitive to arginine deprivation therapy with pegylated arginine deiminase (ADI-PEG20), which also enhances the cytotoxicity of pemetrexed. The TRAP Phase 1 trial (NCT02029690) of ADI-PEG 20 combined with 1st-line pemetrexed (PEM) and cisplatin (CDDP) chemotherapy revealed a 94% disease control rate in non-epithelioid (biphasic and sarcomatoid) MPM subtypes characterized by a 75% rate of ASS1 loss. Thus, we plan to assess the efficacy of ADI-PEG20 or placebo combined with PEM and CDDP in patients (pts) with poor prognosis MPM in a randomized, placebo-controlled, double-blind phase 2/3 global trial. **Methods:** Up to 386 good performance (ECOG 0-1) pts with non-epithelioid malignant pleural mesothelioma will be enrolled in a phase 2/3 adaptive, biomarker-driven study design. Biopsies will be required prior to randomization: ASS1-agnostic pts will be enrolled initially (phase 2 stage) with an option to restrict enrolment to ASS1-deficient MPM (phase 3 stage). Pts will be randomized to receive weekly ADI-PEG20 (36 mg/m2 IM) or placebo with standard doses of PEM and CDDP for a maximum of 18 weeks (6 cycles) of treatment. Pts who develop CDDP toxicity may be switched to carboplatin. Pts will be assessed every 6 weeks using modified RECIST (RECIST 1.1 allowed for pts with significant extra-thoracic disease). The primary endpoint for the phase 2 stage will be overall response rate (ORR) with secondary endpoints of overall survival (OS), safety and toxicity. The phase 2 will test ORR proportions with the placebo triplet set at 15% vs. 35% for the ADI-PEG 20 triplet, with a 1:1 randomization, 80% power. After recruitment of 176 pts, the phase 2 will convert to a phase 3 study with the primary endpoint of OS. In summary, ATOMIC-Meso is the first triplet chemotherapy study to assess the role of targeted arginine deprivation in aggressive subtypes of mesothelioma. Pt accrual has commenced across the US and Asia, with enrolment due in Europe and Australia by 2nd quarter of 2017. [Trial sponsored by Polaris Group]. Clinical trial information: NCT02709512.

TPS8583 **Poster Session (Board #315a), Sat, 8:00 AM-11:30 AM**

A phase III study of rovalpituzumab tesirine maintenance therapy following first-line platinum-based chemotherapy in patients with extensive disease small cell lung cancer (ED SCLC). *First Author: Philip B. Komarnitsky, AbbVie Inc., Cambridge, MA*

Background: SCLC embodies 15-20% of lung cancers. Patients (pts) are staged with either limited or extensive disease; the standard front-line treatment for the latter is chemotherapy with carbo- or cisplatin combined with etoposide or irinotecan. Response rates are high with limited duration. Recurrence may be attributable to chemo-resistant tumor initiating cells (TICs). Delta-like protein 3 (DLL3) is an inhibitory Notch receptor ligand identified as a novel target in SCLC TICs. DLL3 is highly expressed in SCLC but not normal tissue. Rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate composed of a DLL3-targeting IgG1 monoclonal antibody tethered to a DNA cross-linking toxin. Rova-T has shown activity in recurrent/relapsed ED SCLC patients (Rudin et al., Lancet Oncol, 2016). Given DLL3 expression in TICs, exploration of Rova-T front-line maintenance strategies in ED SCLC is warranted. The postulated mechanism of action of Rova-T and its clinical activity indicate potential to improve progression-free and overall survival in this setting. **Methods:** This is a Phase 3, randomized, double-blind, placebo-controlled, international study (NCT03033511, no pts enrolled yet as of 7 February 2017). Approximately 740 ED SCLC pts will be enrolled to include ~480 pts with high DLL3 expression. Eligibility: pts $\geq$ 18 years; histologically or cytologically confirmed ED SCLC with ongoing clinical benefit (complete/partial response or stable disease) after 4 cycles of 1st line platinum-based therapy; definitively treated CNS metastases allowed; > 3 but ≤ 9 wks between the administration of the last cycle of platinum-based chemotherapy and randomization; available tumor tissue for DLL3 expression testing; ECOG performance score 0-1. Pts will be randomly assigned 1:1 to receive 0.3 mg/kg Rova-T or placebo on Day 1 of each 6-wk cycle, omitting every 3rd cycle. Primary objectives: determine if Rova-T improves progression-free and overall survival. Secondary objectives: assess Rova-T antitumor activity by determining objective response rate, clinical benefit rate, duration of response, and changes in pt reported outcomes. Clinical trial information: NCT03033511.

TPS8584 **Poster Session (Board #315b), Sat, 8:00 AM-11:30 AM**

Phase I/III trial of atezolizumab with carboplatin and etoposide in ES-SCLC in first-line setting (IMpower133). *First Author: Leora Horn, Vanderbilt University Medical Center, Nashville, TN*

Background: The first-line standard of care for the majority of patients (pts) with extensive-stage small-cell lung cancer (ES-SCLC) is platinum-based chemotherapy with etoposide, but survival outcomes remain poor (median OS, < 1 year) despite initial response rates ranging from 50-70%. Atezolizumab (atezo), an anti–PD-L1 mAb, prevents the binding of PD-L1 with its receptors PD-1 and B7.1 and restores anticancer T-cell activity. Tolerable safety with promising durability of response has been shown with atezo in pts with ES-SCLC: confirmed ORR was 6% (n = 1/17 [partial response]; DOR of 7 mo) by RECIST v1.1 and 24% by immune-related response criteria (irRC; n = 4/17, with 2 pts on atezo for $\geq$ 12 mo). Preliminary data also indicate the potential synergy between atezo and platinum-based chemotherapy in NSCLC, whereby durable responses may translate into improved survival over atezo alone. IMpower133 (NCT02763579), a global, Phase I/III, randomized, multicenter, double-blinded, placebo-controlled trial will evaluate the efficacy and safety of 1L atezo + carboplatin + etoposide compared with placebo + carboplatin + etoposide in treatment-naive pts with ES-SCLC. **Methods:** Pts with measurable (RECIST v1.1) ES-SCLC, who have ECOG PS 0-1 and no prior systemic anticancer treatment, are eligible for the study. Exclusion criteria include untreated CNS metastases and history of autoimmune disease. The study requires submission of tumor tissue, but pts will be enrolled regardless of biomarker status. Pts will be stratified by sex, ECOG PS and presence of treated brain metastases. Eligible pts will be randomized 1:1 to receive four 21-day cycles of atezo (1200 mg IV) or placebo in combination with carboplatin (AUC 5 mg/mL/min IV, d 1) and etoposide (100 mg/m^2 IV, d 1-3), followed by maintenance therapy with atezo or placebo until PD per RECIST v1.1. Pts can continue with treatment until persistent radiographic PD, symptomatic deterioration or unacceptable toxicity. Co-primary endpoints are investigator-assessed PFS per RECIST v1.1 and OS. Secondary efficacy endpoints include investigator-assessed ORR and DOR. Safety and tolerability will also be assessed. Approximately 400 pts will be enrolled. Clinical trial information: NCT02763579.

TPS8585 Poster Session (Board #316a), Sat, 8:00 AM-11:30 AM

A phase II, open-label, multi-arm study of novel combinations of immunotherapies or DDR inhibitors in platinum-refractory, extensive disease small-cell lung cancer (ED-SCLC): BALTIC. *First Author: Joachim Von Pawel, Asklepios Fachkliniken München-Gauting, Gauting, Germany*

Background: The prognosis of platinum-refractory ED-SCLC is poor, with ~95% of pts failing to respond to topotecan, the only approved 2ndline treatment. SCLC is associated with a high mutation load and genomic instability, and data suggest that enhanced DNA repair could be a resistance mechanism. As such, immunotherapies and DNA damage repair inhibitors may be beneficial in this disease setting. Durvalumab (D) is a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. Tremelimumab (T) is a selective human IgG2 mAb against CTLA-4. In a Phase 1b study in NSCLC (NCT02000947), D + T showed encouraging activity and manageable tolerability. AZD1775 is a small-molecule inhibitor of the DNA damage checkpoint kinase WEE1 that potentiates genotoxic chemotherapies and is being developed for the treatment of advanced solid tumors with genetic deficiencies in DNA repair mechanisms. In a Phase 2 study in platinum-refractory p53 mutated ovarian cancer (NCT01164995), AZD1775 + carboplatin showed promising activity and an acceptable safety profile. **Methods:** BALTIC (NCT02937818) is a Phase 2, open-label, multicenter, multi-arm, exploratory, signal-searching study to assess the preliminary activity of novel treatment combinations in refractory ED-SCLC. Eligible pts will have progressed during, or within 90 days of completing 1st line platinum-based chemotherapy, and have life expectancy ≥8 wks. Each arm is independent and will open sequentially to enroll up to 20 pts. The study will open initially with 2 arms: D 1500 mg + T 75 mg i.v. q4w for 4 doses, followed by D monotherapy 1500 mg i.v. q4w (Arm A); and oral AZD1775 225 mg bid for 2.5 days from Day 1 + carboplatin AUC 5 on Day 1 i.v. q3w (Arm B). Pts will receive treatment until confirmed disease progression or discontinuation. Further arms may be added to assess other combinations once safe and tolerable doses and schedules have been established. The primary endpoint is investigator-assessed ORR (RECIST v1.1). Secondary endpoints include duration of response, disease control rate, time to response, PFS, OS, PK, safety and tolerability. Recruitment is ongoing. Clinical trial information: NCT02937818.

TPS8586 Poster Session (Board #316b), Sat, 8:00 AM-11:30 AM

A phase 3, randomized study of first-line durvalumab (D) ± tremelimumab (T) + platinum-based chemotherapy (CT) vs CT alone in extensive disease small-cell lung cancer (ED-SCLC): Caspian. *First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: SCLC accounts for ~13% of all lung cancers and is characterized by rapid growth and early metastases development. Standard of care CT for pts presenting with ED-SCLC is associated with the development of resistance, leading to poor treatment outcomes. As such, new therapies are needed. The high mutation burden associated with SCLC provides a rationale for investigating immune checkpoint blockade in this tumor type. D is a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. T is a selective human IgG2 mAb against CTLA-4. D alone and in combination with T has demonstrated a manageable safety profile and encouraging antitumor activity in non-small cell lung cancer (NSCLC). D ± T in combination with CT has also shown acceptable tolerability and preliminary signs of clinical activity in advanced NSCLC and thus may provide benefit in SCLC. **Methods:** CASPIAN (NCT03043872) is a Phase 3, randomized, multicenter, open-label, global study to determine the efficacy of CT in combination with D ± T as first-line treatment in ED-SCLC (Stage IV). Treatment-naïve pts (N = ~795; WHO/ECOG PS 0 or 1) will be randomized 1:1:1 to receive D (1500 mg) + T (75 mg) i.v. every 3 weeks (q3w) + CT (Arm 1); D (75 mg) i.v. q3w + CT (Arm 2); or CT alone (Arm 3). D ± T will be concurrently administered with CT in Arms 1 and 2 and will continue post-CT (1 further dose for T; until confirmed progressive disease for D). CT (etoposide [80–100 mg/m^2] i.v. on Days 1–3 q3w + carboplatin [AUC 5–6] i.v. on Day 1 q3w or cisplatin [75–80 mg/m^2] i.v. on Day 1 q3w) will be given for up to 4 cycles in Arms 1 and 2 and up to 6 cycles in Arm 3. The co-primary endpoints are overall survival (OS) and progression-free survival (PFS) using blinded independent central review (RECIST v1.1), for Arm 1 vs Arm 3. Secondary endpoints include OS and PFS for Arm 2 vs Arm 3 and Arm 1 vs Arm 2, ORR, OS at 18 months, proportion of patients alive and progression free at 6 and 12 months, PK, immunogenicity, HRQoL, and safety and tolerability. Exploratory endpoints include PFS after subsequent anticancer therapy and correlation of biomarkers with response to treatment. Recruitment is ongoing. Clinical trial information: NCT03043872.

8509 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Efficacy, safety, and biomarker results of trastuzumab emtansine (T-DM1) in patients (pts) with previously treated HER2-overexpressing locally advanced or metastatic non-small cell lung cancer (mNSCLC). *First Author: Tom Stinchcombe, Duke University, Durham, NC*

Background: T-DM1 is an antibody-drug conjugate approved for HER2-positive metastatic breast cancer. We report primary results from a fully enrolled, ongoing phase 2 study (NCT02289833) of pts with previously treated HER2-overexpressing mNSCLC who received single-agent T-DM1. **Methods:** Eligible pts had HER2-overexpressing mNSCLC and were previously treated with platinum-based therapy. Pts received T-DM1 3.6 mg/kg every 3 weeks and were analyzed in 2 cohorts based on centrally determined HER2 status (immunohistochemistry [IHC]2+ vs IHC3+ [≥10% cells stained with 2+ or 3+ intensity, respectively]). HER2 amplification was assessed via ISH (HER2 gene ratio ≥2.0). The primary endpoint is objective response rate (ORR; proportion of pts with confirmed [≥4 weeks] complete or partial response per RECIST v1.1). **Results:** The clinical cutoff date for this analysis was Oct 26, 2016.Of 393 screened pts, 102 (27%) were IHC2+ and 29 (7%) were IHC3+. In total, 49 pts (IHC2+, n = 29; IHC3+, n = 20) received T-DM1. At cutoff, median follow-up was 16.3 (range 0.9*–22.4; * = censored observation) months. No IHC2+ pt had a response (0%, 95% CI 0–11.9); 4 IHC3+ pts had partial responses (20%, 95% CI 5.7–43.7) with a median duration of response of 7.3 (range 2.9–8.3) months. Median progression-free survival (PFS) in IHC2+ and IHC3+ pts was 2.6 (95% CI 1.4–2.8) and 2.7 (95% CI 1.4–8.3) months, respectively. At 6 months after start of study treatment, 9 pts (IHC2+, n = 4; IHC3+, n = 5) were still at risk for a PFS event. Median overall survival was 12.2 (95% CI 3.8–not estimable [NE]) months in IHC2+ pts and 12.1 (95% CI 9.3–NE) months in IHC3+ pts. Of 16 pts with HER2 amplification (IHC2+, n = 5; IHC3+, n = 11), 3 responded, all in the IHC3+ cohort (27.3%, 95% CI 6.0–61.0). Eleven pts (22%) experienced a grade 3–4 adverse event, with fatigue and dyspnea being the only events reported in > 1 pt (n = 2 each). **Conclusions:** This is the first study to report on the clinical activity of T-DM1 in HER2-overexpressing mNSCLC. Objective responses were observed in IHC3+ pts. Additional molecular analyses are underway to refine markers for optimal pt selection. Clinical trial information: NCT02289833.

8510 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Ado-trastuzumab emtansine in patients with *HER2* mutant lung cancers: Results from a phase II basket trial. *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Human epidermal growth factor receptor 2 (*HER2*, *ERBB2*) mutations occur in 2% of lung cancers, resulting in receptor dimerization and kinase activation with in vitro sensitivity to trastuzumab. Ado-trastuzumab emtansine is a HER2 targeted antibody drug conjugate linking trastuzumab with the anti-microtubule agent emtansine. **Methods:** Patients (pts) with *HER2* mutant lung cancers were enrolled into a cohort of the basket trial of ado-trastuzumab emtansine in *HER2*amplified or mutant cancers, treated at 3.6mg/kg IV every 3 weeks. The primary endpoint was overall response rate (ORR) using RECIST v1.1. A Simon two stage optimal design was used with type I error rate under 2.7% (and a family wise error rate across baskets under 10%), power of 89%, H0 10%, H1 40%; the H0 will be rejected if 5 or more responses are observed in 18 pts. Other endpoints include duration of response (DOR), progression-free survival (PFS) and toxicity. HER2 testing was performed on tumor tissue by next generation sequencing (NGS), fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). **Results:** The cohort completed accrual with 18 pts treated. The median age was 63 (range 47-74 years), 72% were female, 39% were never smokers and all had adenocarcinomas. The median lines of prior systemic therapy was 2 (range 0-4). ORR was 33% (5/15 confirmed, 95% CI 12-62%) not including a partial response awaiting confirmation and 3 pts pending response evaluation. Median DOR was not reached (range 3 to 7+ mo), median PFS was 4mo (95% CI 3mo-not reached). Toxicities were mainly grade 1 or 2 including infusion reaction, thrombocytopenia and transaminitis, there were no dose reductions or treatment related deaths. There were 10 (56%) exon 20 insertions and 8 (44%) point mutations; responders were seen across mutation subtypes (A775_G776insYVMA, G776delinsVC, V659E, S310F). *HER2*amplification was negative for all pts by NGS and positive for 1 of 12 pts by FISH. There was no IHC3+ in 10 pts tested. **Conclusions:** Ado-trastuzumab emtansine is active and well tolerated in pts with *HER2* mutant lung cancers. This study has met its primary endpoint. Further development in a multicenter study is warranted. Clinical trial information: NCT02675829.

8511 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

Impact of MET inhibitors on survival among patients (pts) with *MET* exon 14 mutant (*MET*del14) non-small cell lung cancer (NSCLC). *First Author: Mark M. Awad, Dana-Farber Cancer Institute, Boston, MA*

Background: Dramatic responses to MET inhibitors have been reported in patients with NSCLC harboring activating mutations that cause *MET* exon 14 (*MET*del14) skipping. We conducted a multicenter retrospective analysis of pts with *MET*del14 NSCLC to determine if treatment with MET inhibitors impacts survival. **Methods:** We collected clinicopathologic data on pts with *MET*del14 NSCLC. Event-time distributions were estimated using Kaplan-Meier and compared with the log-rank test. Multivariable Cox models were fitted to estimate hazard ratios. **Results:** Of the 148 pts with *MET*del14 mutant NSCLC, the median age was 72 (range 43-88); 57% were women, and 41% were never smokers. The most common histologies were adenocarcinoma (77%) and pulmonary sarcomatoid carcinoma (14%). Overlap with oncogenic driver mutations in other genes was rare. At the time of diagnosis, 70% of pts had stage I-III disease, and 30% had stage IV disease. Of the 34 pts with metastatic disease who never received a MET inhibitor, the median overall survival (mOS) was 8.1 months. In this cohort, cancers that also had concurrent *MET* amplification had a trend toward worse survival compared to cancers without *MET* amplification (5.2 months vs 10.5 months, P = 0.06). Of the 27 pts with metastatic disease who received at least one MET inhibitor (including crizotinib, glesatinib, capmatinib, and ABBV-399), the mOS was 24.6 months. A model adjusting for receipt of a MET inhibitor as first- or second-line therapy as a time-dependent covariate demonstrated that treatment with a MET inhibitor was associated with a significant prolongation in survival (HR 0.11, 95% CI 0.01-0.92, P = 0.04). Among 22 patients treated with crizotinib, the median progression-free survival (PFS) was 7.36 months. **Conclusions:** Forpts with *MET*del14 NSCLC, treatment with a MET inhibitor is associated with an improvement in overall survival. The prognosis of pts who never received treatment with a MET inhibitor appears to be poor, particularly among *MET*del14 cancers with concurrent *MET* amplification.

8512 Clinical Science Symposium, Sun, 8:00 AM-9:30 AM

PD-L1 expression and response to immunotherapy in patients with *MET* exon 14-altered non-small cell lung cancers (NSCLC). *First Author: Joshua K. Sabari, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *MET* exon 14 skipping alterations (*MET*Δ14) are present in 4% of NSCLCs. Response to MET inhibition has been observed in ongoing prospective trials (44% response rate, phase 1 trial of crizotinib; Drilon et al ASCO 2016), however responses to other types or therapy, such as immunotherapy, is unknown. We evaluated the immunophenotype of *MET*Δ14 lung cancers and response to PD-(L)-1-based immunotherapy. **Methods:** Pts with recurrent/metastatic NSCLC were eligible. *MET*Δ14 was identified by broad hybrid capture-based next-generation sequencing (MSK-IMPACT). PD-L1 expression was determined by immunohistochemistry. Response to immune therapy was evaluated by RECIST v1.1. **Results:** 63 pts with *MET*Δ *14*-positive non-small cell lung cancers were identified; 41 (65%) had sufficient tissue for PD-L1 analysis. Patient characteristics: median age 71 years, 58% female, median pack year smoking 5.85 years, histology: 73% (30/41) adenocarcinoma, 20% (8/41) pleomorphic carcinoma, 7% (3/41) squamous cell. Tumor PD-L1 expression was ≥50% in 44% (18/41, 95% CI 30-59%), 1-49% in 17% (7/41, 95% CI 8-32%), and < 1 in 39% (16/41, 95% CI 26-54%). The median age for patients with *MET*Δ14 and PD-L1 positive (≥1%) tumors was 65 years (range 49-87); 60% (15/25) of patients were female; Histology: 72% (18/25) adenocarcinoma, 24% (6/25) sarcomatoid carcinoma, and 4% (1/25) squamous cell carcinoma. Immunotherapy was given to 15 pts: nivolumab (5), pembrolizumab (3), atezolizumab (2), durvalumab (1), and ipilimumab+nivolumab (4). The overall response rate to immunotherapy was 13% (2/15, 95% CI 3-39%). Overall response was 33% (1/3; 95% CI 6-80%) in patients with tumors PD-L1 ≥50%, and 20% (1/5, 95%CI 2-64%) in patients with tumors PD-L1 0%. Time on therapy ranged from 2 weeks to 9.6+ months. **Conclusions:** A substantial proportion of NSCLCs harboring *MET*Δ14 alterations express PD-L1. Despite frequent PD-L1 expression, responses to immunotherapy were overall uncommon and lower than that observed with targeted therapy for this genomically defined subset of patients with lung cancers. Further exploration of this subset may reveal important mechanisms of immunotherapy resistance in PD-L1 expressing tumors.

9000 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Progression after the next line of therapy (PFS2) and updated OS among patients (pts) with advanced NSCLC and PD-L1 tumor proportion score (TPS) ≥50% enrolled in KEYNOTE-024. *First Author: Julie R. Brahmer, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: In KEYNOTE-024 (NCT02142738), pembrolizumab (pembro) was superior to chemotherapy (chemo) as first-line (1L) therapy for advanced NSCLC with PD-L1 TPS ≥50% and no sensitizing EGFR mutations or ALK translocations. After a median follow-up of 11.2 mo, HR was 0.50 for PFS by independent central radiologic review ($P < 0.001$) and 0.60 for OS ($P = 0.005$). Here we present PFS2 and updated OS. **Methods:** 305 pts were randomly assigned to pembro 200 mg Q3W (n = 154) or investigator (INV)-choice platinum-doublet chemo with optional pemetrexed maintenance for nonsquamous histology (n = 151). Pts in the chemo arm could cross over to pembro upon PD. Poststudy anticancer therapy and INV-assessed outcomes were collected. Kaplan-Meier PFS2 and OS were calculated in all allocated pts. PFS2 was defined as time from randomization to PD per INV after start of 2L+ therapy or death, whichever occurred first; pts alive and without 2L+ PD were censored at last known survival. Kaplan-Meier OS was defined as time from randomization to death. There was no adjustment for multiplicity (cutoff: Jan 5, 2017). **Results:** 2L+ therapy was received by 48 (31.2%) pts in the pembro arm and 97 (64.2%) in the chemo arm, including 80 pts who crossed over from chemo to pembro per protocol and 14 pts who received anti–PD-1 therapy outside of crossover. 56 (36%) 1L pembro pts were on 1L pembro therapy or in follow-up as of data cutoff. Updated median OS and PFS2 results are in the Table. **Conclusions:** Fewer pembro pts received 2L+ therapy vs chemo pts because of the significant improvement in PFS observed for pembro in the 1L setting. Median PFS2 was substantially improved for pembro (not reached [NR]) vs chemo (8.6 mo). Updated OS with median follow-up of 19 mo maintained consistent superiority of 1L pembro, despite increased crossover from 1L chemo. Clinical trial information: NCT02142738.

Outcomes	1L Pembro n = 154	1L Chemo n = 151
OS		
Events, n (%)	63 (40.9)	84 (55.6)
HR (95% CI)	0.63 (0.46-0.88); nominal $P = 0.003$	
Median (95% CI), mo	NR (19.4-NR)	14.5 (9.8-19.6)
12 mo, % (95% CI)	70.3 (62.3-76.9)	54.8 (46.4-62.4)
PFS2		
HR (95% CI)	0.48 (0.34-0.66); nominal $P < 0.001$	
Median (95% CI), mo	NR	8.6 (7.4-14.4)
12 mo, % (95% CI)	67.2 (59.0-74.1)	44.4 (36.1-52.3)

9001 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Impact of atezolizumab (atezo) treatment beyond disease progression (TBP) in advanced NSCLC: Results from the randomized phase III OAK study. *First Author: David R. Gandara, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Cancer immunotherapy (CIT) can have a positive impact on OS that exceeds response rate or PFS effects, termed post progression prolongation of survival (PPPS). This effect can also result from unconventional CIT response due to tumor immune infiltration or delayed response, reducing reliability of RECIST v1.1 (RECIST) PD as an indicator of treatment failure. In the primary analysis (N = 850) of OAK, a study of atezo vs docetaxel (doc) in 2L/3L NSCLC, OS favored atezo (HR 0.73; 95% CI: 0.62, 0.87), despite similar PFS between arms (HR 0.95; 95% CI: 0.82, 1.10). Here we evaluate clinical benefit from TBP, defined by post PD tumor regression, OS and safety. **Methods:** Patients (pts) received atezo 1200 mg IV q3w until PD or loss of clinical benefit per investigator or doc 75 mg/m^2 IV q3w until PD per RECIST. No crossover was allowed. Primary outcome measure: OS. Atezo TBP pts were evaluated for post PD tumor change and for safety pre and post PD. OS from time of PD per RECIST was evaluated in both arms (data cutoff, July 7, 2016; minimum follow-up, 19 mo). **Results:** Among 332 atezo pts with PD, 51% (n = 168) continued atezo TBP; 7% (12/168) achieved subsequent response in target lesions (≥ 30% reduction from new baseline at PD); 49% (83/168) had stable target lesions (best change between +20% and −30%). mOS was 12.7 mo (95% CI: 9.3, 14.9) post PD for pts on atezo TBP (Table). Atezo TBP was not associated with increased safety risk. **Conclusions:** This is the first report from a Phase III study of CIT in NSCLC to evaluate post PD OS in pts continuing treatment beyond RECIST PD. Atezo TBP was associated with high frequency of stable or decreased target lesions, mOS > 1 year and a tolerable safety profile, all supporting prolonged treatment benefit consistent with PPPS. NCT02008227 Clinical trial information: NCT02008227.

mOS (mo) from time of first RECIST PD.

	Atezo Arm (n = 425)		Doc Arm (n = 425)	
	n	mOS (95% CI)	n	mOS (95% CI)
Pts with PD per RECIST	332	8.6 (7.0, 9.9)	290	6.4 (5.3, 7.6)
Post PD therapy				
Atezo	168	12.7 (9.3, 14.9)	0	–
Other anti-cancer therapy	94	8.8 (6.0, 12.1)	167	9.6 (7.9, 11.8)
Non-immunotherapy	87	8.7 (6.0, 11.8)	102	7.5 (6.0, 8.2)
Immunotherapy	7	NE (4.7, NE)	65	17.3 (13.9, 19.6)
No anti-cancer therapy	70	2.2 (1.9, 3.4)	123	3.7 (2.7, 4.0)

NE, not estimable.

9002 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Efficacy of the addition of cisplatin to single-agent first-line chemotherapy in elderly patients with advanced non-small cell lung cancer (NSCLC): A joint analysis of the multicenter, randomized phase III MILES-3 and MILES-4 studies. *First Author: Cesare Gridelli, A.O.S.G. Moscati, Avellino, Italy*

Background: The role of platinum in first line treatment of elderly patients with advanced NSCLC is still debated. We tested its efficacy in two parallel phase 3 trials. **Methods:** Advanced NSCLC patients, > 70 years, ECOG performance status 0-1, were eligible. In MILES-3 (started in 2011) patients with any tumor histology were randomly assigned 1:1 to cisplatin/gemcitabine (C 60 mg/m^2 d1, G 1000mg/m^2 dd1,8) or gemcitabine (G 1200 mg/m^2 dd1,8). In MILES-4 (started in 2013 with a factorial design) patients with non-squamous histology were randomly assigned 1:1:1:1 to CG, G, cisplatin/pemetrexed (C 60 mg/m^2 d1, P 500 mg/m^2 d1) or pemetrexed (P 500 mg/m^2 d1). Six cycles were planned. In each trial, to have 80% power in detecting a HR of death 0.75 (corresponding to 3-month prolongation of median survival), with 0.05 two-tailed α, 382 events were required. The two trials were closed prematurely because of slow accrual but a joint analysis allowed to properly perform the final analysis, according to IDMC advice. Analysis was based on intention-to treat and adjusted by possible confounding factors. **Results:** From Mar 2011 to Aug 2016, 531 patients (MILES-3: 299, MILES-4: 232) were assigned to cisplatin-doublet (n = 263) or single-agent chemotherapy (n = 268). Median age was 75, 79% were male, 70% had non-squamous histology. Median number of cycles was 4 and 3 with and without cisplatin, respectively. With a median follow-up of 2 years, 384 deaths and 448 progression-free survival (PFS) events were reported. With and without cisplatin, median OS was 9.6 vs 7.5 months (HR 0.86, 95% CI: 0.70-1.04, p = 0.14); median PFS was 4.6 vs 3.0 months (HR 0.76, 95% CI: 0.63-0.92, p = 0.005); response rate was 15.5% vs 8.5% (p = 0.02). Significantly more severe hematologic toxicity and fatigue were reported with cisplatin. **Conclusions:** Although improving PFS and response rate, addition of cisplatin to single-agent chemotherapy does not significantly prolong overall survival of elderly patients with advanced NSCLC. QOL data will be reported separately. Partially supported by AIFA (grant FARM8KAJZK) and Eli Lilly. Clinical trial information: NCT01405586 and NCT01656551.

9003 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

IFCT-GFPC-1101 trial: A multicenter phase III assessing a maintenance strategy determined by response to induction chemotherapy compared to continuation maintenance with pemetrexed in patients (pts) with advanced non-squamous (NSQ) NSCLC. *First Author: Maurice Perol, Department of Thoracic Oncology, Centre Léon Bérard, Lyon, France*

Background: Benefit coming from maintenance treatment appears greater for switch maintenance in pts with disease stabilization (SD) while it might be larger for continuation maintenance in pts with objective response (OR). This study assessed a maintenance strategy conditioned by response to cisplatin-gemcitabine (CG): continuation maintenance with G for pts with OR and switch maintenance with pemetrexed (P) for pts with SD compared with a control arm using P continuation maintenance following cisplatin-pemetrexed (CP) induction regimen. **Methods:** Eligibility criteria included age 18-70 years, PS of 0-1, untreated stage IV NSQ NSCLC without EGFR mutation or ALK rearrangement, ineligibility to bevacizumab. Pts were randomized 1:1 to receive either experimental CG arm: CG (4 cycles) followed by G maintenance in case of OR followed by second-line P or switch maintenance with P for pts with SD, or standard CP arm: 4 cycles CP induction regimen followed by maintenance P. Overall survival (OS) was the primary endpoint; secondary endpoints included PFS, response rate and safety. **Results:** Between Jul 2012 and Jun 2016, 932 pts were randomized (CG: 467, CP: 465). Pts characteristics were balanced between the arms. 255 pts (54.6%) in the CG arm received maintenance treatment (G: 142, P: 113) while 274 pts (58.9%) received P maintenance in the CP arm. Median number of maintenance cycles was 5 for G and 4 for P in both arms. The OS adjusted HR was 0.97 (95% CI 0.84, 1.13; p=0.72); median OS: 10.9m CG vs. 10.4m CP. The HR for PFS was 0.96 (95% CI 0.84, 1.10; p=0.56); median PFS: 5.0m CG vs. 4.7m CP. Safety profile was as expected during induction chemotherapy. During maintenance, grade ≥3 hematological AEs occurred in 28% and 31% of pts in CG and CP, respectively, with febrile neutropenia (2.4% vs. 1.1%), anemia (9.4% vs. 11.7%), thrombocytopenia (6.7% vs. 5.8%). No grade ≥3 non-hematological AEs occurred in >5% of pts except for asthenia (3.9% CG vs. 5.1% CP). **Conclusions:** Adapting maintenance strategy according to response to induction chemotherapy does not improve patient outcome. Clinical trial information: NCT01631136.

9004 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Efficacy and safety results from AvaALL: An open-label, randomized phase III trial of standard of care (SOC) with or without continuous bevacizumab (Bev) treatment beyond progression (PD) in patients (pts) with advanced non-small cell lung cancer (NSCLC) progressing after first-line Bev and chemotherapy (chemo). *First Author: Jaafar Bennouna, Institut de Cancerologie de l'Ouest, Nantes, France*

Background: The role of treatment with Bev beyond PD is unclear in the multiline treatment strategy of advanced NSCLC.AvaALL(NCT01351415), a multinational, open-label, randomized phase III trial, assessed continuous Bev and SOC beyond first PD (PD1) in pts with NSCLC following first-line treatment with platinum-based chemo plus Bev. Here we present efficacy and safety data from AvaALL. **Methods:** Pts with NSCLC who received 4–6 cycles of chemo + Bev and ≥2 cycles of maintenance Bev were randomized after PD1 to second-line SOC therapy (docetaxel, pemetrexed or erlotinib) ± Bev. After second PD (PD2) and third PD (PD3), pts received third-line or fourth-line SOC ± Bev treatment, respectively. Primary endpoint was overall survival (OS). Secondary endpoints were OS rates (6, 12, and 18-months [mos]), progression-free survival (PFS) from PD1 to PD2/from PD2 to PD3, overall response rate (ORR), disease control rate (DCR), and safety. Data cut-off: 24 Jun 2016. **Results:** Overall, 485 pts were randomized (n = 475 treated). Pt characteristics were well balanced between the two arms. Bev plus chemo resulted in a median OS of 11.9 mos versus 10.2 mos for SOC alone (HR 0.84, 90% CI 0.71–1.00; p = 0.1016; 387 OS events). The primary endpoint was not met (416 OS events were required, at 10% two-sided significance level). OS rates were 10% higher in the Bev arm vs SOC alone at 6-, 12- and 18-mos. Median PFS2 was 4.9 mos with Bev vs 3.8 mos with SOC (HR 0.85, 90% CI 0.72–1.00; p = 0.0907). PFS3 was significantly improved (3.5 mos for Bev, 2.4 mos for SOC; HR 0.65, 90% CI 0.51–0.84; p = 0.0047). ORR and DCR were slightly higher in the Bev arm versus the SOC arm (ORR 9.7% vs 6.7%; DCR 86.2% vs 79.3%, respectively). No new safety signals were identified. Grade ≥3 adverse events were reported in 78.2% of Bev pts and 61.6% of SOC pts. **Conclusions:** Although the primary endpoint was not met, efficacy data suggest a positive trend for continued Bev plus SOC after PD1 compared with SOC alone. No cumulative safety signals were identified. Clinical trial information: NCT01351415.

9005 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

CNS response to osimertinib in patients (pts) with T790M-positive advanced NSCLC: Data from a randomized phase III trial (AURA3). *First Author: Tony Mok, Chinese University of Hong Kong, Hong Kong, China*

Background: CNS metastases (mets) are common in pts with advanced NSCLC. Preclinical studies have shown CNS penetration of osimertinib, and clinical data from a pooled analysis of 2 Phase II trials (AURA extension: NCT01802632, AURA2: NCT02094261) showed activity in the CNS. We report the first evidence of osimertinib efficacy in CNS mets from a randomized Phase III study (AURA3; NCT02151981) in pts with T790M-positive advanced NSCLC who have progressed on or after prior EGFR-TKI therapy. **Methods:** Pts were randomized 2:1 to osimertinib 80 mg once daily or platinum-based doublet chemotherapy every 3 wks for up to 6 cycles; maintenance pemetrexed was allowed. Pts with stable, asymptomatic CNS mets were eligible for enrolment. A prespecified subgroup analysis was conducted in pts with CNS mets present on baseline brain scan, as assessed by blinded independent central neuroradiology review (BICR), to define CNS objective response rate (ORR), duration of response (DoR) and progression-free survival (PFS) by RECIST v1.1. The CNS full analysis set (cFAS) included pts with ≥1 measurable and/or non-measurable CNS mets present on baseline brain scan by BICR; the CNS evaluable for response set (cEFR) included only pts with ≥1 measurable CNS mets. **Results:** As of 15 April 2016, 116/419 (28%) pts were included in the cFAS. In the cEFR (n = 46), CNS ORR was 70% (21/30; 95% CI 51, 85) with osimertinib and 31% (5/16; 95% CI 11, 59) with chemotherapy (OR, 5.13; 95% CI 1.44, 20.64; p = 0.015). In the cFAS, CNS ORR was 40% (30/75; 95% CI 29, 52) with osimertinib and 17% (7/41; 95% CI 7, 32) with chemotherapy (OR, 3.24; 95% CI 1.33, 8.81; p = 0.014). In the cEFR and cFAS, median CNS DoR was 8.9 months (m) (95% CI 4.3, NC and 4.3, NC) for osimertinib and 5.7 m (95% CI NC, NC and 4.4, 5.7; respectively) for chemotherapy. Median CNS PFS in the cFAS was significantly longer with osimertinib than with chemotherapy (11.7 vs 5.6 m; HR 0.32; 95% CI 0.15, 0.69; p = 0.004). **Conclusions:** Consistent with the overall response to osimertinib reported in pts with T790M-positive advanced NSCLC, osimertinib was superior to chemotherapy in the treatment of pts with CNS mets; CNS response rate was higher, responses were more durable and CNS PFS was longer. Clinical trial information: NCT02151981.

9006 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Efficacy and safety of lorlatinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC) with one or more prior ALK tyrosine kinase inhibitor (TKI): A phase I/II study. *First Author: Alice Tsang Shaw, Massachusetts General Hospital, Boston, MA*

Background: Lorlatinib is a selective, potent, brain-penetrant, next generation ALK/ROS1 TKI active against most known resistance mutations. In Ph I of this Ph I/II study, lorlatinib showed robust clinical activity in ALK+ or ROS1+ advanced NSCLC pts, most of whom had CNS metastases (mets) and were heavily pre-treated. In Ph II of this study, efficacy was explored based on prior ALK TKI tx as well as safety across all patients treated at the recommended Ph II dose. **Methods:** In this ongoing Ph II study (NCT01970865), pts with ALK+ or ROS1+ NSCLC, ± asymptomatic untreated or treated CNS mets, were enrolled into 6 expansion cohorts (EXP) based on prior tx (EXP 1-5, ALK+) and rearrangement status (EXP 6, ROS1+). Pts received lorlatinib 100mg QD. Primary objective was ORR and intracranial ORR (IC-ORR) by independent central review (ICR). **Results:** Efficacy (ALK+ pts with prior tx): At data cut-off (15 Aug 2016), 82 ALK+ pts were enrolled in cohorts EXP 2-5, received C1 no later than 31 Mar 2016 and were evaluated for ORR (ITT population); 52 were evaluated for IC-ORR and 35 were evaluated for IC-ORR response based on target lesions only (≥5mm; no prior radiotherapy or progression post prior radiotherapy). Confirmed response rates by ICR are reported in the table below. Safety (all pts): 116 ALK/ROS1+ pts were evaluated for safety at data cut-off. Most common tx-related AEs (TRAEs) and grade 3/4 TRAEs were hypercholesterolemia (90%, 17%) and hypertriglyceridemia (72%, 17%). Dose interruptions and reductions due to TRAEs were reported in 29% and 20% of pts, respectively. 14% of pts had tx-related SAEs. 5 pts (4%) discontinued tx due to TRAEs and there were no tx-related deaths. 74/116 pts (64%) remain on tx. **Conclusions:** Lorlatinib showed compelling clinical activity, with substantial IC activity, in ALK+ pts who received ≥1 prior ALK TKI, many of whom were heavily pre-treated. Clinical trial information: NCT01970865.

	ORR		IC ORR		IC ORR Target lesions only	
ALK+ cohorts	N	n(%)	N	n(%)	N	n(%)
EXP2 (prior Crizotinib only)	7	4(57)	5	3(60)	2	2(100)
EXP3 (prior Crizotinib + CT or any 1 other ALK TKI ± CT)	18	8(44)	9	5(56)	9	6(67)
EXP4 (2 prior ALK TKI ± CT)	44	11(25)	30	13(43)	17	(7(41)
EXP5 (3 prior ALK TKI ± CT)	13	4(31)	30	4(50)	7	4(57)

CT, chemotherapy

LBA9007 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Dacomitinib versus gefitinib for the first-line treatment of advanced EGFR mutation positive non-small cell lung cancer (ARCHER 1050): A randomized, open-label phase III trial. *First Author: Tony Mok, Chinese University of Hong Kong, Hong Kong, China*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 5, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

LBA9008 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Alectinib versus crizotinib in treatment-naive advanced *ALK*-positive non-small cell lung cancer (NSCLC): Primary results of the global phase III ALEX study. *First Author: Alice Tsang Shaw, Massachusetts General Hospital, Boston, MA*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Monday, June 5, 2017, and in the Annual Meeting Proceedings online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. On site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

9009 Poster Discussion Session; Displayed in Poster Session (Board #335), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Evolution and clinical impact of genomic alterations detectable in circulating tumor DNA of 1150 advanced EGFR-mutant (mt) lung cancer patients. *First Author: Collin M. Blakely, Department of Medicine, University of California San Francisco, San Francisco, CA*

Background: Advanced EGFR-mt lung adenocarcinomas (LUAD) frequently harbor additional genetic alterations. The clinical significance of these concurrent alterations and how they evolve with treatment are unclear. **Methods:** We performed next-generation sequencing (NGS) of ~70 cancer related genes from the circulating tumor DNA (ctDNA) of 1150 consecutive advanced LUAD patients (pts) with detectable EGFR mts. The analysis included 113 samples from 81 pts for whom clinical outcome data were known. Clinical response to EGFR TKI treatment was correlated to mutational status in 12 cancer-related pathways. **Results:** EGFR-mt cases contained an average of 3.6 genetic alterations (range 1-18). There was enrichment for co-alterations in TP53, CDK6, CTNNB1 and SMAD4 in EGFR-mt cases compared to a control cohort of 1008 EGFR WT cases. Enrichment for the EGFR T790M mutation was found upon progression to first-line EGFR TKI treatment, as expected. Analysis of 450 T790M-mt cases showed enrichment for co-alterations in genes controlling the cell cycle (28% vs. 21%, p = 0.01), DNA repair (12% vs. 8%, p = 0.03), and WNT (16% vs. 11%, p = 0.03) signaling. The number of genetic alterations increased during progression on each line of therapy in a manner unlinked to age, gender, or tobacco exposure (mean 3.2 pre-TKI vs. 6.4 after 2nd line, p = 0.001). Upon progression to second-line treatment, analysis revealed further selection for co-alterations in TP53, CCNE1, MYC and PIK3CA and the associated pathway-level classifications. We found an increased frequency of co-alteration in cell cycle genes in EGFR TKI non-responders versus responders (33% vs. 0%, p = 0.0005). **Conclusions:** Within the landscape of advanced EGFR-mt LUAD, we uncover features of evolutionary selection for multiple concurrent oncogenic pathway alterations including TP53, WNT, PI3K, MYC, and cell cycle genes. This large clinical and genetic dataset prompts a re-evaluation of the prevailing paradigm of monogenic-based molecular stratification to monotherapy, and highlights an alternative model of genetic collectives as a previously underappreciated determinant of lung cancer progression and therapy resistance.

9010 Poster Discussion Session; Displayed in Poster Session (Board #336), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Association of *ALK* resistance mutations by *EML4-ALK* variant (v3 vs. non-v3) in *ALK*+ non-small cell lung cancer (NSCLC). *First Author: Sai-Hong Ignatius Ou, University of California Irvine Chao Family Comprehensive Cancer Center, Orange, CA*

Background: *ALK* rearrangements are established targetable drivers in NSCLC. Recent reports indicate differential progression-free survival to ALK inhibitors according to specific *EML4-ALK* variant. **Methods:** We analyzed samples from 634 unique NSCLC patients (704 samples) with tumors harboring *ALK* rearrangements (*ALK*+) detected using hybrid-capture based genomic profiling performed on DNA isolated from FFPE tissue specimens (676 samples) or ctDNA isolated from blood (28 samples) during the course of clinical care. **Results:** Of the 634 *ALK*+ cases, we identified 200 (32%) *EML4-ALK*v1 (E13; A20), 50 (8%) *EML4-ALK*v2 (E20; A20), 204 (32%) *EML4-ALK*v3 (E6; A20), 78 (12%) other *EML4-ALK*, and 102 (16%) non-*EML4 ALK* rearrangements. Despite relatively equal frequency of *EML4-ALK* v1 and v3 in this dataset, the presence of a known *ALK* resistance mutation (n = 40 cases) was significantly associated with v3 as compared to v1 ($P < 0.0002$). G1202R mutation in particular was significantly associated with *EML4-ALK* v3 versus v1 ($P < 0.002$), and as compared to all non-v3 (P = 0.02). The tumor mutation burden (TMB) was generally low (median v1: 1.8, v3: 2.5, non-v3: 1.8 mutations/Mb), and although significantly different between v1 and v3 (P = 0.0008) and v3 and non-v3 (P = 0.003), the difference is not expected to be clinically relevant. Available *ALK*+ cases with paired pre- and post-treatment samples tested for a single patient will also be evaluated by *ALK*fusion variant, as well as for novel non-ALK mechanisms of acquired resistance, including a case with MET kinase domain duplication acquired post-ALK targeted therapy. **Conclusions:** The use of tissue and blood-based next generation sequencing allows for detection of the specific *ALK* fusion partner, increases the understanding of the biology of *ALK*+ NSCLC, and may have value to foretell potential mechanisms of resistance and inform the selection of ALK inhibitor therapy.

	Total	*EML4* (v1)	*EML4* (v2)	*EML4* (v3)	*EML4* (non-v1, 2 or 3)	non-*EML4*
C1156Y	2				2	
D1203N	2	1		1		
F1174C/L/V	5			4		1
F1245C/L	3			1		2
G1128A	1					1
G1202R	12			10		2
G1269A	2			1	1	
I1171N/S/T	5			4		1
L1152R	2			1		1
L1196M/Q	8	3		3	2	
T1151K/M	4	1		2		1
V1180L	1				1	
Total unique cases#	40	4	0	24	5	7

#8 cases had ≥2 *ALK*resistance mutations; v: variant.

9011 Poster Discussion Session; Displayed in Poster Session (Board #337), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

KEYNOTE-001: 3-year overall survival for patients with advanced NSCLC treated with pembrolizumab. *First Author: Natasha B. Leighl, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Pembrolizumab (pembro) is approved as first-line (1L) treatment for advanced NSCLC patients (pts) with PD-L1 tumor proportion score (TPS) ≥50% and as treatment for previously treated advanced NSCLC pts with PD-L1 TPS ≥1%. Here we present 3-y OS results for pts enrolled in KEYNOTE-001 (NCT01295827), the first trial evaluating pembro in advanced NSCLC pts. **Methods:** 550 pts received pembro 2 or 10 mg/kg Q3W or 10 mg/kg Q2W until intolerable toxicity, progression, or investigator or pt decision to withdraw. PD-L1 expression was assessed by IHC using the 22C3 antibody. Survival was assessed every 2 mo after treatment discontinuation. **Results:** 550 advanced NSCLC pts enrolled; 101 were first line (1L), and 449 were previously treated. As of the Sept 1, 2016, data cutoff, median follow-up duration was 34.5 mo (range, 25.7-51.5 mo); 8 (7.9%) 1L pts and 28 (6.2%) previously treated pts were still on treatment. 3-y OS was 26.4% (95% CI, 14.3%-40.1%) in 1L pts and 19% (95% CI, 15.0%-23.4%) in previously treated pts. 3-y OS rate and median OS by PD-L1 status are in the Table. Additional description of the pts with long-term survival, including updated safety data as well as 3-y OS by smoking history, histology, *EGFR*status, and prior radiation therapy, will be presented. **Conclusions:** Pembro provides promising long-term OS benefit for 1L and previously treated advanced NSCLC pts expressing PD-L1. The current data represent the longest efficacy and safety follow-up for pts with advanced NSCLC treated with pembro. Clinical trial information: NCT01295827.

Population	n	Median OS (95% CI), mo	24-mo OS rate, % (95% CI)	36-mo OS rate, % (95% CI)
Treatment naive	101*	22.3 (17.1-31.5)	49.0 (38.9-58.3)	26.4 (14.3-40.1)
TPS ≥1%	79	22.2 (16.7-31.5)	47.4 (36.1-58.0)	16.4 (4.0-36.3)
TPS ≥50%	27	34.9 (20.3-NR)	66.7 (45.7-81.1)	25.2 (5.0-53.1)
TPS 1%-49%	52	19.5 (10.7-26.3)	37.3 (24.3-50.2)	Not yet available
Previously treated	449*	10.5 (8.6-13.2)	29.9 (25.6-34.2)	19.0 (15.0-23.4)
TPS ≥1%	306	11.1 (8.3-14.0)	31.8 (26.6-37.1)	21.1 (16.1-26.6)
TPS ≥50%	138	15.4 (10.5-18.5)	38.6 (30.4-46.7)	29.7 (21.9-37.9)
TPS 1%-49%	90	8.5 (6.0-12.7)	26.2 (19.8-33.1)	13.5 (7.8-20.9)
TPS <1%	90	8.6 (5.5-10.6)	23.8 (15.4-33.2)	8.5 (2.9-18.1)

*Includes unknown PD-L1 status and TPS <1% pts.

9012 Poster Discussion Session; Displayed in Poster Session (Board #338), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Safety of retreatment with immunotherapy after immune-related toxicity in patients with lung cancers treated with anti-PD(L)-1 therapy. *First Author: Fernando Costa Santini, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Anti-PD(L)-1 therapy is generally well tolerated, but immune-related adverse events (irAEs) can occur. No data currently exists to guide decisions related to considering re-treatment following an irAE. **Methods:** Patients (pts) with lung cancer treated with anti-PD(L)-1 (+/- anti-CTLA-4) between 4/2011 to 5/2016 who had a treatment delay of at least one week were identified. Those in whom delay was a result of a definite irAE were included, and subsequent treatment details and outcomes were captured. Pts with an irAE concurrent with disease progression were excluded. **Results:** Among 482 pts treated, 71 (14.7%) had treatment delay related to an irAE. Most events were Grade 2 (38/71, 54%) or Grade 3 (30/71, 42%), and predominantly included pneumonitis (21%), colitis (17%), rash (14%), or hepatitis (13%). 32 pts (45%) were permanently discontinued after the irAE and 39 (55%) were later retreated with anti-PD(L)-1 therapy. In retreated pts, the same irAE recurred in 10/39 (26%), a new irAE occurred in 9/39 (23%), and 20/39 (51%) had no subsequent irAE. The rate of recurrent/new irAEs was similar in those with Grade 3 compared to Grade 2 irAEs (p = 1.0), but were more common following initial irAE that occurred early ($<$ 3 months) compared to later ($\geq$3 months) in treatment course (16/24 [67%] vs 3/15 [20%], p = 0.0079). The rate of recurrent/new irAE was 33% (2/6) in those with pneumonitis, 40% (2/5) with rash, 57% (4/7) with colitis, and 80% (4/5) with arthralgia. Recurrent/new irAEs were successfully managed with immunosuppression in 17/19 (90%) pts. However, 2 pts died, both related to a new irAE different from the one initially experienced. Of the pts retreated, 3 (8%) had onset of objective response to anti-PD(L)-1 therapy following resumption of treatment. **Conclusions:** In pts who develop irAEs and improve, re-treatment with anti-PD(L)-1 therapy was associated with recurrent or new irAEs in half of pts, and was more common in early-onset irAEs. The majority of the pts with recurrent/new irAEs were managed successfully, but two deaths occured. Few objective responses occurred following retreatment.

9013 Poster Discussion Session; Displayed in Poster Session (Board #339), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A phamacoeconomic analysis of personalized dosing versus fixed dosing of pembrolizumab in first-line PD-L1 positive non-small cell lung cancer. *First Author: Daniel A. Goldstein, Davidoff Cancer Center, Petah Tikva, Israel*

Background: In October 2016 pembrolizumab became the new standard of care for first-line treatment of patients with metastatic non-small cell lung cancer (mNSCLC) whose tumors express programmed death ligand 1 in at least 50% of cells. The FDA recommended dose is 200mg every three weeks. Multiple studies have demonstrated equivalent efficacy with weight-based doses between 2mg/kg to 10 mg/kg. The objective of this study was to compare the economic impact of using personalized dosing (2mg/kg) versus fixed dosing (200mg) in the first line setting of mNSCLC. **Methods:** We performed a budget impact analysis from the US societal perspective to compare fixed dosing with personalized dosing. We calculated the target population and weight of patients that would be treated with pembrolizumab annually in the first-line setting. Using survival curves from the KEYNOTE 024 trial with Weibull extrapolation we estimated the mean number of cycles that patients would receive. Using the Medicare average sales price we calculated the difference in cost between personalized and fixed dosing. **Results:** Our base case model demonstrates that the total annual cost of pembrolizumab with fixed dosing is US$ 3,440,127,429, and with personalized dosing it is US$ 2,614,496,846. The use of personalized dosing would lead to a 24% annual saving of US$ 825,630,583 in the United States. **Conclusions:** Personalized dosing of pembrolizumab may have the potential to save approximately 0.825 billion dollars annually in the United States, likely without impacting outcomes. This option should be considered for the first-line management of PD-L1 positive advanced lung cancer.

9014 Poster Discussion Session; Displayed in Poster Session (Board #340), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Efficacy and safety of epacadostat plus pembrolizumab treatment of NSCLC: Preliminary phase I/II results of ECHO-202/KEYNOTE-037. *First Author: Tara C. Gangadhar, Abramson Cancer Center, Philadelphia, PA*

Background: ECHO-202/KEYNOTE-037 is an open-label, phase 1/2 study of epacadostat (a potent and selective oral inhibitor of the immunosuppressive enzyme indoleamine 2,3-dioxygenase 1) plus pembrolizumab (E + P) in patients (pts) with advanced tumors. We report preliminary efficacy and safety outcomes for the phase 1/2 NSCLC cohort. **Methods:** Adult pts with prior platinum-based therapy (tx) and no prior checkpoint inhibitor tx were eligible. Phase 1 dose-escalation tx was E (25, 50, 100, 300 mg PO BID) + P (2 mg/kg or 200 mg IV Q3W); MTD was not exceeded. E (100 mg BID) + P (200 mg Q3W) tx doses were selected for phase 2 cohort expansion. Efficacy was evaluated by tumor proportion score (TPS [% viable tumor cells, PD-L1 staining]: $<$ 50% and $\geq$50%) and by prior lines of tx in RECIST 1.1 evaluable pts. Safety was assessed in pts receiving $\geq$1 E + P dose. **Results:** As of 29OCT2016,43 pts (phase 1, n = 12; phase 2, n = 31) were evaluated. Median age was 65 years, 58% of pts were women, 12% were *EGFR*-positive, and 23% were *KRAS*-positive. Most pts had a history of smoking (84%), $\leq$2 prior lines of tx (84%), and no prior TKI tx (93%). For the 40 efficacy-evaluable pts, ORR (CR+PR) and DCR (CR+PR+SD) were 35% (14/40; 14 PR) and 60% (24/40; 10 SD), respectively. PD-L1 TPS test results were available in 28/40 efficacy-evaluable pts. ORR and DCR for pts with TPS $\geq$50% and $\leq$2 prior tx were 43% (3/7; all PR) and 57% (4/7; 1 SD), respectively; for pts with TPS $<$ 50% and $\leq$2 prior tx, ORR and DCR were 35% (6/17; all PR) and 53% (9/17; 3 SD). Among the 40 efficacy-evaluable pts, 12/14 responses were ongoing (range, 1+ to 519 days) at data cutoff. PFS and biomarker analyses are ongoing. Across all 43 pts, most frequent TRAEs were fatigue (19%), arthralgia (9%), and increased AST (9%); 16% of pts had grade $\geq$3 TRAEs, and increased lipase (asymptomatic) was the only grade $\geq$3 TRAE that occurred in $>$ 1 pt (n = 2). Two pts discontinued due to TRAEs (grade 3 increased AST, grade 2 increased ALT [n = 1]; grade 2 brain edema [n = 1]). **Conclusions:** E + P was generally well tolerated and associated with promising responses in pts with NSCLC. A phase 3 NSCLC study is planned. Clinical trial information: NCT02178722.

9015 Poster Discussion Session; Displayed in Poster Session (Board #341), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Molecular determinants of response and resistance to anti-PD-(L)1 blockade in patients with NSCLC profiled with targeted next-generation sequencing (NGS). *First Author: Matthew David Hellmann, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Anti-PD-(L)1 therapy has revolutionized treatment for patients (pts) with NSCLC. We previously reported that non-synonymous tumor mutation burden (TMB) by whole exome sequencing associates with immunotherapy benefit. Targeted NGS is increasingly routine in clinical practice and may be a useful tool for predicting benefit to anti-PD-(L)1 blockade. **Methods:** Pts had advanced NSCLC treated with anti-PD-(L)1 (+/- aCTLA-4) therapy and profiling by hybrid-capture NGS of 341-468 genes (MSK-IMPACT). Efficacy assessed by RECIST v1.1; durable clinical benefit (DCB) defined as PR or SD $>$ 6mo. TMB and copy number alteration burden ("fraction of genome altered", FGA) were normalized by size of genome covered. Comparisons were also made to a cohort of all NSCLCs profiled by MSK-IMPACT (n = 1679). **Results:** Of 437 evaluable pts treated with anti-PD-(L)1, 197 (45%) had NGS profiling, of whom 30% had DCB. TMB was higher in those with DCB vs no DCB (mean 10.2 vs 7.1 SNV/MB, p = 0.02) and compared to all NSCLCs ($<$ 0.0001). DCB was more common and PFS was longer in pts with $>$ vs $<$ 85th percentile TMB of all NSCLCs (Odds ratio 2.3, 95% CI 1.1-4.9, p = 0.03; HR = 0.59, p = 0.004), but were similar when dichotomized at the 50th or 75th percentile. FGA was higher in pts with no DCB compared to all NSCLCs (p = 0.02). Molecular signatures related to deficient homologous-recombination-based DNA repair and smoking were more common in DCB vs no DCB (p = 0.042, p = 0.058) and vs all NSCLCs (p = 0.026, p = 0.01). Compared to all NSCLCs profiled by NGS, alterations in *STK11*and *EGFR*were enriched in no DCB (p = 0.0008, p = 0.02). Alterations in *JAK2*and *CD274*(PD-L1) were uncommon (2.1%, 1.6%) but exclusively associated with no DCB. For a subset (n = 52) of these cases also profiled by whole exome sequencing, comparison with targeted NGS will be presented. **Conclusions:** In pts with NSCLC, targeted NGS profiling is a routinely available tool that can provide insight into predicting benefit with anti-PD-(L)1 therapy. Increased TMB associates with clinical benefit. Increased copy number alterations (FGA) and alterations in genes including *STK11*, *JAK2*, and *CD274* may associate with resistance to anti-PD-(L)1 therapy.

9016 Poster Discussion Session; Displayed in Poster Session (Board #342), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

STK11/LKB1 co-mutations to predict for de novo resistance to PD-1/PD-L1 axis blockade in KRAS-mutant lung adenocarcinoma. *First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Identification of molecular predictors of response to PD-1/PD-L1 inhibitors is critical in order to maximize their therapeutic potential. We previously reported that *KRAS*-mutant lung adenocarcinomas (LUAC) with co-occurring genetic events in *STK11/LKB1*(KL) or *TP53* (KP) define subgroups with marked differences in immune contexture, including a paucity of CD8+ TILs in KL LUAC. Here, we assess clinical responses to PD-1/PD-L1 therapy in KL and KP subsets, with data assembled under the auspices of the SU2C/ACS Lung Cancer Dream Team. **Methods:** Patients (pts) with metastatic *KRAS*-mutant LUAC who received at least one cycle of PD-1/PD-L1 therapy, were alive for ≥14 days thereafter, and had available molecular profiling were identified retrospectively. Efficacy assessment was based on RECIST v1.1. PD-L1 expression was tested using 22C3 pharmDx or E1L3N IHC assays and quantified as percent of staining tumor cell membranes. Isogenic derivatives of the LKR10 *Kras*$^{LA1/+}$ murine LUAC cell line with CRISPR/Cas9-mediated *Lkb1*knockout were used in preclinical experiments. **Results:** 165 pts with *KRAS*-mutant LUAC who received PD-1/PD-L1 therapy were included [KL: 27%, KP: 36%, K-only: 37%]. Best overall response differed significantly in the KL (PR: 9.1%, SD: 15.9%, PD: 75%) and KP (PR: 33.3%, SD: 20%, PD: 46.7%) sub-groups (P = 0.005, Fisher's exact test). PFS was significantly longer in KP compared to KL LUAC (median 12.9 wks vs 8.4 wks, HR = 0.64, 95% CI 0.39-0.95, P = 0.032, log-rank test). ORR in K-only tumors was 21.3% and median PFS 11.4 wks. PD-L1 positivity (≥1%) was more frequent in KP tumors compared to KL (75% vs 22%, P = 0.03, Fisher's exact test). In syngeneic murine models of *KRAS*-mutant LUAC, loss of LKB1 promoted resistance to PD-1 inhibitor monotherapy, suggesting a causative role. **Conclusions:** Mutational inactivation of *STK11/LKB1* represents a novel genomic predictor of *de novo* resistance to immune checkpoint blockade in *KRAS*-mutant LUAC, whereas *TP53* co-mutations are associated with high likelihood of response. Precision immunotherapy will require tailoring to the co-mutation status of individual tumors.

9017 Poster Discussion Session; Displayed in Poster Session (Board #343), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Osimertinib compared to docetaxel-bevacizumab as third-line treatment in EGFR T790M mutated non-small cell lung cancer. *First Author: Keke Nie, Qingdao Central Hospital, Qingdao University, Qingdao, China*

Background: Osimertinib, an oral irreversible EGFR tyrosine kinase inhibitor, had promising results in patients with EGFR T790M resistance mutation of non-small-cell lung cancer (NSCLC). This study compared efficacy and toxicities of osimertinib versus docetaxel -bevacizumab as third-line treatment in EGFR T790M mutated NSCLC. **Methods:** In this phase 3, open-label, three-center study, we randomly assigned previously treated with TKI-chemotherapy or chemotherapy-TKI recurrent or metastatic advanced non-squamous lung cancer patients who had acquired EGFR T790M resistance mutation confirmed by tumor tissues or serum genetic test. Patients were randomly assigned in a ratio of 1:1 to receive oral osimertinib (80mg/day) or receive intravenous infusion docetaxel (75mg/m2) and bevacizumab (7.5mg/kg) until disease progression or unacceptable toxic effects. Docetaxel -bevacizumab group patients might crossover to osimertinib group after disease progression. The primary end-point of this study was progression-free survival and the secondary end-point were response rates, toxicities and OS. **Results:** A total of 147 patients were treated. Among them, 74 enrolled in the osimertinib group and 73 in the docetaxel-bevacizumab group. The median progression-free survival was 10.20 months and 2.95 months in the osimertinib group and docetaxel -bevacizumab group respectively (Hazard ratio 0.23; 95% confidence interval, 0.12 to 0.38; P < 0.0001). The overall response rate and disease control rate was 61.6% or 87.6% in osimertinib group 8.3% or 43.0% in docetaxel-bevacizumab group respectively. The median overall survival time was not reached. The main grade 3 or 4 toxic effects were diarrhea (2.7%) and interstitial lung disease (1.2%) in the osimertinib group and alopecia (15.1%), anorexia (12.3%), neutropenia (9.6%) and nausea (8.6%) in docetaxel -bevacizumab group. **Conclusions:** Response rate and progression-free survival of osimertinib group were superior to docetaxel-bevacizumab group in third-line treatment of EGFR T790M positive NSCLC. There was no survival difference between patients with EGFR 19 Del-T790M mutation and EGFR L858R-T790M mutation. Clinical trial information: NCT02959749.

9018 Poster Discussion Session; Displayed in Poster Session (Board #344), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Complete clearance of plasma EGFR mutations as a predictor of outcome on osimertinib in the AURA trial. *First Author: Kenneth Stephen Thress, AstraZeneca, Waltham, MA*

Background: Osimertinib, an EGFR T790M-selective tyrosine kinase inhibitor (TKI), provides high and durable response rates in patients (pts) with T790M positive advanced NSCLC whose disease has progressed following EGFR-TKI therapy. We investigated whether changes in the levels of plasma *EGFR*mutations post-osimertinib treatment are associated with clinical outcome. **Methods:** We studied pts from the AURA Phase I study (NCT01802632) with acquired resistance to EGFR-TKIs, T790M positive baseline genotyping (in tumor or plasma), and plasma samples collected at baseline and 6 weeks (wks) post- osimertinib (20–240 mg daily) treatment. Plasma samples were analyzed for the presence of detectable *EGFR* mutations (Ex19del, L858R and T790M) using BEAMing digital PCR (Sysmex/Inostics). In pts with detectable plasma *EGFR* mutations at baseline, clinical outcomes (by investigator, per RECIST 1.1) were compared for pts with or without detectable plasma *EGFR*mutations at 6 wks. **Results:** Evaluable baseline and 6 wk plasma samples were collected from 160 pts with T790M positive genotyping, of whom 143 had detectable *EGFR* mutations at baseline (median allelic fraction for Ex19del: 7.09%; L858R: 3.81%; T790M: 2.12%). In this cohort, the overall median progression-free survival (mPFS) was 9.3 months (m; 95% CI 8.2, 9.7). Clearance of plasma *EGFR*mutations at 6 wks was seen in 92/143 (64%) pts. mPFS was longer in pts with plasma clearance (10.9 m; 95% CI 9.5, 15.2) compared with pts without (5.5 m; 95% CI 3.9, 6.7), as was objective response rate (ORR; 70%; 95% CI 59%, 79% vs. 35%; 95% CI 22%, 50%). **Conclusions:** Clearance of plasma *EGFR* mutations after 6 wks of osimertinib therapy appears to be associated with improved ORR and mPFS in pts with T790M positive NSCLC. Evidence or lack of such a "plasma response" measured at 6 wks could, potentially, be used to predict subsequent outcomes on therapy. Further research is needed to better understand whether continued detection of plasma *EGFR* mutations at 6 wks may indicate the presence of heterogeneous resistance mechanisms, which could, potentially, be targeted by combination therapies. Validation of these results in an independent cohort of pts is ongoing. Clinical trial information: NCT02228369.

9019 Poster Discussion Session; Displayed in Poster Session (Board #345), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A randomized, controlled, open label phase II study of erlotinib (E) with or without the MET antibody emibetuzumab (Emi) as first-line treatment for *EGFR*mt non-small cell lung cancer (NSCLC) patients who have disease control after an 8-week lead-in treatment with erlotinib. *First Author: Giorgio V. Scagliotti, Department of Oncology - University of Torino, Turin, Italy*

Background: MET expression is a mechanism of resistance to EGFR inhibition in *EGFR*mt NSCLC and correlated with poor prognosis. Emi (LY2875358) is a humanized IgG4 monoclonal bivalent MET antibody that blocks ligand dependent and independent HGF/MET signaling. This Phase 2 study compared the clinical activity of Emi + E versus single agent E in 1st line *EGFR*mt metastatic NSCLC. **Methods:** Stage IV, *EGFR*mt NSCLC pts with disease control following an 8-week lead-in E (150 mg PO QD) treatment were randomized 1:1 to receive Emi (750 mg IV Q2W) + E or E alone. Pts were stratified by ECOG PS, ethnicity, MET expression status, and response at the end of the lead-in. The primary endpoint was PFS from randomization. Additional endpoints included safety, OS, PK, and exploratory analysis of MET-expressing populations. **Results:** Out of181 pts enrolled, 141 pts were randomized (Emi+E: 71; E: 70). In the ITT population, median PFS for EMI+E was 9.3 months (m) compared with 9.5 m for E (HR = 0.89: 90% CI 0.64-1.23; p = 0.534). Exploratory analysis of MET-high expressing pts (MET 3+ expression in ≥90% of tumor cells; n = 24 pts) showed a 15.3 m improvement in PFS (EMI+E: 20.7 m; E: 5.4 m [HR: 0.39; 90% CI: 0.17-0.91]). No difference in PFS was observed in the complementary population (HR: 1.1 [90% CI: 0.7-1.7]). Similar frequencies of related AEs were reported for both treatment arms. Drug-related TEAEs that were more frequent (> 10%) for Emi+E were peripheral edema and fatigue (all grade 1 or 2). Emi serum concentrations were consistent with previously obtained PK results, and no apparent exposure-response was observed. Median OS in the ITT population was not achieved (NA) for either arm. In MET-high expressing pts, median OS was 20.6 m for E (90% CI: 8.87, NA) whereas it was not achieved for Emi+E (90% CI: NA, NA). **Conclusions:** No statistically significant difference in PFS was noted in the ITT population.Exploratory analysis confirmed that high MET expression is a negative prognostic marker for pts treated with E and indicated that these pts may receive clinically meaningful benefit from Emi+E. Clinical trial information: NCT01897480.

9020 Poster Discussion Session; Displayed in Poster Session (Board #346), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

MET amplification (amp) as a resistance mechanism to osimertinib. *First Author: Zofia Piotrowska, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Osimertinib (osi) is an EGFR T790M inhibitor. Mechanisms (mech) of acquired resistance (AR) are under study. We report a cohort of osi-AR pts with extensive pre/post-osi tissue and plasma. **Methods:** We analyzed 23 pts with AR to osi. Tumor biopsies (bx) underwent NGS (SNaPshot, MGH) and FISH for EGFR, MET amp (target: CEP7 > 2.2.) Plasma underwent ctDNA NGS (Guardant360). **Results:** Of the 23 osi-treated EGFR-mutants (13 with EGFR del19, 10 L858R), 2 had *de novo* T790M, 21 acquired T790M. 13 had prior 3rd gen EGFR TKIs before osi - rociletinib(11), ASP8273 (1), EGF816(1). Median time on osi was 12 mo (range 2-25), med total time on 3rd-gen EGFR TKIs was 18 mo. Bx types were tissue (16), plasma (18), and both (11, med interval 31d). All pts retained their founder EGFR mutation, but 15/23 (65%) "lost" T790M post-osi, suggesting AR arose from a T790wt subclone (Table). Common AR mech were MET amp (7/23; 30%) and EGFR C797S (5/23; 22%). 1 pt each had SCLC transformation, PIK3CA E545K/PIK3CA amp and FGFR1 D60N/FGFR1 amp. 2 pts had 2 distinct post-osi tissue bx showing heterogeneity. Pt 8 had plasma and a lung nodule with C797S/T790M while a mediastinal LN was wt at both loci. Pt 22 had MET-amp in pleural fluid but no MET amp on lung bx. Plasma identified AR mech not seen in tissue in 2/11 pts with both bx types. Among 7 pts with MET amp, 3 received combo EGFR/ MET TKI; all 3 had a RECIST PR. **Conclusions:** In this osi-resistant cohort, we commonly saw MET amp (30%) and C797S (22%). MET amp seems more common post-osi than after 1st-line TKIs, and 3/3 pts responded to EGFR+MET TKIs. AR heterogeneity was seen in 2 pts with matched tissue/plasma and 2 with >1 tissue bx, underscoring the complementary roles of plasma and tissue.

Pt	Tissue Result (T790M Status)	Plasma Result (T790M)
1	METa (-)	METa (-)
2	X	U (-)
3	X	U (-)
4	METa/EGFRa (g)	X
5	EGFRa (-)	U (-)
6	U (-)	U (-)
7	X	U (+)
8	C797S (+)*	C797S (+)
9	U (+)	X
10	X	PIK3CA E545K/a (-)
11	METa/EGFRa (-)	U (-)
12	X	C797S (+)
13	U (-)	X
14	U (-)	U (-)
15	U (-)	FGFR1 D60N/a (-)
16	METa (-)	METa/EGFRa (-)
17	U (-)	U (-)
18	SCLC (-)	EGFRa (-)
19	U (-)	C797S/METa/EGFRa (+)
20	METa/EGFRa (-)	X
21	X	C797S/EGFRa (+)
22	METa (-)*	X
23	X	C797S (+)

*Different AR mech in concurrent bx; U- unknown, no mech identified; X- testing not done; T790M: (+) positive; (-) not detected; (g) germline; a- amplified

9021 Poster Session (Board #347), Sat, 8:00 AM-11:30 AM

Characteristics and outcomes of patients (pts) with metastatic KRAS mutant lung adenocarcinomas: Lung Cancer Mutation Consortium (LCMC) database. *First Author: Badi Edmond El Osta, Atlanta VA Medical Center; Winship Cancer Institute of Emory Unviersity, Atlanta, GA*

Background: To better understand outcome heterogeneity in pts with KRAS mutant lung cancers, we analyzed the largest multi-institutional database of pts with metastatic KRAS mutant lung adenocarcinomas. **Methods:** We reviewed data of all pts who consented to LCMC between 2009-2015. Pts with known KRAS status were included in analyses. Mutation data along with co-mutations were obtained along with clinical outcomes. We evaluated baseline characteristics and association of KRAS data with overall survival (OS), calculated from date of distant metastasis to death, in a univariate and multivariable analyses. The median follow-up was 2.15 years (95% CI: 2.01-2.27). **Results:** 1655 (86%) of 1918 pts' data were analyzed. Comparative characteristics are summarized in the Table. Among 450 (23%) pts with KRAS mutations: 58% female, 93% ever smokers, and median age 65 years. Main KRAS subtypes: G12C 39%, G12D and G12V were 18% each. Never smokers with KRAS mutation were more likely to have G12D subtypes (18%; $p < 0.001$). Pts with KRAS mutation, the median OS was 1.96 years, with 2-year OS rate of 49%. Co-mutations (1-16) were checked in all KRAS mutant pts. Co-mutations were rare (14 pts; 3%). KRAS co-mutations were associated with improved OS in multivariable analyses (HR 0.35; 95% CI: 0.13-0.97; $p = 0.04$), but not KRAS main subtypes / codons. Co-mutation STK-11 in particular (17 of 92 pts; 18%) was associated with poor OS in univariate (HR 2.16; 95% CI: 1.03-4.54; $p = 0.04$) and multivariable analyses (HR 2.31; 95% CI: 1.18-5.50; $p = 0.02$). Pts with KRAS mutations had a trend towards a shorter survival (median OS 1.96 vs. 2.22 years; $p = 0.08$) and a decreased 2-year OS when compared to KRAS wildtype [49% (95% CI: 44-54%) vs. 55% (95% CI: 52-58%)], respectively. **Conclusions:** KRAS mutation is a significant predictor of worse survival outcomes in pts with metastatic lung adenocarcinomas. The presence of STK-11 co-mutation was associated with especially poor OS.

Characteristics	KRAS mutant N=450	KRAS wild type N=1205	P-value
Age, median	65 years	62 years	< 0.001
White	89%	81%	< 0.001
Ever smoker	93%	64%	< 0.001
Co-mutations	3%	41%	< 0.001

9022 Poster Session (Board #348), Sat, 8:00 AM-11:30 AM

NGS to reveal heterogeneity between cerebrospinal fluid and plasma ctDNA among non-small cell lung cancer patients with leptomeningeal carcinomatosis. *First Author: Ben-Yuan Jiang, Division of Pulmonary Oncology, Cancer Center, Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: In current clinical setting, NSCLC patients harboring specific driver mutation were usually treated guiding by prior profiling of the primary tumor when developed to brain metastasis. Some studies have shown that circulating tumor DNA (ctDNA) derived from cerebrospinal fluid (CSF) can reveal unique genomic alterations present in brain malignancies. We assessed CSF as a liquid biopsy media and compared to matched plasma. **Methods:** We performed capture-based ultra deep sequencing on ctDNA derived from matched CSF, plasma of 40 non-small cell lung cancer (NSCLC) patients with suspected leptomeningeal carcinomatosis (LC) using a panel consisting of 168 genes. **Results:** Among the 40 suspected LC cases, 35 were confirmed to have LC, ctDNA in CSF from the 5 non-LC cases are all undetectable. Circulating tumor DNA was detected in 93.8% of CSF and 66.7% of plasma. We compared mutation profiles and identified 86 and 46 SNVs from CSF and plasma, respectively, with 42 SNVs overlapping. Furthermore, ctDNA from CSF revealed many copy number variations (CNVs) that were not detected from plasma (189 CNVs vs. 3 CNVs). The average maximum allelic fraction (AF) of CSF ctDNA is significantly higher than in plasma (56.7% vs. 4.4% $p < 10\text{^-}6$). Twenty-eight patients were pre-treated with EGFR-TKIs and developed subsequent resistance. *EGFR* T790M and MET amplification were detected in 21% and 39% in CSF, respectively, showing a unique resistance profile among leptomeningeal metastases patients compared to the general population. Interestingly, 60% of CSF samples harbor TP53 loss of heterozygosity, only 11% of which were detected in the matched plasma samples. Such heterogeneity may reflect unique biological themes for brain metastatic tumor sub-clones. Furthermore, 26 patients received molecular targeted therapy based on the results from CSF, and 23 reported alleviation of symptoms at subsequent evaluations. **Conclusions:** Collectively, our data reveal that ctDNA derived from CSF provides a unique and more comprehensive characterization of genomic alterations of leptomeningeal carcinomatosis than plasma, supporting the importance of CSF as a liquid biopsy media.

9023 Poster Session (Board #349), Sat, 8:00 AM-11:30 AM

Rapid/warm autopsy to reveal APOBEC-mutagenesis as driver of heterogeneity of metastatic thoracic tumors. *First Author: Nitin Roper, National Cancer Institute, Bethesda, MD*

Background: Intratumor heterogeneity has been characterized among multiple cancer types. In lung adenocarcinoma, APOBEC-mutagenesis has been shown to be a source of heterogeneity. However, these data are largely limited to early stage primary tumors. There is limited information about the role of APOBEC-mutagenesis and somatic variants, copy number changes, transcript and protein expression in influencing tumor heterogeneity in metastatic lung adenocarcinoma and other thoracic tumors. **Methods:** We applied whole exome sequencing, RNA-seq, OncoScan CNV and mass spectrometry-based proteomic analyses on 46 tumor regions from metastatic sites including lung, liver and kidney, obtained by rapid/warm autopsy from 4 patients (pts) with stage IV lung adenocarcinoma, 1 pt each with pleural mesothelioma and thymic carcinoma. The autopsy procedure was initiated between 2-4 hours of death. **Results:** All tumors displayed organ-specific, branched evolution that was consistent across exome, transcriptome and proteomic analyses. The degree of heterogeneity at the genomic and proteomic level was patient-specific. There was extensive heterogeneity within the tumors of one of four patients with lung adenocarcinoma and in the thymic carcinoma patient (both non-smokers) with multiple driver mutations and copy number changes occurring in only some of the tumors suggesting ongoing late tumor evolution. Further examination of the heterogenous thymic and lung adenocarcinoma tumors showed strong enrichment with the APOBEC-mutagenesis pattern and high associated levels of APOBEC3B mRNA. **Conclusions:** Metastatic lung adenocarcinoma, thymic carcinoma and mesothelioma evolve through a branched, organ-specific process with marked differences in the acquisition of significant driver mutations and copy number changes. APOBEC3B is a potential driver of heterogeneity in pts with advanced, heterogeneous metastatic lung adenocarcinoma and thymic carcinoma and needs to be evaluated further.

9024 Poster Session (Board #350), Sat, 8:00 AM-11:30 AM

Evaluation of stored liquid biopsies for molecular profiling in patients with non-small cell lung cancer (NSCLC). *First Author: Penelope Ann Bradbury, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Molecular profiling is often limited by access to sufficient tumour tissue for comprehensive analysis and due to tumour heterogeneity, the complete range of tumor DNA abnormalities may not be represented nor accurately reflect the clinical evolution of disease. Circulating tumour DNA (ctDNA) can be used as a liquid biopsy for molecular abnormalities detection, quantification and monitoring for personalised treatment strategies. **Methods:** Plasma was collected at baseline (BL) and during study therapy from advanced NSCLC patients (pts) enrolled in a placebo controlled phase III trial of a novel irreversible EGFR inhibitor; all patients had received standard therapy with chemotherapy and gefitinib or erlotinib. Archival tissue was collected when available but biopsy was not required prior to enrolment. BL Plasma ($<$ 3ml), stored for ~8 years was used to extract DNA and analysed using InVision (enhanced tagged-amplicon sequencing). **Results:** BL plasma from 387 pts was tested; 289 pts had available tissue results (from archival tissue collected at diagnosis) for *EGFR* (174WT/115Mut) and 243 for *KRAS* (205WT/38Mut). Despite age of plasma samples, ctDNA analysis detected cancer mutations in 310 pts (82%): *TP53 (45%), KRAS (15%)*, and *EGFR* (43%; 56% were *EGFR* del19 and 29% L858R); T790M was detected in 80 patients. *EGFR* mutations were identified in 29 patients and *KRAS* in 10 patients with unknown tissue status. Also of note, STK11 (32 pts, 12 with *KRAS*), *BRAF* (5pts, 3 with V600E), *MET*(7 pts, 4 with MET_{amp}), *ERBB2* (16pts, 10 with $ERBB2_{amp}$) were identified in ctDNA analysis. Median time and median number of lines of systemic therapy between tissue biopsy and blood was 714 days and 3 lines respectively. Further analyses of ctDNA analyses in context of patient and trial outcomes are in progress. **Conclusions:** Liquid biopsies provide opportunity to evaluate molecular mutation profile in NSCLC patients. We demonstrate a highly sensitive method for ctDNA analysis which is complementary to tissue molecular analysis.

9025 Poster Session (Board #351), Sat, 8:00 AM-11:30 AM

Genomic profiling of circulating tumor DNA (ctDNA) from patients (pts) with advanced non-small cell lung cancer (NSCLC). *First Author: Ibiayi Dagogo-Jack, Dana-Farber Cancer Institute, Boston, MA*

Background: Tissue biopsy is the gold standard for detection of genomic alterations (GA) and selection of matched targeted therapies in NSCLC, but ctDNA assay provides a possible complementary approach for some pts. **Methods:** Hybrid-capture based genomic profiling of 62 genes using a ctDNA assay (FoundationACT™) was performed on blood samples from 1,019 consecutive NSCLC pts. The fraction of ctDNA in the blood was estimated using the maximum somatic allele frequency (MSAF) for each sample. **Results:** Pt characteristics: Median age 69 years (range 8-94); 54% were female. Histologies included adenocarcinoma (n = 720), NSCLC not otherwise specified (NSCLC NOS; n = 179), squamous cell (n = 57), LC NOS (n = 51), large cell (n = 6), and sarcomatoid (n = 6). $\geq$1 reportable GA was detected in 71% of all cases and in 83% of cases with evidence of ctDNA in the blood (MSAF $>$ 0). For 22 pts with paired blood and tissue samples collected within 30 days and MSAF $>$ 0, 33/64 (52%) GA detected in tissue were also detected in ctDNA. In 55 pts for whom tissue was insufficient for analysis, $\geq$1 GA was detected in ctDNA in 43 (78%) cases. For 856 cases with MSAF $>$ 0, an average of 1.8 GA/sample were reported. GA were most frequently detected in *TP53* (57%), *EGFR* (23%) and *KRAS* (17%). Comparative analysis with the tissue-based FoundationCORE™ database (n = 19,264) showed similar frequencies of GA per gene, although *KRAS* mutation was more frequent in tissue than ctDNA (27% vs 17%, P $<$ 0.0001), and EGFR T790M was more frequent in ctDNA than tissue (7% vs 2%, P $<$ 0.0001), likely reflecting use of liquid versus tissue biopsy after relapse on targeted therapy.Kinase fusions (*ALK*, *ROS1*, *RET*, *FGFR3*, *PDGFRA*) were identified in 5% (39/856) of cases. Diverse and novel mechanisms of acquired resistance (AR) were detected in ctDNA including MET Y1230C and *EGFR* amplification post-crizotinib, *FGFR3-TACC3* fusion post-EGFR inhibitor, and multiple *EGFR*AR mutations post-osimertinib. **Conclusions:** In this series, use of a rigorously validated capture-based assay revealed evidence of ctDNA in the blood in 84% of cases. Our results provide clinical support for use of this assay as a complementary technology to tissue-based genomic testing in a subset of pts with NSCLC.

9027 Poster Session (Board #353), Sat, 8:00 AM-11:30 AM

Predictive impact of complete molecular response in plasma: A phase II, liquid biopsy study in *EGFR* mutated NSCLC patients treated with afatinib (WJOG 8114LTR). *First Author: Kohei Otsubo, Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*

Background: Liquid biopsy has been approved as an alternative method to detect clinically relevant *EGFR* mutations in NSCLC. However, it is unknown whether the early assessment of molecular response in plasma could be a surrogate of clinical response and/or longer efficacy. Here, we conducted a prospective, multi-institutional study of liquid biopsy in *EGFR*mutated NSCLC patients (WJOG 8114LTR). **Methods:** Chemotherapy naïve, advanced NSCLC patients with EGFR-sensitizing mutation received afatinib monotherapy (40 mg/body) until progressive disease (PD) or unacceptable toxicity. Plasma DNA was obtained from patients at baseline, weeks 2, 4, 8, 12, 24, 48, and at PD. Three types of clinically relevant *EGFR*mutations (exon 19 deletion, exon 20 T790M and exon 21 L858R) will be analyzed using plasma DNA with multiplexed, pico-droplet digital PCR assay (RainDrop system, RainDance Technologies, Billerica, MA). Complete molecular response (CMR) was defined as mutant allele event/frequency of exon 19 deletion or exon 21 L858R below the cutoff for the positivity by digital PCR in plasma. This study was registered at UMIN (ID: 000015847). **Results:** Fifty-seven patients were registered in the study. Efficacy of afatinib was comparable to previous reports (overall response rate: 78.6%, and median progression-free survival (mPFS): 14.2 months). At baseline, 62.5% of patients were positive for *EGFR* mutation in plasma. Plasma positive patients had slightly shorter PFS than plasma negative patients, but not significant (p = 0.24, log-rank). Among those who were positive at baseline, CMR was achieved in 60.6% of patients at two weeks, and 87.5% at four weeks, respectively. Patients with CMR at two weeks had significantly longer PFS than those without one (13.6 versus 7.5 months, $p = 0.0001$). Patients with CMR at four weeks also demonstrated longer PFS than those without one (13.6 versus 5.1 months, $p < 0.0001$). Among patients who achieved CMR by week four, time to achieve CMR did not affect PFS (p= 0.59). **Conclusions:** This is the first report on the predictive impact of early CMR in plasma for longer therapeutic efficacy of afatinib in *EGFR* mutated NSCLC patients. Clinical trial information: 000015847.

9028 Poster Session (Board #354), Sat, 8:00 AM-11:30 AM

The predictive value of uncommon *EGFR* mutation in patients with non-small-cell lung cancer. *First Author: Haiyan Tu, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: Non-small-cell lung cancers with uncommon epidermal growth factor receptor (*EGFR*) mutations are regarded as a heterogeneous group with variable responses to EGFR-targeted drugs. Here we designed this retrospective study to describe the epidemiology and clinical outcomes of uncommon *EGFR* mutations in a Chinese cohort of lung cancer patients. **Methods:** Between June 2007 and June 2014, 5363 lung cancer patients whose *EGFR* genotyping was performed successfully at Guangdong Lung Cancer Institute (GLCI, Guangzhou, China) were screened. 1837 patients were included in the epidemiological analysis. The clinical outcome was analyzed in 97 advanced-stage patients harboring uncommon *EGFR* mutations with follow-up data. **Results:** 218 patients harbored uncommon *EGFR* mutations, making up 11.9% of all cancers with documented *EGFR* mutations. Compared with common mutants, those with uncommon mutations were more commonly found in smokers and male patients. The most frequently detected uncommon mutations were exon 20 insertions, G719X mutations and L858R complex mutations, occurring in 30.7%, 21.1% and 17.0% of all *EGFR*-uncommon-mutation cases. G719X and L858R complex mutations were associated with similar benefit from EGFR-TKI; median PFS was 15.2 (95% CI 8.7-21.7) and 11.6 (95% CI 3.6-19.6) months, respectively. T790M or 20INS was associated with a poorer EGFR-TKI response; median PFS was 1.0 (95% CI 0.0-2.2) and 3.0 (95% CI 1.3-4.7) months, respectively. Of note, two patients with 23% and 65% tumor shrinkages had N771_P772insN and H773_V774insQ, with PFS of 5.7 and 6.1 months respectively. **Conclusions:** Favorable responses were observed in specific subtypes including complex L858R and G719X, and our results suggested first-line EGFR-TKI should be preferable in such patients.

9029 Poster Session (Board #355), Sat, 8:00 AM-11:30 AM

Lung cancers with mutations in *EGFR* exon 18: Molecular characterization and clinical outcomes in response to tyrosine kinase inhibitors. *First Author: Wei-Chu Victoria Lai, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Little data is available to guide clinical management of individuals with less common oncogenic drivers such as exon 18 mutations (ex18m) in *EGFR*. To better understand the impact of these rare mutations on treatment outcomes, we reviewed clinicopathologic data in patients (pts) with ex18m treated with tyrosine kinase inhibitors (TKI) in *EGFR*-mutant lung cancers. **Methods:** Pts with *EGFR* ex18m were detected via molecular diagnostics using Sequenom™, FoundationOne™ or MSK IMPACT™ NGS testing from 2003-2016. We reviewed their clinical data for molecular alterations in *EGFR*, treatment outcomes in response to TKI (time on treatment) and median overall survival (OS). **Results:** We identified mutations in *EGFR* ex18m in 63 pts. Median age at diagnosis was 68; 63% were women; 29% never smokers. Overall, 74 ex18m were found in 63 pts, including: G719A = 38, G719S = 11, G719C = 8, E709K = 6, E709_T710delinsD = 6, E709A = 3, G719D = 2. E709 and G719 co-mutations in ex18 were found in 9 pts, and 1 pt was found to have 3 separate tumors, each with a distinct ex18m. 29/63 (46%) patients with ex18m had a co-occurring *EGFR* mutation: 9 with another ex18m; 20 with ex19-21m. Using our IMPACT NGS, the median number of co-mutations was 8 (range 1-17). Two out of 63 pts had a pre-treatment T790M mutation. The 25 pts with non-metastatic disease presented in the following stages: IA = 19; IB = 3; IIB = 1; IIIA = 2; IIIB = 2. 34/38 pts with metastatic disease were treated with the following first-line EGFR-TKIs: erlotinib = 28, afatinib = 5, osimertinib = 1. Median duration on TKI treatment in months was: erlotinib = 10 mo, (range 1-25), afatinib = 3 mo (range 2-9), osimertinib = 4 mo. Median OS from the date of diagnosis of metastatic disease was 22 months (95% CI 18-29). In comparison, a similar cohort of pts with sensitizing *EGFR* exon19del/L858R mutations had a median OS of 31 months (95% CI 28-33) (Naidoo *Cancer*2015). **Conclusions:** Almost half of ex18m occur concurrently with another *EGFR* mutation. Overall, ex18m pts have a shorter median OS when compared to similar patient cohorts. EGFR-TKIs appear to be an effective treatment for pts with ex18m in *EGFR*-mutant lung cancers.

9030 Poster Session (Board #356), Sat, 8:00 AM-11:30 AM

Antitumor activity of osimertinib in NSCLC harboring EGFR exon 20 insertions. *First Author: Jonathan Riess, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: EGFR exon 20 insertions (Ex20Ins), the 3rd most common EGFR activating mutation, are generally unresponsive to 1st and 2nd generation EGFR-TKIs. Development of EGFR-TKIs that effectively target NSCLC with Ex20Ins mutations represents a major unmet need. Osimertinib is an EGFR TKI approved for the treatment of advanced NSCLC harboring EGFR T790M, but the potential of osimertinib remains to be fully assessed in patients (pts) with Ex20Ins NSCLC. **Methods:** CRISPR engineered Ex20Ins cell line xenografts representing the two most common Ex20Ins (D770_N771InsSVD and V769_D770InsASV) and pt derived xenograft (PDX) of 3 EGFR Ex20Ins (V769_D770InsASV, M766_A767insASV, H773_V774insNPH) were used for in vivo experiments. Xenografts were treated by oral gavage with vehicle, erlotinib (50 mg/kg/day) or afatinib (20 mg/kg/day), osimertinib metabolite AZ5104 (50 mg/kg/day) and osimertinib (25 mg/kg/day) and assessed for tumor growth inhibition (TGI). Immunoblotting was performed for EGFR and relevant signaling pathways. A pt from whom the V769_D770InsASV Ex20ins PDX was derived was treated on a UC Davis IRB approved protocol with osimertinib at 160 mg PO once-daily (QD). **Results:** At completion of treatment, QD administration of osimertinib or AZ5104 induced significant TGI in xenografts across the 4 EGFR Ex20ins tested (range 60-95% TGI, $p < 0.001$ compared to control for all models) that was superior to either afatinib or erlotinib. Robust decrease in p-EGFR, p-ERK, p-Akt, p-Stat3 was observed with osimertinib treatment. The patient corresponding to the V769_D770InsASV Ex20ins PDX treated with osimertinib exhibited clinical improvement and tumor shrinkage; unfortunately he was found to have interstitial pneumonitis that necessitated drug discontinuation. **Conclusions:** Osimertinib at clinically representative doses has *in vivo* activity across multiple EGFR Ex20ins that comprising the most common Ex20ins detected in patients (~50% prevalence); metabolite AZ5104 may contribute to efficacy. Tumor shrinkage was observed in a patient with lung cancer harboring an Ex20ins treated for a limited time with osimertinib. Based on this in vivo xenograft and pt data, osimertinib warrants further study in pts with EGFR Ex20ins NSCLC.

9031 Poster Session (Board #357), Sat, 8:00 AM-11:30 AM

Clinical implications of the T790M mutation in disease characteristics and treatment response in patients with EGFR-mutated NSCLC. *First Author: Daria Gaut, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: The secondary T790M mutation accounts for more than 50% of acquired tyrosine kinase inhibitor (TKI) resistance in epidermal growth factor receptor (EGFR)-mutant NSCLC patients. Recent reports suggest this resistance mutation may be more common among patients with longer progression-free survival (PFS) on first-line TKI therapy, but much is still unknown about this resistance mechanism's association with response to other therapies. **Methods:** Our group collected medical records from patients who underwent a biopsy for T790M mutation testing in the process of screening for clinical trials involving third generation EGFR inhibitors. Medical records were retrospectively analyzed for demographic data, PFS, best response (BR) to previous therapies, and presence or absence of an acquired T790M mutation. Progression-free survival was estimated using the Kaplan-Meier method and compared across two groups using the log-ranked test followed by univariate and multivariate cox proportional hazard regression analysis. Response rates were compared using Fisher's exact test. **Results:** Out of 102 patients who obtained a diagnostic biopsy, 73 patients had a T790M mutation. Patients who later developed a T790M mutation had a longer PFS on first-line TKI therapy (12.0 months in T790M+ vs. 8.0 months in T790M-, p = 0.038, HR 1.66, 95% CI 1.03-2.67), though there was no difference in response rate (75.5% in T790M+ vs 77.3% in T790M-, p = 1.00). T790M+ patients also had a longer PFS on initial chemotherapy treatment (5.0 months in T790M+ vs. 4.0 months in T790M-, p = 0.020, HR 1.97, 95% CI 1.11-3.49) and a higher response rate to chemotherapy (22.7% in T790M+ vs 0% in T790M-, p = 0.033). Median PFS was short (3.0 months) for patients treated with immunotherapy with no difference based on T790M mutation status (p = 0.33). **Conclusions:** Our study confirms that tumors expressing T790M have a more indolent progression of disease compared to their T790M negative counterparts when treated with both first-line TKI and cytotoxic chemotherapy. This data provides context for therapeutic decision making in EGFR-mutant NSCLC patients.

9032 Poster Session (Board #358), Sat, 8:00 AM-11:30 AM

The novel detection of EGFR-T790M mutations in exhaled breath condensate. *First Author: Robert Smyth, Department of Molecular Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland*

Background: The EGFR-T790M somatic mutation is the most common mechanism of resistance to Tyrosine Kinase Inhibitors (TKI) in NSCLC. However patients with advanced disease are not always amenable to repeat biopsy for further molecular analysis. Developing non-invasive methods to detect T790M in cell-free DNA (cfDNA), in the absence of tissue is being actively investigated. Furthermore these 'liquid biopsies' may also overcome the problem of tumour genomic heterogeneity. Unfortunately the sensitivity of plasma for T790M detection has been disappointing with a significant chance of a false negative result. Exhaled breath condensate (EBC) is an easily collected sample and is known to harbour cfDNA, including lung cancer mutations. We explored the potential of EBC as a novel method of T790M detection. **Methods:** We recruited 26 patients who were either 1) known T790M positive pre/during Osimertinib therapy or 2) other mEGFR positive patients on 1st/2nd generation TKI. We collected matched plasma and EBC samples in the majority of cases. EBC samples were collected using the RTube device. Plasma was collected using standard EDTA tubes and extracted within 90 minutes. Using UltraSEEK chemistry, a targeted PCR for ultra-sensitive somatic mutation profiling on the MassARRAY system (Agena Bioscience), we compared the performance of EBC to plasma for the detection of T790M. **Results:** See Table. **Conclusions:** In this pilot study we describe the first ever report of the successful and consistent detection of T790M in the EBC of patients with EGFR mutated NSCLC, using a commercially available targeted assay. Our results suggest EBC is responsive to recognised dynamic molecular changes that occur on TKI treatment. We believe this makes EBC analysis an attractive avenue for future research, to optimise the detection of T790M mutations in liquid biopsies.

Status	EBC	Plasma	p value
T790M+ pre- osimertinib	4/4 (100%)	2/4 (50%)	0.43
T790M+ on osimertinib	1/8 (12.5%)	1/7 (14%)	1.0
mEGFR (non-T790M)	3/17 (18%)	2/15 (13%)	1.0

9033 Poster Session (Board #359), Sat, 8:00 AM-11:30 AM

A phase 1 study of osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancers. *First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: EGFR tyrosine kinase inhibitors (TKI) are the recommended first line treatment for EGFR-mutant lung cancers. Osimertinib, an EGFR TKI that inhibits both sensitizing EGFR mutations and EGFR T790M, is approved for use after progression on an EGFR TKI with evidence of EGFR T790M, and is currently being assessed as initial treatment for EGFR-mutant lung cancers. The addition of bevacizumab to erlotinib resulted in improved progression free survival (PFS) compared to erlotinib alone as initial treatment (16 vs 10 months, HR 0.41). This phase 1/2 study is assessing osimertinib and bevacizumab as initial treatment for patients with EGFR-mutant lung cancers. **Methods:** We evaluated toxicity and efficacy of osimertinib and bevacizumab as initial treatment for patients with advanced EGFR-mutant lung cancers. Using a 3+3 design, full doses of osimertinib (80mg PO daily) and bevacizumab (15mg/kg IV q3 weeks) were given, with a planned dose de-escalation (osimertinib 40mg PO daily) should grade 3 or greater toxicity be seen. Six patients must be treated without a dose-limiting toxicity (DLT) to determine the MTD. 43 additional patients will be treated at the MTD in the phase 2 study, with a primary endpoint of PFS at 12 months. Response was evaluated by RECIST 1.1. **Results:** From Sept 2016 to Jan 2017, 15 patients were enrolled. Median age: 63; Women 11; EGFR L858R = 8, Ex19del = 6, G709A/G719S = 1. After median duration of treatment of 2.7 months, no DLTs were seen in any patient. The MTD was determined to be osimertinib 80mg, bevacizumab 15mg/kg q3 weeks. In total, 15 patients are being treated at the MTD to date. Treatment-related adverse events (AE) were all grade 1-2, except for grade 3 hypertension. The most frequent treatment-related AEs (any grade) were rash (53%), diarrhea (40%), hypertension (33%), fatigue (20%), and itching (20%). All 15 patients continue on study. **Conclusions:** Combination osimertinib and bevacizumab is a tolerable first-line treatment for patients with EGFR-mutant lung cancers and the MTD is osimertinib 80mg and bevacizumab 15mg/kg q3 weeks. Assessment of efficacy with an endpoint of PFS at 12 months is ongoing. Supported by AstraZeneca (NCT02803203). Clinical trial information: NCT02803203.

9034 Poster Session (Board #360), Sat, 8:00 AM-11:30 AM

Afatinib (Afa) plus bevacizumab (Bev) combination after acquired resistance (AR) to EGFR-tyrosine kinase inhibitors (TKIs) in *EGFR*-mutant non-small cell lung cancer (NSCLC): Multicenter single arm phase II trial (ABC-study). *First Author: Akito Hata, Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Kobe, Japan*

Background: Irreversible EGFR-TKI monotherapies showed only moderate efficacy after AR to reversible EGFR-TKIs. Preclinical studies suggested that addition of Bev to EGFR-TKIs could overcome AR, and Bev demonstrated synergistic effects with Afa in TKI-resistant xenograft models. **Methods:** ECOG PS 0-2 patients (pts) with *EGFR*-mutant NSCLC after AR to EGFR-TKIs were enrolled at any lines. Rebiopsy was essential to confirm T790M status after AR. Afa was prescribed at 30 mg, and Bev administered at 15 mg/kg tri-weekly until progression. **Results:** Between October 2014 and September 2016, 33 eligible pts were enrolled. Median age was 66 (range, 48-86). Twenty-one (64%) pts were female, and 22 (67%) were never smoker. Mutation subtypes were 20 (61%) Del-19, 12 (36%) L858R, and 1 (3%) L861Q. T790M was detected in 14 (42%) pts. Median number of prior regimens was 4 (range, 1-10). First prior TKIs were 20 (61%) gefitinib, 10 (30%) erlotinib or 3 (9%) Afa. Six pts obtained partial response and 23 stable disease, resulting in response rate (RR) of 18.2% (95% confidence interval [CI], 7.0-35.5%) and disease control rated of 87.9% (95% CI, 71.8-96.6%). Median progression-free survival (PFS) and overall survival were 5.9 (95% CI, 3.5-8.8) months and not reached, respectively. Median RR and PFS of T790M+ vs. T790M- were 14.3% vs. 21.2% ($p = 0.6189$) and 6.2 vs. 5.2 months ($p = 0.8619$), respectively. Median RR and PFS of Del-19 vs. L858R were 20.0% vs. 8.3% ($p = 0.3789$) and 5.9 vs. 5.1 months ($p = 0.8996$), respectively. Afa dosage was reduced to 20 mg in 15 (45%) pts and increased to 40 mg in 2 (6%) pts. Median number of Bev administrations was 6 (range, 1-14). Bev was interrupted in 5 (15%) pts. Adverse events ≥grade 3: rash (3%); paronychia (24%); mucositis (6%); diarrhea (3%); liver dysfunction (3%); hypertension (39%); and proteinuria (15%) were observed. There were no treatment-related deaths, interstitial lung disease, nor Bev-associated severe bleedings. **Conclusions:** Afa + Bev demonstrated the efficacy and safety after AR to EGFR-TKIs. It could be a therapeutic salvage option for T790M- populations. Clinical trial information: UMIN000014710.

9035 Poster Session (Board #361), Sat, 8:00 AM-11:30 AM

Gefitinib as third-line re-challenge treatment in advanced NSCLC patients with *EGFR* activating mutation who benefited from first-line gefitinib treatment followed by second-line chemotherapy. *First Author: Yong Song, Nanjing General Hospital of Nanjing Military Command, Nanjing, China*

Background: Several studies show that *EGFR*-mutant NSCLC patients (pts) gained response to EGFR-TKI treatment again after a TKI free interval. To date, no prospective evaluation of the clinical effects of EGFR-TKI re-challenge in *EGFR*-mutant NSCLC pts has been performed. **Methods:** This was a multicenter, open-label, single-arm, phase II study (CTONG1304, NCT01933347). Stage IIIB/IV NSCLC pts with *EGFR* exon 19del/L858R mutation, who previously benefited from first-line gefitinib treatment followed by second-line chemotherapy, took gefitinib 250mg/d until disease progression or death or intolerable toxicity occurred. Blood samples were dynamically collected for *EGFR*mutation testing using droplet digital PCR at every visit (from baseline to the end of gefitinib treatment). The primary objective was disease control rate (DCR) at week 8. Secondary objectives were objective response rate (ORR), progression free survival (PFS), and overall survival (OS). **Results:** From March 2014 to May 2016, 45 eligible pts were enrolled and 43 pts were included in the full analysis set (FAS) for efficacy analysis. Gefitinib re-challenge achieved DCR of 69.8%. ORR was 4.7%. Median PFS and OS were 4.4 and 8.0 months (m) respectively. T790M- subgroup at baseline had higher DCR, longer mPFS and mOS, compared with T790M+ subgroup. *EGFR*status changed significantly after gefitinib re-challenge. **Conclusions:** Gefitinib re-challenge was an effective option in *EGFR*-mutant NSCLC pts. T790M negativity is a potentially predictive efficacy biomarker for gefitinib re-challenge. Clinical trial information: NCT01933347.

Efficacy and EGFR testing data for Iressa re-challenge (*p value for T790M+ vs. T790M-).

	Efficacy			
	FAS (n = 43)	T790M+ subgroup (n = 11)	T790M - subgroup (n = 32)	*p* value*
DCR	30/43 (69.8%)	5/11 (45.5%)	25/32 (78.1%)	p = 0.0418
ORR	2/43 (4.7%)	0	2/32(6.3%)	p = 1.0
mPFS (m)	4.4	1.9	4.7	p = 0.0006
mOS (m)	8.0	7.7	9.4	p = 0.0537
	EGFR status			
	19del/L858R with T790M+	T790M+ alone	19del/L858R without T790M+	Undetected
Baseline (N = 45)	11 (24.4%)	1 (2.2%)	15 (33.3%)	18 (40%)
Disease progression (N = 24)	14 (58.3%)	0	7 (29.2%)	3 (12.5%)

9036 Poster Session (Board #362), Sat, 8:00 AM-11:30 AM

ASTRIS: A real world treatment study of osimertinib in patients (pts) with EGFR T790M positive non-small cell lung cancer (NSCLC). *First Author: Filippo De Marinis, European Institute of Oncology, Milan, Italy*

Background: Osimertinib is an oral, irreversible, central nervous system (CNS) active EGFR tyrosine kinase inhibitor (TKI) selective for both EGFR-TKI sensitizing and T790M resistance mutations. We report results from the first predefined interim analysis of the ongoing ASTRIS study (NCT02474355). **Methods:** Pts received osimertinib 80 mg once daily. Eligible pts had Stage IIIB-IV NSCLC harbouring a T790M mutation determined by local validated molecular test (not restricted by sample type), received prior EGFR-TKI therapy, WHO performance status (PS) 0−2, acceptable organ and bone marrow function and no history of interstitial lung disease (ILD) or QTc prolongation. Asymptomatic, stable CNS metastases were permitted. The primary efficacy outcome was overall survival; other outcomes included investigator-assessed response rate (RR), progression-free survival and time to treatment discontinuation. Safety data are also reported. **Results:** From study start (18 Sept 2015) to data cut-off (DCO; 3 Nov 2016), 1217 pts received osimertinib from 120 sites with a median follow-up of 4.1 mths (< 1−14 mths), median age 64 yrs (27–92 yrs), 67% female, 61% White, 37% Asian, 87% WHO PS 0/1, 44% prior chemotherapy, 45% prior radiotherapy. All pts tested positive for T790M, identified from tissue in 682 pts (56%), plasma ctDNA in 433 pts (36%) and from other specimens in 102 pts (8%). At DCO, 317 pts (26%) had discontinued treatment, 900 pts (74%) were ongoing, median duration of exposure 3.8 mths (< 1–13.2 mths), 168 pts (14%) had disease progression and 156 pts (13%) had died. In pts evaluable for response, the investigator-assessed RR was 64% (569/886; 95% CI 61, 67). Adverse events (AEs) leading to dose modification and treatment discontinuation were reported in 122 (10%) and 54 pts (4%), respectively. Serious AEs were reported in 165 pts (14%) and AEs leading to death in 30 pts (2%). ILD/pneumonitis-like events were reported in 25 pts (2%), and QTc prolongation in 9 pts (1%). **Conclusions:** ASTRIS, the largest reported clinical study of osimertinib in T790M-positive NSCLC, demonstrates clinical activity similar to that observed in the osimertinib clinical trial program with no new safety signals. Clinical trial information: NCT02474355.

9037 Poster Session (Board #363), Sat, 8:00 AM-11:30 AM

Tolerability and antitumor activity of ASP8273 in TKI-naive Japanese subjects with EGFR mutation–positive non-small cell lung cancer. *First Author: Shunichi Sugawara, Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan*

Background: EGFR-activating mutations (eg, exon 19 deletions [ex19del], L858R) occur in ~50% of East Asian patients with non-small cell lung cancer (NSCLC) and confer sensitivity to tyrosine kinase inhibitor (TKI) treatment. ASP8273, an orally administered EGFR TKI that inhibits EGFR-activating mutations, has demonstrated clinical activity in subjects with EGFR mutation-positive ($EGFR^{mut+}$) NSCLC. **Methods:** EGFR TKI-naïve adult subjects (≥20 yr) with $EGFR^{mut+}$ NSCLC were enrolled in this single arm Phase 2 study conducted in Japan (NCT02500927). Subjects received open-label ASP8273 300 mg once daily until discontinuation criteria were met. Primary endpoint was tolerability; secondary endpoint was antitumor activity defined by RECIST v1.1. **Results:** A total of 31 Japanese subjects (12 M/19 F; median age 64 years [range: 31–82]) were enrolled. Based on local testing, 27 subjects had an ex19del (n = 13, 42%) or a L858R (n = 14, 45%) EGFR activating mutation; 4 subjects (13%) had other EGFR activating mutations (L861Q [n = 2], G719X [n = 2]). ASP8273 300 mg had tolerable adverse events with diarrhea and peripheral neuropathy being most common; no interstitial lung disease events were reported (Table). Across all 31 subjects, based on investigator assessment, treatment with 300 mg ASP8273 was associated with an overall response rate (ORR) of 52%, disease control rate (DCR) of 94%, and a median duration of progression-free survival (PFS) of 11.3 months (95% CI: 7.2, 15.5). In subjects with ex19del, ASP8273 300 mg was associated with an ORR of 46% and DCR of 85%; median PFS was 8.3 months (95% CI: 2.9, -). In subjects with the L858R, ASP8273 300 mg was associated with an ORR of 57% and DCR of 100%; median PFS was 15.5 months (95% CI: 7.2, 15.5). **Conclusions:** Once-daily ASP8273 300 mg was tolerable in TKI-naïve Japanese subjects with $EGFR^{mut+}$ NSCLC and demonstrated antitumor activity. Clinical trial information: NCT02500927.

TEAE occurring in ≥30% of the study population, n (%)		Total (N = 31)
Diarrhea	Any Grade	24 (77)
	Grade ≥3	2 (6)
Peripheral neuropathy	Any Grade	18 (58)
	Grade ≥3	0
Nausea	Any Grade	12 (39)
	Grade ≥3	0
Increased ALT	Any Grade	11 (35)
	Grade ≥3	2 (6)
Hyponatremia	Any Grade	10 (32)
	Grade ≥3	7 (23)
Decreased appetite	Any Grade	10 (32)
	Grade ≥3	1 (3)

9038 Poster Session (Board #364), Sat, 8:00 AM-11:30 AM

Updated survival outcomes of NEJ005/TCOG0902, a randomized phase II study of concurrent (C) versus sequential alternating (S) gefitinib and chemotherapy in previously untreated non-small cell lung cancer (NSCLC) with sensitive epidermal growth factor receptor (*EGFR*) mutations. *First Author: Satoshi Oizumi, Department of Respiratory Medicine, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan*

Background: North East Japan Study Group (NEJ) 005/ Tokyo Cooperative Oncology Group (TCOG) 0902 study has demonstrated that first-line concurrent (C) and sequential alternating (S) combination therapies of EGFRtyrosine kinase inhibitor (gefitinib) plus platinum-based doublet chemotherapy (carboplatin/pemetrexed) offer promising efficacy with predictable toxicities for patients with *EGFR*-mutant NSCLC (ASCO2014, Ann Oncol 2015). However, overall survival (OS) data were insufficient because of the lack of death events in the primary report. **Methods:** Progression-free survival (PFS) and OS were re-evaluated at the final data cutoff point (November 2016) for the entire population (N = 80). **Results:** At the median follow-up time of 35.6 months, 88.8% of patients had progressive disease and 72.5% of patients had died. Median PFS was 17.5 months for the C regimen and 15.3 months for the S regimen (p = 0.13). Median OS time was 43.3 with the C regimen and 30.7 months with the S regimen (p = 0.018). Updated response rates were similar in both groups (90.2% and 82.1%, respectively; p = 0.34). Patients who had common mutations showed no significant differences in PFS according to type of mutation. Patients with Del19 displayed relatively better OS (median: 45.3 and 33.3 months for C and S regimens) than those with L858R (31.4 and 28.9 months). No severe adverse events including interstitial lung disease have occurred during the follow-up period since the primary report. **Conclusions:** This updated analysis has confirmed that PFS is improved with first-line combination therapies compared to that with gefitinib monotherapy, and the C regimen in particular offers an overall survival benefit of 43 months in the *EGFR*-mutated setting. Our on-going NEJ009 study will clarify whether this combinational strategy can be incorporated into routine clinical practice. Clinical trial information: UMIN000002789.

9039 Poster Session (Board #365), Sat, 8:00 AM-11:30 AM

Pulse-continuous dose erlotinib as initial targeted therapy for patients with *EGFR*-mutant lung cancers with untreated brain metastases. *First Author: Mark G. Kris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Clarke (Neurooncol 2010) reported responses with intermittent high pulse doses of erlotinib (leading to higher concentrations in CSF) given to patients with *EGFR*-mutant central nervous system metastases developing on standard erlotinib doses. In a phase 1 study of pulse-continuous dose erlotinib, no patient developed progression in existing or new brain or leptomeningeal metastases (Yu Ann Oncol 2016). This phase 2 trial tested pulse-continuous dose erlotinib in patients with lung cancers with *EGFR*-mutations with brain metastases. **Methods:** Patients had no prior EGFR TKI or radiation to the brain and at least 1 target brain metastasis. All received initial daily "pulse" doses of erlotinib 1200 mg days 1&2 and "continuous" 50 mg doses days 3-7 (doses and schedule from the Yu Phase 1 study), weekly until progression. The co-primary endpoints were overall and brain metastasis response by RECIST 1.1. **Results:** We enrolled 19 patients with *EGFR*-mutant lung cancers: median age 61yrs (range 45-80), 74% women, 95% Karnofsky PS ≥80%, 1 leptomeningeal disease, 33% prior pemetrexed-based chemotherapy. The median size of target brain metastases was 13 mm (range 10-19 mm). 32% were on dexamethasone for cerebral edema. The partial response rate overall was 74% (95% CI 51-89%) and also 74% in brain metastases. Of 10 patients with progression, 9/10 occurred in non-brain sites (4 *EGFR*T790M, 1 with progression in brain as well), 1 with leptomeningeal. The median progression free survival was 10 mo (range 7-NR mo). Pulse doses were reduced in 68% (median delivered pulse dose 1050 mg days 1&2, range 600-1200 mg). Incidences of *any grade*of rash and diarrhea were 84% and 63% respectively. There were no grade 4 or 5 toxicities. **Conclusions:** Pulse-continuous dose erlotinib alone controlled brain and leptomeningeal metastases in 89% (95% CI 67-98%) of patients with *EGFR*-mutant lung cancers with central nervous system spread pretreatment, with an overall response rate of 74% and progression free survival and rates of rash and diarrhea comparable to series with erlotinib 150 mg daily. Supported by Astellas, CA 129243, CA 008748. NCT01967095 Clinical trial information: NCT01967095.

9040 Poster Session (Board #366), Sat, 8:00 AM-11:30 AM

EGFR analysis of 21,039 patients with NSCLC: Age-related gradual increase of the L858R mutation frequency in adenocarcinomas and high occurrence of ex19del/L858R mutations in squamous cell carcinomas from females and/or nonsmokers. *First Author: Evgenii Imianitov, N. N. Petrov Research Institute of Oncology, St. Petersburg, Russia*

Background: EGFR testing in Russia is carried out upon the patronage of Russian Society of Clinical Oncology (RUSSCO), and the results are accumulated in a centralized database. Squamous cell carcinomas (SCC) constitute 60-70% of NSCLC incidence in Russia, however physicians are often discouraged to send NSCLC-SCC for EGFR testing due to low frequency of mutations. **Methods:** We considered all NSCLC patients analyzed by means of PCR for the presence of EGFR mutations (ex19del and L858R) within years 2012-2017. **Results:** 21,039 NSCLC patients were tested. EGFR analysis was successful in 20,768 patients (98.7%). EGFR mutations were detected in 3566/17717 (20.1%) adenocarcinomas (AdCa) of the lung (ex19del: 2203 (12.4%); L858R: 1363 (7.7%)). There was an evident age-related increase in the frequency of L858R substitution in AdCa patients (p =0.000, Table). This set of patients included 1,139 NSCLC-SCC cases, and the EGFR mutation was observed in 41 (3.6%) subjects. Among 189 females with NSCLC-SCC, ex19del or L858R were detected in 25 (13.2%) cases. Stratification by smoking status revealed EGFR mutation in 19/242 (7.9%) non-smokers. **Conclusions:** Elderly NSCLC patients have particularly increased probability to be diagnosed with L858R mutation. In the real-world setting, patients with NSCLC-SCC may have high frequency of EGFR mutations, either due to imprecise histological subtyping or due to yet unknown reasons. All female and non-smoking patients with NSCLC have to undergo EGFR testing irrespectively of tumor histology.

Age, years	EGFR mutation frequency
18-30	2/87 (2.3%)
31-40	19/431 (4.4.%)
41-50	78/1601 (4.9%)
51-60	348/5819 (6.0%)
61-70	560/6773 (8.3%)
71-80	291/2425 (12.0%)
81-100	35/197 (17.8%)

9041 Poster Session (Board #367), Sat, 8:00 AM-11:30 AM

Molecular panel sequencing of pre-treatment samples to reveal mechanisms of innate resistance to 3rd generation EGFR TKI treatment in T790M-positive NSCLC patients. *First Author: Sebastian Yves Friedrich Michels, Lung Cancer Group Cologne, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany*

Background: Resistance to early generation epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKI) inevitably develops in *EGFR*-mutant lung cancer. The secondary *EGFR* p.T790M mutation is the driving factor in 60% of cases and 3rd generation EGFR TKIs have been developed to overcome T790M-mediated resistance. However, besides T790M other genetic aberrations such as amplifications of *MET* may contribute to resistance to EGFR inhibition in the same patient. We here report on the systematic analysis of co-occurring genetic aberrations that may influence response to 3rd generation EGFR TKIs. **Methods:** Thirty-six patients were treated with 3rd generation EGFR TKIs in the setting of acquired resistance to EGFR inhibition in cancer centers in Germany and Switzerland. Pre-treatment samples were analyzed for co-occurring genetic aberrations in a subset of resistance-related genes including *MET*, *HER2*, *RAS*-gene family, *PIK3CA*, *CTNNB1* and *PTEN* using next-generation sequencing and fluorescence in-situ hybridization assays. We investigated the association between clinical, epidemiological and molecular data and response to treatment (RECIST 1.1). **Results:** Co-occurring genetic aberrations were found in 68% of the pre-treatment samples where both, analyses by sequencing and FISH were feasible (N = 25). Efficacy of 3rd generation EGFR TKIs significantly dropped in the presence of high-level *MET* amplification as compared to wild-type *MET* (ORR, 0.0%; 95% CI, 0.0-60.4 vs. 70.0%; 95% CI, 45.7-87.2; p = 0.02; median PFS, 1.0 month; 95% CI, 0.37-1.72 months vs. 8.2 months; 95% CI, 1.69-14.77 months; $p \leq 0.001$). No statistically significant association was found between treatment efficacy and the molecular status of the genes analyzed or the number of prior EGFR TKIs. **Conclusions:** Prevalence of additional genetic aberrations is frequent in the setting of acquired resistance to early generation EGFR TKIs and may not necessarily mediate resistance to 3rd generation EGFR TKIs. However, in our analysis high-level amplification of *MET* was associated with primary treatment failure and might be the main factor underlying resistance in this setting.

9042 Poster Session (Board #368), Sat, 8:00 AM-11:30 AM

Trastuzumab and paclitaxel in patients (pts) with EGFR mutated non-small-cell lung cancer (NSCLC) that express HER2 after progression on EGFR TKI treatment. *First Author: Joop De Langen, VU University Medical Center, Amsterdan, Netherlands*

Background: HER2 expression as well as amplification has been well recognized in tumor biopsies of pts with an EGFR mutation who developed EGFR TKI resistance. It is unknown whether HER2 targeting in this setting can result in tumor responses. **Methods:** Single arm open label phase II study to study the safety and efficacy of paclitaxel-trastuzumab treatment in pts with a sensitizing EGFR mutation who show tumor membrane HER2 expression in a tumor biopsy (immunohistochemistry (IHC) $\geq$1) after progression on EGFR TKI treatment. Paclitaxel (60 mg/m2) and trastuzumab (first dose 4 mg/kg, thereafter 2 mg/kg) were dosed weekly until disease progression or unacceptable toxicity. Primary end-point was tumor response according to RECIST. Sample size of 20 pts was calculated to evaluate the primary objective of $\geq$30% objective response rate. The study was deemed positive when $\geq$7 pts would show a partial or complete response. **Results:** 21 pts were enrolled from 08-2012 to 02-2017. 7 pts were exon 21 L858R positive and 14 exon 19 del. Last TKI was erlotinib (n = 6), gefitinib (n = 4), rociletinib (n = 3) or osimertinib (n = 8). Median HER2 IHC was 2+ (range 1-3). 17 pts were evaluable for response assessment, while 4 pts are awaiting their first response scan. The primary end-point was met with 7/17 pts (41%) showing a partial response. 2 pts showed stable disease, 7 progressive disease and 1 pt had clinical progression before CT response evaluation. Median duration of response was 9 (range 6-18) months with one ongoing responder. 3 pts experienced grade $\geq$3 toxicity, including fatigue, neuropathy and neutropenia. Upon progression on study treatment, all responding pts were rebiopsied. 4/6 samples were negative for HER2 (IHC), suggesting that the combination effectively targeted HER2 positive tumor cells. **Conclusions:** The study met its primary end-point. Paclitaxel-trastuzumab induces durable objective tumor responses in EGFR TKI pretreated pts with an activating EGFR mutation and HER2 bypass track activation. The treatment was well tolerated. Post-progression tumor biopsies showed absence of HER2 staining in the majority of pts, suggesting effective HER2 targeting. Clinical trial information: NCT02226757.

9043 Poster Session (Board #369), Sat, 8:00 AM-11:30 AM

YES1 amplification as a mechanism of acquired resistance (AR) to EGFR tyrosine kinase inhibitors (TKIs) identified by a transposon mutagenesis screen and clinical genomic testing. *First Author: Pang-Dian Fan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Overcoming AR to EGFR TKIs remains challenging, and in many cases the mechanisms are still unclear. To identify novel mechanisms of resistance to EGFR TKIs, we performed a forward genetic screen using transposon mutagenesis in *EGFR*-mutant lung adenocarcinoma cells. **Methods:** EGFR TKI-sensitive PC9 cells were co-transfected with plasmids encoding a mutagenic *piggyBac*transposon and hyperactive piggyBac transposase. Transposon-tagged, afatinib-resistant clones were generated by sequential selection of transfected cells with puromycin and 1μM afatinib. Transposon insertion sites were mapped using a modified TraDIS-type method and next-generation sequencing (NGS). Selected clones were characterized using Western blots, receptor tyrosine kinase (RTK) arrays, and viability assays following treatment with TKIs or siRNA-mediated gene knockdowns. We reviewed MSK-IMPACT™ NGS data on 100 patient tumors with EGFR TKI AR. Available tumor samples were analyzed by fluorescence in situ hybridization (FISH). **Results:** In 187/188 afatinib-resistant clones, transposon insertion sites consistent predominantly with gene upregulation were found in *MET*, the Src family kinase (SFK) member *YES1*, or both. Clones with activating *YES1* insertions exhibited resistance to all three generations of EGFR TKIs; high levels of expression of tyrosine-phosphorylated YES1; sensitivity to the SFK TKI dasatinib and to siRNA-mediated knockdown of *YES1*; and tyrosine phosphorylation of YAP1 and ERBB3. A query of the MSK-IMPACT™ data on EGFR TKI AR patients revealed amplification of *YES1* and no alteration of *MET*, *ERBB2* or *BRAF* in 3/54 T790M-negative (95% CI 1 to 16%) and 1/46 (95% CI 1 to 12%) T790M-positive cases. Amplification of *YES1*was confirmed by FISH in 2/2 cases, and was absent in matched pre-TKI samples in 2/2 cases. **Conclusions:** *YES1* amplification is found in 4% of patients with acquired resistance to EGFR TKIs and is potentially targetable by Src family kinase inhibitors. Forward genetic screens using transposon mutagenesis and routine clinical NGS of patient samples can identify novel mechanisms of resistance to targeted therapies.

9044 Poster Session (Board #370), Sat, 8:00 AM-11:30 AM

Association between hospital volume and overall survival of patients with metastatic non-small cell lung cancer. *First Author: Gaurav Goyal, Creighton University Medical Center, Omaha, NE*

Background: Prior studies have shown superior surgical outcomes of stage I-III non-small cell lung cancer (NSCLC) in centers with higher patient volumes. However, there is a lack of such information in stage IV NSCLC. In this study, we aim to determine the association between the number of patients with stage IV NSCLC treated annually at a treatment facility (volume) and all-cause mortality (outcome). **Methods:** Using the National Cancer Database, we identified patients diagnosed with stage IV NSCLC between 2004 and 2013. We classified the facilities by quartiles (Q; mean patients with NSCLC treated per year): Q1: $<$ 13.8; Q2: 13.8 to 23.6, Q3: 23.6 to 30.3, and Q4: $>$ 30.3. We used sandwich variance estimators to account for clustering of patients within facilities and Cox regression to determine the volume-outcome relationship, adjusting for demographic (sex, age, race), socio-economic (insurance type), receipt of chemotherapy, and comorbid (Charlson-Deyo score) factors and year of diagnosis. **Results:** There were 281,654 patients with stage IV NSCLC treated at 1,275 facilities. The median age at diagnosis was 66 years, and 55.7% were men. The median annual facility volume was 23.6 patients per year (range, 1.0 to 301.4). The distribution of patients according to facility volume was: Q1: 6.6%, Q2: 14.9%, Q3: 25.4%, and Q4: 53.1%. The unadjusted median overall survival by facility volume was: Q1: 4.4 months, Q2: 4.5 months, Q3: 4.7 months, and Q4: 5.3 months ($P<$ .001). Multivariable analysis showed that facility volume was independently associated with all-cause mortality. Compared with patients treated at Q4 facilities, patients treated at lower-quartile facilities had a small but significantly higher risk of death (Q3 hazard ratio [HR], 1.05 [95% CI, 1.03 to 1.07]; Q2 HR, 1.06 [95% CI, 1.03 to 1.09]; Q1 HR, 1.09 [95% CI, 1.06 to 1.13]). **Conclusions:** Patients who were treated for stage IV NSCLC at lower-volume facilities had a significantly higher risk of all-cause mortality compared with those who were treated at lower-volume facilities.

Outcomes in stage IV non-small cell lung cancer based on hospital volume.

Survival	Q1 (%)	Q2 (%)	Q3 (%)	Q4 (%)
1-year	22.7	23.6	24	27
2-year	10	10.4	10.8	12.5
5-year	3	3.2	3	3.6

9045 Poster Session (Board #371), Sat, 8:00 AM-11:30 AM

Recurrent versus de novo metastatic NSCLC: Impact on outcomes. *First Author: Sara Moore, BC Cancer Agency, Vancouver, BC, Canada*

Background: Metastatic non-small-cell lung (NSCLC) cancer has a poor prognosis, with a 5 year survival less than 5%. The majority of patients present with stage IV and many patients treated curatively with stage I-III will develop recurrent metastatic disease. It is unknown if the natural history differs between patients with recurrent versus de novo metastatic NSCLC. We hypothesized that de novo metastatic disease is associated with decreased overall survival compared to recurrent metastatic disease. **Methods:** A retrospective review was completed of all patients with NSCLC referred to the BC Cancer Agency from 2005-2012. Two cohorts were created; de novo metastatic disease and patients treated with curative intent (surgery or radiotherapy) that developed recurrent, metastatic disease. Information was collected on known prognostic and predictive factors. Overall survival was calculated from the date of diagnosis of metastatic disease. **Results:** A total of 9656 patients were referred, 5783 (60%) with de novo stage IV disease, and 3873 (40%) with stage I-III disease. Of patients with initial stage I-III, 1801 received curative therapy (751 surgery, 1050 radiotherapy) and 802 developed metastases. Patients in the de novo cohort were more likely to be male (52% vs 47%), have poorer performance status (ECOG≥2 50% vs 43%), and receive no palliative chemotherapy (67% vs 61%). The median overall survival in the de novo cohort was 4.7 m vs 6.9 m in the recurrent cohort ($p < 0.001$). De novo status was associated with shorter overall survival and this remained significant in a multivariate model that incorporated gender, ECOG and lines of palliative chemotherapy (hazard ratio 1.228[95% confidence interval 1.134-1.330], p-value < 0.001). **Conclusions:** In a large population based study of NSCLC, de novo metastatic status was independently associated with decreased overall survival from the time of metastatic disease diagnosis. De novo versus recurrent status should be used as a prognostic factor to inform patient decisions and ensure balanced stratification of patients in clinical trials.

9046 Poster Session (Board #372), Sat, 8:00 AM-11:30 AM

Describing the value of the most common first line NSCLC regimens in a real world setting. *First Author: Lee N. Newcomer, UnitedHealth Group, Edina, MN*

Background: We aim to describe clinical and economic outcomes of common chemotherapy regimens for first line therapy of metastatic non-small cell lung cancer (mNSCLC).The data are intended to help clinicians and patients understand the real world results for patients like themselves. **Methods:** This retrospective analysis used clinical data obtained from a prior authorization (PA) program for chemotherapy linked with administrative claims data from 6/1/2015 to 5/31/2016 from a large national managed care organization. Clinical data included cancer type, stage at diagnosis, biomarkers, treatment line and evidence of progression/relapse. Eligible patients were commercially insured members with a PA request for commonly used NCCN recommended regimens for first line therapy of mNSCLC. Outcomes, including duration of therapy, % of patients hospitalized and total cost of care were tracked from first claim for chemotherapy until end of treatment due to discontinuation, death or start of a second line, with remaining patients censored at 5/31/2016 or end of enrollment. **Results:** Of 830 mNSCLC patients, 498 (60%) completed first line therapy during the study period. 345 initiated one of the following: Carbo/cisplatin + pemetrexed (CA), Carbo/cisplatin + paclitaxel (CP), Carbo/cisplatin + bevacizumab + pemetrexed (CBA), nivolumab (N), and docetaxal (D). Outcomes are summarized in the Table. **Conclusions:** Patients treated with the five most commonly prescribed first line therapies for mNSCLC have much shorter duration of therapies (52-76 days) than reported in published clinical trials with a significant risk of hospitalization (18% -30%) and at substantial cost ($34,971 - $108,100). These data are an important consideration for the patient and clinician making treatment decisions in routine clinical practice and will become more valuable as the database grows over time.

	CA	CP	CBA	N	D
Frequency N (%)	146 (29)	87 (17)	50 (10)	31 (6)	31 (6)
Duration (days) mean (SD)	69 (54)	56 (37)	76 (59)	52 (39)	53 (42)
Inpatient stay %	18	26	30	29	16
Inpatient stay costs US$ mean (SD)	7399 (21919)	6500 (14752)	9488 (17135)	8864 (23468)	3748 (12843)
Total cost US$ mean (SD)	61357 (58480)	41032 (41334)	108100 (86745)	64500 (64871)	34971 (47100)

9047 Poster Session (Board #373), Sat, 8:00 AM-11:30 AM

Phase 2 trial of chemotherapy followed by consolidative radiation therapy for initial treatment of oligometastatic NSCLC. *First Author: Tamjeed Ahmed, Wake Forest Baptist Health, Winston-Salem, NC*

Background: Unselected patients with stage 4 lung cancer who receive front line platinum based chemotherapy and maintenance chemotherapy have demonstrated a PFS less than 6 months with very few patients alive at 5 years. Patients with a small number of metastatic lesions may have a different biology, and aggressive local treatment of oligometastases is an active area of investigation. **Methods:** Patients were required to have stable disease or response after 3-6 cycles of platinum based chemotherapy and PS 0-2. Oligometastatic disease was defined as a maximum number of 5 metastatic lesions for all disease sites including no more than 3 active extracranial metastatic lesions. Limited mediastinal lymph node involvement was allowed. **Results:** 29 patients were enrolled between 10/2010 and 10/2015. 3 patients were excluded from analysis due to concerns regarding eligibility/treatment response. Despite closing early due to slow accrual, the study met its primary endpoint for success which was PFS greater than 6 months. The median PFS (95% CI) was 11.0 months (7.4-15.9 months) and the median OS was 22.2 months (13.3-45.7 months). The 1-year, 3-year, and 5-year OS were 73%, 35%, and 29%. **Conclusions:** Patients with oligometastatic NSCLC who received platinum based chemotherapy followed by oligometastatic consolidative radiation without maintenance chemotherapy demonstrated prolonged disease control and overall survival. Clinical trial information: nct01185639.

9048 Poster Session (Board #374), Sat, 8:00 AM-11:30 AM

Microwave ablation in combination with chemotherapy versus chemotherapy in advanced non small cell lung cancer: A prospective, randomized, phase III clinical trial. *First Author: Zhig Wei, Shandong Provincial Hospital Affliated to Shandong University, Jinan, China*

Background: Previous studies showed that advanced non small cell lung cancer (NSCLC) benefited from microwave ablation in combination with platium-based doublet chemotherapy. This prospective, randomized, phase III clinical trial aimed to determining the survival benefit and safety of MWA combined with chemotherapy compared with chemotherapy alone, which was registered in ClinicalTrials. gov (NCT02455843). **Methods:** Patients with untreated, stage IIIB or IV NSCLC and at least one additional measurable site other than the primary tumor site were recruited. They were divided into MWA/chemotherapy group and chemotherapy group, the former received MWA in the primary tumor sites, followed by chemotherapy and the latter treated with chemotherapy only. The primary endpoint was progression-free survival (PFS), the second endpoint included objective response rate (ORR), overall survival (OS) and adverse events (AE). **Results:** From Mar 1st, 2015 to Oct 31th, 2016, Two hundreds and eighty-six patients were enrolled , including 141 in MWA/chemotherapy group and 145 in chemotherapy group. Complete ablation was observed in 95.0 % patients. ORR were 38.3 % and 34.1 % in the MWA/chemotherapy group and chemotherapy group, respectively($p = 0.677$). MWA prolonged PFS [MWA/chemotherapy group 7.3 (95 % CI,5.3–13.6) ms vs. chemotherapy group 5.2 (95 % CI, 4.0–12.4) ms, $p = 0.003$]. Multivariate analyses showed that MWA was an independent prognostic factor of PFS. OS was immature. AEs of MWA were observed in 67.4 % patients, mainly was pheumothorax, and only 15% needing chest tube insertion. No ablation associated death was observed. Chemotherapy-associated AEs were observed in 49.1 and 53.6 % of patients in the MWA/chemotherapy and chemotherapy group, respectively. **Conclusions:** MWA plus chemotherapy combination improved the PFS of advanced NSCLC compared to chemotherapy alone. Adverse events of MWA was tolerable. Clinical trial information: NCT02455843.

9049 Poster Session (Board #375), Sat, 8:00 AM-11:30 AM

Objective response rate and progression-free survival as surrogate endpoints for overall survival and the impact of crossover and unbalanced post-progression treatments: A systematic review and meta-analysis in first-line therapy of advanced non-small cell lung cancer. *First Author: Boris Pfeiffer, Merck KGaA, Darmstadt, Germany*

Background: Correlations between overall survival (OS) and objective response rate (ORR) or progression-free survival (PFS) are poor. We aimed to evaluate the impact of crossover and unbalanced subsequent treatments on ORR and PFS as surrogate endpoints for OS in patients with advanced NSCLC receiving first-line therapy. **Methods:** A systematic literature review of randomized clinical trials of systemic treatment for patients with stage IIIB/IV NSCLC receiving first-line therapy was performed. Weighted (by trial size) linear regression models were fitted with the absolute difference in ORR or median PFS as an independent variable and the absolute difference in median OS as a dependent variable. The analysis was repeated in predefined subsets based on crossover and balance of post-progression therapies. Surrogate threshold effect (STE) was estimated using prediction intervals. **Results:** 317 trials (78,644 patients) fulfilled the eligibility criteria. In all treatment arms, the mean ORR, median PFS, and median OS were 28.2% (standard deviation (SD) = 12.4%), 5.1 months (SD = 2.1), and 10.4 months (SD = 2.5), respectively. ORR and PFS had weak (R = 0.351; 95% CI: 0.251-0.443) and (R = 0.397; 95% CI: 0.267-0.512) associations with OS, respectively. However, within phase III trials that did not allow crossover and reported balanced post-progression treatments, both ORR and PFS had stronger associations with OS (ORR and OS: R = 0.601, 95% CI: 0.399-0.747; PFS and OS: R = 0.695, 95% CI: 0.446-0.844). STE estimation indicated that trials that show statistically significant treatment effect size of $\geq$43% ORR or $\geq$3.2 median PFS months can be expected to show significant OS benefit with sufficient certainty. **Conclusions:** Surrogacy of ORR and PFS for OS might be better estimated in trials that do not allow crossover and report balanced post-progression treatments. Presented STE calculation can be used to estimate the expected effect on OS when either ORR or PFS are used as primary endpoints.

9050 Poster Session (Board #376), Sat, 8:00 AM-11:30 AM

Clinical comparison of ABP 215 and bevacizumab in patients with NSCLC: Pharmacokinetic results and justification for extrapolation across bevacizumab indications. *First Author: Nick Thatcher, The Christie Hospital, Manchester, United Kingdom*

Background: Approval of biosimilars is based on totality of evidence (TOE) that includes demonstration of analytical, functional, and pharmacokinetic (PK) similarity, and comparable clinical efficacy, safety, and immunogenicity. The TOE supports scientific justification for extrapolation across other indications that a share common mechanism of action (MOA). The proposed biosimilar ABP 215 is similar to bevacizumab (BEV) with respect to inhibition of vascular endothelial growth factor (VEGF)-induced signaling; PK in healthy adults; and clinical efficacy, safety, and immunogenicity in patients with non-small cell lung cancer (NSCLC). The PK results from the NSCLC study are reported here. **Methods:** In this double-blind study, adults with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel were randomized 1:1 to ABP 215 or BEV (15 mg/kg IV Q3W for 6 cycles). Trough (pre-dose) PK samples were collected at baseline, at weeks 4, 7, and 13, and at end of study. Clinical evaluations included efficacy, safety, and immunogenicity. **Results:** 642 patients (ABP 215, n = 328; BEV, n = 314) were randomized. Demographic and baseline characteristics were well balanced. The primary endpoint of risk ratio for objective response rate was 0.93 (2-sided 90% CI, 0.80-1.09), which was contained within the pre-specified equivalence margin. The incidence of adverse events was comparable between ABP 215 and BEV. During the study, 4 (1.4%) and 7 (2.5%) patients in the ABP 215 and BEV group, respectively, developed binding antibodies; no patient tested positive for neutralizing antibodies. Steady-state trough serum concentrations for both ABP 215 and BEV were reached by week 13 (median 124.9 vs 124.4 μg/mL, respectively) and were consistent between ABP 215 and BEV throughout the study. **Conclusions:** ABP 215 is similar to BEV in multiple analytical, functional, and clinical assessments. PK results in patients presented here provide further evidence for similarity between ABP 215 and BEV and contribute to the TOE supporting extrapolation of clinical similarity across BEV indications based on its common MOA. Clinical trial information: NCT01966003.

9051 Poster Session (Board #377), Sat, 8:00 AM-11:30 AM

Impact of prior radiation on survival in metastatic lung cancer ECOG-ACRIN trials. *First Author: Saad A. Khan, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Up to 50% of advanced NSCLC patients receive radiation therapy at some point in their course. We sought to determine whether patients with prior radiation demonstrate altered outcomes on subsequent metastatic clinical trials. **Methods:** We reviewed 8 ECOG-ACRIN advanced non-small cell lung cancer studies conducted between 1993 and 2011 in which information was collected about receipt of prior radiation. Whether radiotherapy was given with curative or palliative intent, or to specific sites was not recorded. Median follow-up among all trials was 66 months. We used the log-rank, Wilcoxon and Fisher's exact tests to compare patients, and Cox Model and Kaplan-Meier method to calculate survival. **Results:** 574/3041 (18.9%) patients had received prior radiation. These patients were more likely to be male (64% vs 58%), have squamous histology (20% vs 14%) and have had prior surgery (48% vs 33%) compared to those with no prior radiation. At registration, prior radiation patients were more likely to have an ECOG PS of 1 (66% vs 58%), while they were less likely to have a PS of 0 (24% vs 36%) or have a pleural effusion (23% vs 37%). Patients who received radiation were more likely to have been registered on to studies between 1993-1999 than 2000-2011 (69% vs 31%) (all $p < 0.001$). Median Overall Survival (OS) for patients with prior radiation was 7.6 months (range 7-8.3) vs 9.5 (9.1-9.8) for those without ($p < 0.001$). Median Progression Free Survival (PFS) for those with prior radiation was 3.5 months (3-3.9) vs 4.2 (4.1-4.4) for those without ($p < 0.001$). In multivariable analysis controlling for stage IIIB/IV, sex, PS, histology, and prior surgery, the impact of prior radiation on overall survival remained significant (p = 0.042, HR (95% CI) = 1.11 (1.00, 1.22)). **Conclusions:** Almost one-fifth of lung cancer patients on systemic therapy trials for advanced disease previously received radiation. They are more likely to be male, have squamous histology, have an ECOG PS of 1 and have had prior surgery. Prior radiation is significantly associated with inferior OS and PFS. For advanced NSCLC clinical trials, documentation of whether curative intent/palliative intent radiation was given and stratification by prior radiation exposure should be considered.

9052 Poster Session (Board #378), Sat, 8:00 AM-11:30 AM

A phase 1b/2 study of napabucasin with weekly paclitaxel in advanced, previously treated non-squamous non-small cell lung cancer. *First Author: Carlos Becerra, Texas Oncology, Dallas, TX*

Background: Napabucasin is a first-in-class cancer stemness inhibitor, identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells (Li et al PNAS 112 (6):1839, 2015). Napabucasin has shown potent synergistic preclinical anti-tumor activity with paclitaxel (PTX). In a phase Ib dose escalation study in patients (pts) with advanced solid tumors, napabucasin plus weekly PTX was well tolerated. A phase II expansion cohort was opened for pts with advanced non-small cell lung cancer (NSCLC). **Methods:** Pts with metastatic non-squamous NSCLC were enrolled to confirm safety and preliminary anti-cancer activity. Prior platinum-based systemic therapy was required, and patients with an EGFR or ALK mutation required appropriately targeted therapy. Napabucasin was administered orally at a starting dose of 240 or 480 mg BID with PTX 80 mg/m2 IV weekly 3 of every 4 weeks. AEs were evaluated using CTCAE v4.03 and objective assessments were performed every 8 weeks per RECIST 1.1. **Results:** A cohort of 23 pts with advanced non-squamous NSCLC was evaluated. The median number of prior systemic treatment lines was 3, including taxane-based therapy in 100% and immune checkpoint inhibitor in 48% (n = 11). Treatment was well tolerated; related grade 3 AE included diarrhea (n = 4) and fatigue (n = 1). The objective response rate was 26% (6 partial responses [PR]) and the disease control rate (DCR; proportion with SD at 8 weeks plus PR per RECIST) was 70% (n = 16). Tumor regression, including PR, occurred in 35% (n = 8). The median progression-free survival (mPFS) was 5.4 months, and 43% (n = 10) of pts were alive and free of progression at the 24 week time-point or longer. The median overall survival (mOS) was 11.0 months, and 30% (n = 7) of pts were alive for 52 weeks or longer. **Conclusions:** Clinical safety and encouraging signs of anti-cancer activity were observed in pts with heavily pretreated non-squamous NSCLC who received napabucasin plus weekly paclitaxel. The objective response rate, progression free survival, and overall survival in this population warrant further clinical evaluation and a controlled phase 2/3 trial (CanStem43L) has been initiated. Clinical trial information: NCT01325441.

9053 Poster Session (Board #379), Sat, 8:00 AM-11:30 AM

Third-line treatment: A randomized, double-blind, placebo-controlled phase III ALTER-0303 study—Efficacy and safety of anlotinib treatment in patients with refractory advanced NSCLC. *First Author: Baihui Han, Department of Pulmonary, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China*

Background: Anlotinib hydrochloride, an oral TKI targeting VEGFR, FGFR, PDGFR and c-Kit, showed promising efficacy in PhaseIIstudy. Here, we evaluated the efficacy and safety of anlotinib as third-line treatment for advanced NSCLC, a randomized, double-blind, placebo-controlled Phase IIItrial (ALTER-0303). **Methods:** Eligible IIIB/IV NSCLC pts who progressed after at least 2 lines of prior therapies were randomized 2:1 to receive anlotinib or placebo (12 mg QD from day 1 to 14 of a 21-day cycle) till progression or intolerable toxicity. Enrolled pts harboring EGFR or ALK mutations must had failed in previous match-targeted therapies. The primary endpoint is OS; secondary endpoint includes PFS, DCR and ORR. **Results:** As of Aug 2016, total of 437 pts from 31 sites were randomized. The baseline characteristics of Anlotinib arm (N=294) and placebo arm (N=143) were well balanced in the age, gender, ECOG PS and gene states. With 292 OS events (66.82%), significant superiorities in OS, PFS, DCR and ORR were observed in Anlotinib arm according to investigator-assessed results. Grade ≥ 3 treatment-related AEs were hypertension, dermal toxicity and hypertriglyceridemia. There was no treatment–related death in either arm. (Data presented in the Table.) **Conclusions:** ALTER-0303 trial met its primary endpoint. Anlotinib significantly improved OS and PFS in advanced NSCLC with a manageable safety profile. The results strongly suggest that anlotinib should be considered as a candidate for the third-line treatment or beyond in advanced NSCLC. Clinical trial information: NCT02388919.

	Anlotinib arm N = 294	Placebo arm N = 143	p-value
Efficacy			
OS, median, months	9.63 (95% CI: 8.17, 10.60)	6.30 (95% CI: 5.00, 8.10) HR: 0.68 (95% CI: 0.54, 0.87)	0.0018
PFS, median, months	5.37 (95% CI: 4.40, 5.63)	1.40 (95% CI: 1.07, 1.50) HR: 0.25 (95% CI: 0.19, 0.31)	<0.0001
ORR (CR+PR), %	9.18	0.7	<0.0001
DCR (CR+PR+SD), %	80.95	37.06	<0.0001
Treatment-related AEs (≥ 3 grade), %			
Hypertension	13.61	0.00	<0.0001
Dermal toxicity	3.74	0.00	0.019
Hypertriglyceridemia	3.06	0.00	0.034

9054 Poster Session (Board #380), Sat, 8:00 AM-11:30 AM

A phase II study of GDC-0032 (taselisib) for previously treated PI3K positive patients with stage IV squamous cell lung cancer (SqNSCLC): LUNG-MAP sub-study SWOG S1400B. *First Author: James Lloyd Wade, Heartland NCORP, Decatur, IL*

Background: Lung-MAP (S1400) is a National Clinical Trials Network "umbrella" trial for previously-treated SqNSCLC. Sub-study S1400B included patients (pts) with tumors harboring PI3K mutations.Taselisib (GDC-0032), a potent, small molecule inhibitor of Class 1 PI3K with beta isoform sparing selectivity, has been shown to be a potent inhibitor in preclinical models of PIK3CA-mutant tumors. **Methods:** Eligibility stipulated progressive SqNSCLC after primary platinum-based therapy and presence of a PIK3CA mutation as determined by Foundation Medicine (FMI+) NGS. . The primary analysis population was a subgroup of the total PIK3CA mutation group (GNE+) with alterations limited to substitutions: E542K, E545A, E545G, E545K, E545Q, H1047L, H1047R, H1047Y. Primary endpoint was response rate (RR) in GNE+ pts. The initial protocol randomized PIK3 mt (+) pts to taselisib 4 mg po daily or docetaxel, but was amended to single arm phase II trial of taselisib with interim analysis based on first 20 eligible GNE+ pts evaluable for response, stipulating closure for futility if < 2 responses were observed. **Results:** 26 eligible pts, 7% of those registered to S1400, received taselisib; of these , 21 (81%) were GNE+. Of the 20 eligible, response-evaluable GNE+ pts, one pt with PIK3CA E545K gene alteration responded (5% RR, 95% Confidence Interval [CI] 1%, 24%). 13 pts had stable disease. Median PFS was 2.5 mos (95% CI, 1.7-4.0 mos) and 2.7 mos (95% CI, 1.8-3.4 mos) among GNE+ and FMI+ pts, respectively. 26 FMI+ pts were evaluable for toxicity: two grade 5 events (cardiac arrest, respiratory failure), neither clearly attributable to treatment, were recorded, along with one instance each of grade 4 AEs (dyspnea, thrombocytopenia, pneumonitis). Grade 3 AEs included 5 pts each with hyperglycemia or diarrhea, and 3 with lymphopenia. Overall survival data is premature. **Conclusions:** Study S1400B failed to meet its primary endpoint and was closed December 2016 at interim analysis for futility. Toxicities were manageable. The trial is unique in cataloguing the diversity of mutations in the PI3K pathways in SqNSCLC Clinical trial information: NCT02785913.

9055 Poster Session (Board #381), Sat, 8:00 AM-11:30 AM

Phase II study of the FGFR inhibitor AZD4547 in previously treated patients with FGF pathway-activated stage IV squamous cell lung cancer (SqNSCLC): LUNG-MAP sub-study SWOG S1400D. *First Author: Charu Aggarwal, Abramson Cancer Center, Philadelphia, PA*

Background: LungMAP is a National Clinical Trials Network umbrella trial for previously-treated SqNSCLC. S1400D is a phase II biomarker-driven therapeutic sub-study evaluating the FGFR inhibitor AZD4547 in patients (pts) with FGFR positive chemo-refractory SqNSCLC. **Methods:** Eligible pts had tumor FGFR alteration and/or mutation by next generation sequencing (Foundation Medicine), measurable disease, Zubrod PS 0-2, progression after 1 line of systemic therapy, and adequate end organ function. Receipt of prior immunotherapy was allowed. Eligible pts received AZD4547 80 mg bid orally. Primary endpoint was overall response rate (ORR) by RECIST; secondary endpoints included progression-free survival (PFS) and duration of response (DoR). Originally designed as a randomized trial of AZD4547 versus docetaxel, it was redesigned to be a single arm AZD4547 trial with the emergence of immunotherapy as standard 2ndline therapy. Forty pts were required to rule out an ORR of < = 15% if the true ORR was > 35% (90% power, alpha 0.05). **Results:** 93 pts (13% of pts screened on S1400) were assigned to S1400D; 43 were enrolled with 28 receiving AZD4547. Pt characteristics: median age 66.3 y (49-88), female (n = 8, 29%), & Caucasian (n = 25; 89%). Biomarker profile: FGFR1 amplification (n = 38; 86%); FGFR3 S249C (n = 4; 9%); FGFR3 amplification (n = 3; 7%); and FGFR3 fusion (n = 2; 5%). Nine pts (26%) had more than one biomarker alteration. The study was closed at interim analysis for futility in October 2016. Treatment related Grade 3 AEs were seen in 5 pts (dyspnea, fatigue, hyponatremia, lung infection & retinopathy); 1 pt had Grade 4 sepsis. There were no Grade 5 AEs. Median follow up among alive pts was 4.3 months (mos). Of 25 response evaluable pts, one with FGFR3 S249C had unconfirmed PR (4%, 95% CI 1-20%) with DoR of 1.5 mos. Median PFS was 2.7 mos (95% CI 1.4 - 4.3 mos). **Conclusions:** This is the first Phase II trial to evaluate AZD4547 as a targeted approach in pts with previously treated FGFR-altered SqNSCLC. AZD4547 had an acceptable safety profile but minimal activity in this biomarker-enriched cohort. Evaluation of other targeted agents in LUNG-MAP is currently ongoing. Clinical trial information: NCT02965378.

9056 Poster Session (Board #382), Sat, 8:00 AM-11:30 AM

A phase II study of palbociclib (P) for previously treated cell cycle gene alteration positive patients (pts) with stage IV squamous cell lung cancer (SCC): Lung-MAP sub-study SWOG S1400C. *First Author: Martin J. Edelman, Fox Chase Cancer Center, Philadelphia, PA*

Background: S1400 is a master platform trial designed to assess targeted therapies in SCC. Study C evaluated the response rate (RR) to P, a CDK 4/6 inhibitor, in pts with cell cycle gene abnormalities. **Methods:** Pts with SCC, PS 0-2, normal organ function, who had progressed after at least one prior platinum-based chemotherapy for any NSCLC indication were eligible. Tumor specimens were required and evaluated for gene alterations (Foundation Medicine, Foundation One NGS assay). Pts with CDK 4 or CCND1/2/3 amplifications were eligible. The study was originally designed as a phase II/III trial comparing P to docetaxel (D), but was modified to a 2-stage phase II trial with primary endpoint of response rate. If > 3 responses (R) of the first 20 pts were seen the study would continue to 40 pts, with 10 R for the 40 pts considered a positive study. **Results:** 89 pts (14% of pts screened) were assigned to S1400C, 53 pts enrolled (including 17 to D). One pt assigned to D re-registered to P. Frequency of cell cycle gene alterations for the enrolled pts: CCND1 amplification (n = 44, 83%); CCND2 amplification (n = 7, 13%); CCND3 amplification (n = 5, 9%); and CDK4 amplification (n = 3, 6%). (Note: some pts with multiple alterations.) Of the 37pts enrolled to P: 5 were ineligible (4 inadequate baseline labs, 1 did not progress on prior therapy). 1 not determinable for response. For the 32 eligible pts the median age was 67 (53-81), 21M/11F. Response: 2 PR (6% RR, 95% CI: 2%, 20%), 12 SD (38%, 95% CI: 21%, 54%) for a disease control rate (DCR) of 44% (95% CI: 27%, 61%). Median PFS was 1.7 mo (95% CI 1.6-2.9 mo). Of the 2 PR, one has progressed (duration of response, DOR, 7.7 mo), one still responding (DOR, 4 mo). Both responders had CCND1 amplification. 32 pts have been assessed for adverse events (AE). 4 experienced Grade 4 AE including lymphopenia (3), and thrombocytopenia (1). 13 others experienced Grade 3 treatment-related AE. **Conclusions:** 1. P failed to demonstrate the pre-specified RR to justify advancement to phase III. 2. P was well tolerated in this population. 3. Further analysis of those who derived benefit (e.g. response or prolonged SD) is underway. Clinical trial information: NCT02785939.

9057 Poster Session (Board #383), Sat, 8:00 AM-11:30 AM

Clinical features of squamous cell lung cancer with targetable gene alterations in a nationwide genomic screening network in Japan (LC-SCRUM-Japan). *First Author: Eri Sugiyama, Division of Cancer Immunology, National Cancer Center, Kashiwa, Japan*

Background: Molecular-targeted therapies for precision medicine in squamous cell lung cancer (SqLC) have not yet been established. To identify precise patients for targeted therapies and to reveal their clinical characteristics, we have operated clinical sequencing of advanced SqLCs in our nationwide genomic screening project in Japan (LC-SCRUM-Japan) since March 2015. **Methods:** As of December 2016, 190 institutions across Japan were participating and 263 advanced SqLC patients had been enrolled in this project. Submitted tumor samples were subjected to a next-generation sequencing system, Oncomine™ Comprehensive Assay, enabling the simultaneous analysis of 143 cancer-related genes. **Results:** The median age of the 263 patients was 74 years (range, 27-87 years). Two hundred thirty (87%) were male and most patients (97%) were smokers. Among 211 available samples, potentially targetable gene alterations were detected in 58 (27%). Based on these gene alterations, the patients were subdivided into 4 groups, consisting of 25 (12%) with genetic alterations of FGFR family (FGFR type; 23 FGFR1 amplifications, 1 FGFR2 amplification and 1 FGFR3 fusion), 20 (9%) with genetic alterations of the PI3K pathway (PI3K type; 10 PIK3CA mutations, 8 PTEN mutations and 2 AKT mutations), 15 (7%) with other oncogene alterations (KRAS/EGFR/ALK type; 10 KRAS mutations, 3 EGFR mutations and 2 ALK fusions) and others. Comparative analyses of clinical characteristics between the 4 types showed that brain metastases were significantly more frequent in the FGFR type than the others (24% vs. 5%, p = 0.0007), and females (40% vs. 11%, p = 0.0009) and never-smokers (21% vs. 3%, p = 0.0004) were significantly frequent in the KRAS/EGFR/ALK type compared to the others. The prognostic significance of these genetic alterations has not yet been evaluated because of short follow-up time (median, 8.5 months). **Conclusions:** A series of potentially targetable gene alterations have been identified in SqLC patients. The SqLC patients had distinct clinical features according to the molecular subtypes, and genotype-directed therapeutic strategy should be developed for the individual subtypes.

9058 Poster Session (Board #384), Sat, 8:00 AM-11:30 AM

Safety and efficacy of *nab*-paclitaxel (*nab*-P)–based therapy in patients (pts) with non-small cell lung cancer (NSCLC) and performance status (PS) 2: Results from ABOUND.PS2. *First Author: Ajeet Gajra, State University of New York Upstate Medical University, Syracuse, NY*

Background: Chemotherapy can benefit pts with advanced NSCLC with poor Eastern Cooperative Oncology Group (ECOG) PS, despite an increased toxicity risk vs those with good PS. Safety and efficacy of *nab*-P/carboplatin (*nab*-P/C) induction followed by *nab*-P monotherapy in pts with advanced NSCLC and ECOG PS 2 are reported. **Methods:** Chemotherapy-naive pts with histologically/cytologically confirmed stage IIIB/IV NSCLC and ECOG PS 2 received 4 cycles of *nab*-P 100 mg/m^2 d 1, 8 + C AUC 5 d 1 q3w. Pts without disease progression were eligible for monotherapy with *nab*-P 100 mg/m^{2}d 1, 8 q3w until progression/unacceptable toxicity. Primary endpoint: percentage of pts discontinuing within the first 4 cycles due to treatment-emergent adverse events (TEAEs). Other endpoints: PFS, DCR, OS, ORR, and QoL. **Results:** Forty pts were treated during the first 4 cycles. Median age was 67.5 y, 60.0% were male, 92.5% were white, and 65.0% had nonsquamous histology. In the primary analysis, 9/40 pts (22.5%) discontinued due to TEAEs during induction. In total, 16/40 pts (40.0%) received *nab*-P as monotherapy. At the time of data cutoff, 4/40 pts remained on therapy beyond 11 cycles. In all treated pts, the median percentage of per-protocol dose of *nab*-P was 79.8% and the median *nab*-P dose intensity was 53.2 mg/m^2/week (expected, 66.67 mg/m^2/week). See table for other key safety and efficacy data. QoL by LCSS (global) was improved during the study, and similarly EQ-5D-5L dimensions were stable/improved at least once in the majority of pts. **Conclusions:** This *nab*-P–based regimen was well tolerated in PS 2 pts with advanced NSCLC. Efficacy outcomes are comparable with previous chemotherapy data with promising QoL. The results support the efficacy and tolerability of this regimen in these pts. NCT02289456. Clinical trial information: NCT02289456.

Safety	All Treated Pts N = 40
Grade ≥ 3 TEAEs of special interest, n (%)	
Neutropenia	9 (22.5)
Anemia	7 (17.5)
Thrombocytopenia	2 (5.0)
Peripheral neuropathy	1 (2.5)
Efficacy	
PFS, median (95% CI), mo	4.4 (3.2-5.7)
OS, median (95% CI), mo	8.6 (5.1-13.2)
ORR (RECIST v1.1), n (%)	11 (27.5)
DCR, %	30 (75.0)
SD	19 (47.5)
PR	11 (27.5)
CR	0
PD, %	2 (5.0)

9059 Poster Session (Board #385), Sat, 8:00 AM-11:30 AM

ABOUND.70+: Safety and efficacy of *nab*-paclitaxel/carboplatin (*nab*-P/C) in elderly patients (pts) with advanced non-small cell lung cancer (NSCLC). *First Author: Corey J. Langer, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: Treatment (tx) of elderly pts with NSCLC is challenging. *nab*-P/C demonstrated efficacy in a subset of pts with NSCLC ≥ 70 y in a phase III trial. ABOUND.70+ was designed to determine whether a 1-week break can further improve tolerability of *nab*-P/C in pts ≥ 70 y with NSCLC. Safety and efficacy were evaluated and are reported. **Methods:** Pts ≥ 70 y with tx-naive locally advanced/metastatic NSCLC were randomized (1:1) *nab*-P 100 mg/m^2 d 1, 8, 15 + C AUC 6 d 1 q3w (Arm A) or the same *nab*-P/C dose q3w followed by a 1-week break (Arm B). Primary endpoint: percentage of pts with either grade ≥ 2 peripheral neuropathy (PN) or grade ≥ 3 myelosuppression AEs. Key secondary endpoints: PFS, ORR, OS, for which statistical analyses do not control for type I error (*P* values unadjusted). **Results:** At interim evaluation, the primary endpoint was similar across arms, resulting in early closure of enrollment. In Arms A and B, 71 and 72 pts were randomized; median age was 76 and 75 y, majority of pts were male (57.7% vs 55.6%) and had ECOG PS 1 (70.4% vs 72.2%). There were no differences in histology across tx arms. See table for primary endpoint data. Median number of tx cycles for Arms A and B was 4.0 and 5.5, median cumulative *nab*-P dose was 875.0 and 1287.5 mg/m^2, and median weekly dose intensity was 62.0 and 54.1 mg/m^2. *nab*-P dose modifications (Arms A and B): ≥ 1 dose reduction in 64.7% and 58.6%, ≥ 1 dose delay in 58.8% and 48.6%, and ≥ 1 missed dose in 80.9% and 72.9%, respectively. Median PFS (Arms A and B) 3.9 vs 7.0 mo (HR 0.49; 95% CI, 0.30 - 0.79; *P* = 0.003), confirmed ORR 23.9% vs 40.3% (*P* = 0.037), and median OS 15.2 vs 16.2 mo (HR 0.76; 95% CI, 0.46 - 1.26; *P* = 0.292). **Conclusions:** Incidence of grade ≥ 2 PN or grade ≥ 3 myelosuppression AEs was similar between the 2 *nab*-P/C schedules in pts ≥ 70 y with advanced NSCLC. There appears to be a signal of improvement in PFS and ORR observed in Arm B, potentially due to increased tx exposure. NCT02151149 Clinical trial information: NCT02151149.

Primary endpoint.

Event, n (%)	Arm A n = 68	Arm B n = 70
Pts with either grade ≥ 2 PN or grade ≥ 3 myelosuppression	51 (75.0)	54 (77.1)
Grade ≥ 2 PN	25 (36.8)	25 (35.7)
Grade ≥ 3 myelosuppression	47 (69.1)	45 (64.3)
Neutropenia	38 (55.9)	38 (54.3)
Anemia	14 (20.6)	16 (22.9)
Thrombocytopenia	17 (25.0)	12 (17.1)

9060 Poster Session (Board #386), Sat, 8:00 AM-11:30 AM

Retinoblastoma mutation to predict poor outcomes in non-small cell lung cancer (NSCLC). *First Author: Priyanka Bhateja, University Hospital Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: Genomic profiling of tumor DNA has revealed the diversity in NSCLC. The retinoblastoma gene (*RB1)* encodes for RB pocket protein that plays an important role in cell cycle progression by interacting with various transcriptional factors. Here we determine the frequency and prognostic significance of *RB1*mutation in NSCLC and compare it to that in small cell lung cancer (SCLC). **Methods:** This IRB-approved retrospective review on NSCLC patients included Stage III and IV patients with genomic and clinical data. Primary outcome was median overall survival (OS) and secondary outcome was progression-free survival (PFS). OS and PFS were calculated by the Kaplan-Meier method and compared between mutant and wild-type (wt) *RB1*using the Log-Rank test. The effect of *RB1*mutation status on OS and PFS was further evaluated using the multivariable Cox model, controlling the effects of age, sex, stage, smoking history and chemotherapy. All tests are two-sided and *p*-values ≤ 0.05 were considered statistically significant. **Results:** We identified *RB1* mutation in 8.2% of NSCLC patients (16 of 195 patients). With a median follow-up of 15.1 months, the median OS for wt *RB1*was 28.3 months and for mutant *RB1* was 8.3 months (HR = 2.59, *p*-value = 0.002). The median PFS for wt *RB1* was 21.8 months vs 6.4 months for mutant *RB1* (HR = 2.85, *p*-value = 0.0002). *RB1* mutation was associated with worse OS (*p*= 0.017, HR = 2.17) and PFS (*p*= 0.005, HR = 2.37) in multivariate analyses after adjusting for traditional risk factors like, age, sex, stage, smoking history and chemotherapy. Interestingly, a previously described benign deletion (A16-A18) in RB1 protein was identified in 5 of the 16 *RB1* mutant patients and was associated with far worse outcomes compared to other *RB1* mutations. In contrast to NSCLC, *RB1* mutation was identified in 75% of 64 SCLC patients. Furthermore, wt *RB1* was associated with significantly shorter OS (*p*= 0.002), PFS (*p*= 0.004) and chemotherapy refractoriness (*p*= 0.033) in SCLC. **Conclusions:** *RB1* mutation is present in a minority of patients with advanced NSCLC and is associated with poor prognosis. In contrast, *RB1* mutation is present in the majority of SCLC patients and is associated with a favorable prognosis.

9061 Poster Session (Board #387), Sat, 8:00 AM-11:30 AM

Genetic subtypes of large cell neuroendocrine carcinoma (LCNEC) to predict response to chemotherapy. *First Author: Jules Derks, Maastricht University Medical Centre+, GROW School for Oncology and Developmental Biology, Maastricht, Netherlands*

Background: To treat LCNEC with non-small cell lung carcinoma type chemotherapy (NSCLC-ct, i.e. gemcitabine/taxanes or pemetrexed) or small cell lung carcinoma type (SCLC-ct, i.e. platinum-etoposide) is subject of debate. Molecular studies have identified two mutually exclusive subtypes in LCNEC, the co-mutated *TP53* and *RB1*and the *STK11*/*KEAP1* (predominantly *RB1* wildtype(^{wt})) group. We investigated if overall survival (OS) and progression free survival (PFS) correlates with targeted next-generation sequencing (TNGS) results in LCNEC treated with NSCLC-ct or SCLC-ct. **Methods:** For this population based retrospective cohort study all diagnoses of stage IV ct treated high grade neuroendocrine carcinomas (NEC, not being SCLC) were retrieved from the Netherlands Cancer Registry and Pathology Registry (PALGA) (2003-2012). Panel-consensus pathology revision of original tumor slides was performed on (N = 230) and TNGS for genes *TP53*, *RB1*, *STK11* and *KEAP1* analyzed with a multi-sample variant caller (Needlestack). **Results:** LCNEC was consensus diagnosed in 146/230 and 77 passed quality control for TNGS. Mean coverage was 2832x, a mutation(^{mt}) in *TP53* was present in 87%, *RB1*^{mt} in 46%, *STK11*^{mt} in 13% and *KEAP1*^{mt} in 18% of sequenced LCNEC. *RB1* was co-altered with *TP53* in 94% of LCNEC; mutually exclusive to *STK11*^{mt} (100%) but not *KEAP1*^{mt} (57%). NSCLC-ct or SCLC-ct was specified in 92% of patients and *RB1*^{wt} LCNEC treated with NSCLC-ct (n = 22) showed a trend to better OS compared to SCLC-ct (n = 13) (8.5 months (95% confidence interval (CI): [6.3-10.6]) vs. 5.8 [5.5-6.1] months, p = 0.055). Due to reported resistance in NECs we analyzed NSCLC-ct without pemetrexed-ct; OS was significantly longer for NSCLC-ct (n = 15) compared to SCLC-ct (9.6 [7.7-11.6] vs. 5.8 [5.5-6.1] months, p = 0.026). PFS of *RB1*^{wt} NSCLC-ct treated patients was significantly longer than SCLC-ct (p = 0.044), without pemetrexed (p = 0.018). In patients with *RB1*^{mt} LCNEC OS/PFS was not significantly different for NSCLC-ct vs. SCLC-ct. **Conclusions:** In LCNEC with *RB1*^{wt}, NSCLC-ct correlates with a more favorable outcome compared to SCLC-ct. However, *RB1*^{mt} *LCNEC* treated with NSCLC-ct do similarly worse as SCLC-ct.Prospective studies should be initiated.

9062 Poster Session (Board #388), Sat, 8:00 AM-11:30 AM

Response of germline and somatic smoothened (SMO) mutations in non-small cell lung cancer (NSCLC) to hedgehog inhibitor vismodegib. *First Author: Anne S. Tsao, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Smoothened (SMO) gene somatic mutations activate hedgehog signaling in basal cell cancers (BCC) and medulloblastomas but have not been reported in NSCLC. We detected somatic and germline *SMO*mutations in NSCLC patients (A-C) and sought to characterize the mutations further. **Methods:** We performed tumor/blood germline sequencing of *SMO* mutations, familial germline mutation testing (saliva specimens), somatic mutation analysis of TCGA lung carcinoma datasets, and germline mutation analysis of the TCGA and 3 additional large cohorts (n = 1933). To evaluate the functional significance of *SMO*P641A, HCC4011 lung cancer cells were transfected with a wild-type SMO or *SMO*P641A expression vector and a predictive model was created. **Results:** NSCLC *SMO*P641A *in vitro* activated the hedgehog pathway, and vismodegib/cyclopamine inhibited tumor cell growth. Structural modeling suggests that *SMO* P641A induces conformational changes and disrupts PTCH-SMO interaction leading to constitutive activation. In the NSCLC TCGA databases, somatic *SMO* mutations occur 1.7%. In the overall TCGA database, germline *SMO* P641A occurred in 0.11% of cancer patients (multiple cancers) compared with 0% in cancer-free individuals. Patient A (never-smoking SCC) had a 46% RECIST reduction within 6 weeks for 6 months on vismodegib. His 3-generation family pedigree identified germline *SMO*P641A in one daughter (who developed BCC early). Two additional NSCLC patients (B – germline P641A and C –M525L received vismodegib; B initially stabilized but stopped vismodegib after 14 weeks for toxicity while patient C had no response. **Conclusions:** *SMO* mutations are targetable, potentially heritable, oncogenic drivers in NSCLC and other cancers. Tumor genetic profiling should consider including *SMO* gene, especially in never-smoking lung SCC patients. Additional studies are needed to define the role of germline/somatic SMO alterations in promoting carcinogenesis, interactions with P53 alterations, and the responsiveness of different SMO mutations to hedgehog inhibitors. Currently, the ongoing ECOG-ACRIN MATCH study (NCT02465060) treats SMO/PTCH mutated patients with vismodegib.

9063 Poster Session (Board #389), Sat, 8:00 AM-11:30 AM

Primary resistance to *ALK* inhibitor in *ALK*-positive non-small-cell lung cancer. *First Author: Jin Kang, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: Crizotinib is a standard of care in anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancers (NSCLC). Undoubtedly, the resistance to crizotinib is a current bottleneck which resists its clinical application. However, there are few reports about the primary resistance to crizotinib, especially the difference between the primary and acquired resistance. **Methods:** Totally,171 ALK-positive NSCLC patients treated with crizotinib were reviewed at the Guangdong General Hospital in China from October 2010 to July 2016. The status of an ALK gene rearrangement was assessed by Vysis ALK Break Apart fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), or ALK Ventana immunohistochemistry (IHC). Among 18 patients with primary resistance, 12 had tumor tissue (n = 6) or plasma (n = 6) at the baseline and meanwhile tumor tissue (n = 2) or plasma (n = 2) specimens were collected for 4 patients after primary resistance. Next generation sequencing was used to test the tissue or plasma from 16 patients with primary resistance to crizotinib. **Results:** Among 171 patients treated with crizotinib, 47.9% (82/171) developed acquired resistance, and 10.5%(18/171) had primary resistance. Using the specimens at the baseline, there were 6 (33.0%) patients with uncommon ALK fusion partners, 4 (22.2 %) with BIM deletion polymorphism, 2 (11.1%) with PTEN/mTOR mutations, and 1 (5.5 %) with a pre-existing ALK G3709A mutation.These uncommon ALK fusion partners included ZC3H8-ALK, ALK-LOC102723854 and ALK-DTNB-ASXL2. In addition, one patient was found to coexsist with *KIT* mutation after primary resistance. Median PFS was significantly shorter in patients with primary resistance than those with acquired resistance (2.2 vs. 10.8 months, P < 0.001). **Conclusions:** Uncommon ALK fusion partners, *BIM* deletion polymorphism, PTEN/mTOR mutation, pre-existing ALK G3709A mutation and *KIT* mutation might contribute to molecular mechanisms of primary resistance to crizotinib in ALK-positive NSCLC. Further investigations are warranted to overcome these primary resistances.

9064 Poster Session (Board #390), Sat, 8:00 AM-11:30 AM

Updated efficacy and safety of the j-alex study comparing alectinib (ALC) with crizotinib (CRZ) in ALK-inhibitor naïve *ALK* fusion positive non-small cell lung cancer (*ALK*+ NSCLC). *First Author: Yuichi Takiguchi, Graduate School of Medicine Chiba University, Chiba, Japan*

Background: ALC is a highly selective, CNS-active ALK tyrosine kinase inhibitor. In the J-ALEX study, ALC proved superior efficacy and tolerability compared to CRZ at the pre-planned interim analysis at 83 progression free survival (PFS) events (51% of target events) . Here we report the updated data with a further 10 months of follow up. **Methods:** Patients with advanced *ALK+* NSCLC were randomized 1:1 to receive ALC 300 mg b.i.d or CRZ 250 mg b.i.d and stratified by ECOG PS, treatment line, and clinical stage. Study Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was PFS according to the blinded independent review. Secondary endpoints included investigator-assessed PFS, overall survival, objective response rate and safety. **Results:** From Nov 2013 to Aug 2015, 207 patients were enrolled. Data cut off for the present analysis was Sep 2016. Median durations of PFS follow up were 20.5 months in the ALC arm and 20.4 months in the CRZ arm with 116 events by independent review observed. The updated PFS HR was 0.38 (95% CI: 0.26-0.55, $p< 0.0001$). Median PFS was 25.9 months (95% CI: 20.3-not estimated) with ALC and 10.2 months (95% CI: 8.3-12.0) with CRZ. For patients without brain metastasis at baseline (n = 164), ALC prevented CNS metastasis onset compared to CRZ (HR = 0.19, 95% CI: 0.07-0.53). For patients with brain metastasis at baseline (n = 43), ALC also prevented CNS progression compared to CRZ (HR = 0.51, 95% CI: 0.16-1.64). Adverse events (AEs) with frequency of more than 30% were constipation (37.9%) and nasopharyngitis (32.0%) in the ALC arm, while in the CRZ arm nausea (76.0%), diarrhea (74.0%), vomiting (57.7%), visual disturbance (54.8%), dysgeusia (51.9%), constipation (46.2%), increased ALT (32.7%), and increased AST (31.7%) were observed. Grade 3-4 AEs occurred with greater frequency in the CRZ arm (ALC: 32.0% vs CRZ: 56.7%). There were no Grade 5 AEs in either arm. **Conclusions:** In the updated analysis, ALC consistently showed superior efficacy compared to CRZ in systemic disease and prevention of CNS progression. ALC was also associated with a more favorable tolerability profile than CRZ. Clinical trial information: JapicCTI-132316.

9065 Poster Session (Board #391), Sat, 8:00 AM-11:30 AM

Activity of brigatinib (BRG) in crizotinib (CRZ)-resistant ALK+ NSCLC patients (pts) according to ALK plasma mutation status. *First Author: Lyudmila Bazhenova, University of California San Diego Moores Cancer Center, La Jolla, CA*

Background: BRG is a potent and selective ALK inhibitor with preclinical and clinical activity against wild-type ALK and a broad range of mutants associated with clinical CRZ resistance, including G1202R. Herein we examine the association between BRG efficacy and ALK mutation status using plasma specimens from the initiation of BRG treatment (baseline [BL]) and the end of BRG treatment (EOT) in CRZ-resistant ALK+ NSCLC pts enrolled in the BRG Ph1/2 or pivotal Ph2 (ALTA) trials. **Methods:** Plasma samples were analyzed using the Resolution Bioscience ctDx Lung Panel v3.0. BRG activity was described using the confirmed objective response rate (cORR) (RECIST v1.1). Data are reported as of May 31, 2016 for the Ph1/2 (NCT01449461) and ALTA (NCT02094573) trials. **Results:** Of 291 CRZ-resistant ALK+ NSCLC pts enrolled in the Ph1/2 (N = 69) and ALTA (N = 222) trials, evaluable plasma samples were obtained from 67 pts at BL. cORR to BRG in these pts was 49% (33/67). An ALK fusion was detected in plasma in 45% (30/67) of these pts (cORR 57% [17/30]), of whom 33% (10/30) had secondary ALK mutations (cORR 50% [5/10]) and 67% (20/30) did not (cORR 60% [12/20]). Best responses in pts with secondary ALK mutations were: 2 CR (ALK amplification [Amp] copy number [CN] = 10; T1151M); 3 PR (L1196M; E1408V; Amp CN = 6); 4 SD (L1196M; E1419K; F1174C; C1156Y+S1206F+G1269A); 1 PD (T1151R+C1156Y+E1161D+F1174L). Of 67 pts with evaluable plasma at BL, 35 discontinued BRG therapy, of whom 20 had evaluable samples collected at EOT. No new mutations were detected at EOT in 75% (15/20) of pts. Complex mutation patterns were associated with resistance in the remaining 25% (5/20): High-level ALK-Amp (CN = 58); ALK-Amp (CN = 14)+MET-Amp (CN = 6); ALK-S1206F+S1206C+Amp (CN = 6); ALK-G1202R+L1196M+L1198Q; ALK-G1202R+BRAF-V600E+KRAS-G12D. **Conclusions:** ALK fusions were detected in plasma in $<$ 50% of CRZ-resistant ALK+ NSCLC pts. BRG had substantial activity in ALK fusion–positive pts with a range of CRZ-resistance mutations. Neither primary nor secondary resistance to BRG was associated with any single plasma ALK mutation. The therapeutic implications of complex secondary resistance patterns associated with BRG require further exploration. Clinical trial information: NCT01449461, NCT02094573.

9066 Poster Session (Board #392), Sat, 8:00 AM-11:30 AM

Patient-reported outcomes and quality of life in ALTA: The randomized phase 2 study of brigatinib (BRG) in advanced ALK+ non–small cell lung cancer (NSCLC). *First Author: Corey J. Langer, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: The ALTA trial (NCT02094573), an open-label, phase 2, randomized, multicenter, international study, evaluated the efficacy and safety of BRG (arm A: 90 mg qd and arm B: 180 mg qd with 7-day lead-in at 90 mg) in patients (pts) with advanced anaplastic lymphoma kinase–positive (ALK+) NSCLC whose disease had progressed on prior therapy with crizotinib (CRZ). The objective of this analysis was to describe pt-reported outcomes (PROs) in the ALTA study. **Methods:** PROs were collected using the EORTC QLQ-C30 at baseline and on the first day of each cycle. Multivariable mixed effects models were constructed to estimate adjusted mean changes from baseline in QLQ-C30 scores. Cumulative distribution function (CDF) plots of EORTC QLQ-C30 change scores from baseline to Cycle 5 were generated to evaluate a clinically meaningful threshold of individual pt change, which was determined through anchor- and distribution-based methods. **Results:** Among 222 randomized pts, 208 (94%) completed the questionnaire at baseline and at least 1 on-treatment PRO follow-up. In multivariable analyses, there were no statistically significant differences in Global Health Status (GHS)/QOL between arms over time when adjusted for baseline score, ECOG status, and presence of liver or bone metastases. At Cycle 5, CDF plots indicated that 80% of all pts experienced an increase or no change in GHS/QOL scores; 50% of all pts experienced a clinically meaningful improvement. At Cycle 5, 80% of all pts reported a reduction or no change in pain score, and 90% of all pts reported a reduction or no change in dyspnea score. Approximately 30% of pts had clinically meaningful reductions in these symptoms. Less than 15% and $<$ 5% of all pts reported clinically meaningful worsening of nausea/vomiting and diarrhea scores, respectively, at Cycle 5. **Conclusions:** Treatment with BRG for CRZ-refractory ALK+ NSCLC resulted in improved GHS/QOL scores and reduction in pain and dyspnea scores, while rates for nausea/vomiting and diarrhea were minimally worse. These pt-level benefits support BRG as a promising treatment option. Clinical trial information: NCT02094573.

9067 Poster Session (Board #393), Sat, 8:00 AM-11:30 AM

Differential crizotinib efficacy among ROS1 fusion partners in ROS1-positive non-small cell lung cancer. *First Author: Shun Lu, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China*

Background: ROS1 rearrangement non–small-cell lung cancers can be effectively treated with ALK inhibitor such as crizotinib, but the response magnitude and duration are heterogeneous. Several ROS1 fusion partners have been identified, but few studies have focused on the effects of different fusion partners on the efficacy of crizotinib. **Methods:** Among 49 RT-PCR assay ROS1 rearrangement patients treated with crizotinib between April 2014 and November 2016, we identified 36 patients with tumor specimens that could be evaluated for the presence of different ROS1 fusion partners by Sanger sequencing. Patients continued crizotinib until RECIST-defined progression. We retrospectively evaluated the efficacy of crizotinib on the basis of the objective response rate(ORR), progression-free survival (PFS) and overall survival (OS) according to the different ROS1 fusion partners. **Results:** The most frequent ROS1 fusion partner was CD74-ROS1 (CD74-E6; ROS1-E34) in 16 patients (44.4%), followed by EZR-ROS1 (EZR-E10; ROS1-E34) in 7 patients (19.4%), SDC4 (SDC4-E2; ROS1-E32) in 4 patients (12%), SLC34A2-ROS1 (SLC34A2-E14del; ROS1-E32) in 2 patients (5.6%) and TPM3 (TPM3-E8; ROS1-E35) in 2 patients (5.6%). We also found that SDC4+EZR (SDC4-E2; ROS1-E32/EZR-E10; ROS1-E34) in 2 patients (5.6%), dual CD74-ROS1 (CD74-E6; ROS1-E32/34) in 2 patients (5.6%), CD74+SDC4 (SDC4-E2; ROS1-E32/CD74-E6; ROS1-E34) in 1 patient (2.8%). ORR was 83.3% in all patients, whereas it was 70.58% and 92.35% in the CD74 and non–CD74 groups, respectively (P = 0.17). The median PFS was longer in non–CD74 than in those with CD74 (median PFS, 17.67 months [95% CI, 12.14 to 23.19] vs 19.30 months [95% CI, not reached], respectively; P = 0.405) with no statistical significance. The median OS was significantly longer in patients with non–CD74 than in those with CD74 (median OS, 28.07 months [95% CI, 23.93 to 32.1] vs not reached, respectively; P = 0.043). Multivariable analysis identified 1 significant factor associated with OS, brain metastasis before crizotinib treatment (P $<$ 0.001). **Conclusions:** Our results indicate the better OS of crizotinib in patients with non–CD74 vs CD74. The ROS1 fusion partnerS might affect the efficacy of ALK-TKIs.

9068 Poster Session (Board #394), Sat, 8:00 AM-11:30 AM

Cost-effectiveness analysis comparing companion diagnostic tests for EGFR, ALK and ROS-1 versus next-generation sequence (NGS) in advanced adenocarcinoma lung cancer patients. *First Author: Luciene Schluckebier, Brazilian Cancer Foundation, Rio De Janeiro, Brazil*

Background: Success of a target therapy is directly correlated with the accuracy of its companion diagnostic test. Without a corresponding biomarker, target therapy may yield shorter survival, waste time, increase burdens and costs. As important as conducting cost-effectiveness studies for therapies, it is also valuable to compare different molecular tests. In lung cancer, the mutational status of EGFR and translocation of ALK and ROS-1 are commonly tested to offer the best intervention. Our objective is to evaluate the cost-effectiveness of a unique exam using NGS versus other routinely used tests such as the ones which involve RT-PCR and FISH. **Methods:** Target population is NSCLC, adenocarcinoma, and candidates to first-line therapy. Strategy 1: test EGFR mutation if EGFR test is negative, individual follow to FISH for ALK; if FISH is negative, follow to FISH for ROS-1. Strategy 2: differs from 1 since FISH for ALK and ROS are requested together. Strategy 3: all individuals are submitted to NGS (multicomplex platform which include EGFR, ALK, ROS-1 and other genes). Tests could also be classified as unknown due to the quality of tumor sample. Prevalence of biomarker, test accuracy and proportion of unknown results were used to calculate each decision tree branch. Sensitivity and specificity was obtained from literature review using Sanger as reference standard for RT-PCR tests and NGS. The study was analyzed from a healthcare-payer perspective based on Brazilian private sector. Costs were based on data from diagnostic companies, ANS and AMB-CBHPM 2016. **Results:** The use of NGS added 24% extra cases correct identified as well as extra costs (US$ 800.76; PPP 2015) attributed to the molecular testing. The ICER comparing NGS with sequential tests was US$ 3,381.82/correct case detected. Comparing strategy 2:1, the ICER was US$937.86/correct case detected. **Conclusions:** this study is part of an effort to integrate companion diagnostics discussions on precision medicine and covered drugs in the Brazilian health system. These findings can also subsidy cost-effectiveness studies that incorporates subsequent treatments and survival.

9069 Poster Session (Board #395), Sat, 8:00 AM-11:30 AM

Baseline frequency of brain metastases and outcomes with multikinase inhibitor therapy in patients with *RET*-rearranged lung cancers. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In phase 2 trials, multikinase inhibitors with activity against RET are active in a subset of patients (pts) with *RET*-rearranged lung cancers (response rate of 28%, phase 2 study of cabozantinib; Drilon et al Lancet Oncol 2016). Data on the incidence of brain metastases and outcomes with multikinase inhibitor therapy in pts with intracranial disease have not previously been reported. **Methods:** The frequency of brain metastases at diagnosis of metastatic disease was evaluated in pts accrued to a global registry of *RET*-rearranged lung cancer pts identified by a multicenter network of thoracic oncologists (Gautschi et al JCO 2017). A proportion of pts were treated with 9 multikinase inhibitors including cabozantinib, vandetanib, lenvatinib, alectinib, and ponatinib. On a prospective phase 2 trial (NCT01639508), patients with asymptomatic brain metastases were eligible. Intracranial response to cabozantinib (RECIST v1.1) was evaluated in an exploratory fashion. **Results:** 114 registry pts with *RET*-rearranged lung cancers had metastatic disease at diagnosis. Baseline brain metastases were identified in 27% (95%CI 18-34%, n = 20/75) of pts with available information. No differences ($p > 0.05$) in age, smoking history, or upstream fusion partner (*KIF5B* 100% vs 84%, with and without brain metastases, p = 0.53) were noted. In 37 pts treated with multikinase inhibitors with activity against RET, there were no significant differences in median PFS (2.1 vs 2.1 months, p = 0.41) or median OS (3.9 vs 7.0 months, p = 0.10) in pts with (n = 10) and without (n = 27) brain metastases. On a phase 2 trial of cabozantinib, baseline untreated brain metastases were present in 5 pts. Intracranial disease control (stable disease; -34% and -1% in 2 pts with measurable disease) was achieved in 4 of 4 pts with measurable or evaluable intracranial disease with time to treatment discontinuation ranging from 2.4 months to 2.9 years. **Conclusions:** Brain metastases are present in a substantial proportion of *RET*-rearranged lung cancer pts. Intracranial disease control can be achieved in select pts by a multikinase inhibitor. Novel RET-directed targeted therapy strategies should address intracranial disease. Clinical trial information: NCT01639508.

9070 Poster Session (Board #396), Sat, 8:00 AM-11:30 AM

A single-arm phase II trial of afatinib in pretreated patients with advanced NSCLC harboring a *HER2* mutation: The ETOP NICHE trial. *First Author: Egbert F. Smit, Vrije Universiteit VU Medical Centre, Amsterdam, Netherlands*

Background: *HER2* mutations are identified in about 2% of lung adenocarcinomas and are critical for lung carcinogenesis. Afatinib is a selective and irreversible erbB family blocker with a manageable toxicity profile and promising results in small retrospective studies targeting HER2 in NSCLC. **Methods:** NICHE is a single-arm phase II trial exploring the potential of afatinib to control disease (complete or partial response or disease stabilization for ≥12 weeks) in pre-treated patients with advanced NSCLC harboring *HER2* exon 20 mutations. Patients were treated with afatinib 40 mg/day *p.o.* until tumor progression or lack of tolerability. A Simon's two stage phase II design was adopted, to explore whether afatinib can achieve a DCR of 75%, as opposed to a DCR of 50% under the current treatment options. For a 1-sided type I error of 10% and power of 80%, a total of 22 patients were needed. **Results:** As of 24 November 2016, 13 patients were recruited into the trial. Median age was 60 years, 69% female and 62% never smokers. The overall toxicity profile was in the expected range, with 5 patients experiencing serious adverse events (dyspnea, diarrhea, dehydration, epistaxis, pleural, pericardial and renal insufficiency). The median follow-up was 23 weeks (IQR 12 – 39). Three patients died and 10 were still on follow-up, among them five were still on treatment. Total of 7 patients (54%) achieved DC at 12-weeks, 3 patients had PD before and 3 at 12-weeks. The 12-week PFS was 51% (95% CI: 22 - 75) and the median PFS 13 weeks (95% CI 6 - NE). In the 1st stage analysis of the Simon's design, with 9 patients included, the stopping boundary was crossed. Therefore and upon recommendations of the ETOP IDMC, recruitment into the trial was stopped prematurely in December 2016. Treatment and follow-up of the enrolled patients continues as planned. **Conclusions:** Based on the interim results, afatinib did not show the expected potential to control disease in this patient population. However in the full analysis set with 13 patients, clear signs of activity were seen. A comprehensive biomolecular analysis of the tumors is currently ongoing in order to identify a subgroup of patients who might still derive benefit from afatinib treatment. Clinical trial information: NCT02369484.

9071 Poster Session (Board #397), Sat, 8:00 AM-11:30 AM

Afatinib in patients with metastatic *HER2*-mutant lung cancers: An international multicenter study. *First Author: Wei-Chu Victoria Lai, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Human epidermal growth factor 2 (*HER2, ERBB2*) mutations have been identified as oncogenic drivers in 3% of lung cancers. Afatinib is an irreversible tyrosine kinase inhibitor of HER1 (EGFR), HER2 and HER4 and has been described in case reports to have activity in *HER2*-mutant lung cancers. However, there is little data to inform the clinical use of afatinib. **Methods:** We reviewed patients with metastatic *HER2*-mutant lung cancers treated with afatinib among 7 institutions between 2009 and 2016. The primary endpoint was investigator assessed overall response rate using RECIST v1.1. Other data collected included types of *HER2* mutations, duration of afatinib treatment and overall survival. **Results:** We identified 27 patients with metastatic *HER2*-mutant lung cancers treated with afatinib. Median age at diagnosis was 63 (range 40 to 84); majority were men (n = 16; 59%) and never-smokers (n = 18; 67%). All tumors were adenocarcinomas, and the majority were Stage IV at initial diagnosis (n = 16; 59%). A 12-base pair (bp) in-frame insertion YVMA in exon 20 (p.A775_G776insYVMA) was present in 16 patients (59%). In addition, there were three 9-bp insertions, two 3-bp insertions and two single bp substitutions (L755F and D769H) in exon 20; two single bp substitutions (S310F) in exon 8; one exon 17 V659E mutation; and one single-nucleotide polymorphism (Ile655Val). Median duration on afatinib was 2 months (range 1 to 27); median line of prior treatment was 3 (range 1 to 6). Eight patients had previously received trastuzumab prior to afatinib and one concurrently with afatinib. Overall response rate was 15% (n = 4; 95% CI 4 to 34%); the four partial responses lasted 5, 5, 6 and 10 months. The 3 longest partial responders had a 12-bp insertion in exon 20 (YVMA); the remaining partial responder had a 9-bp insertion in exon 20. Median overall survival from diagnosis date of metastatic disease was 23 months (95% CI 18 to 62). **Conclusions:** Afatinib produced partial responses in 15% of patients with metastatic *HER2*-mutant lung cancers, including insertion YVMA. Our findings confirm the activity of afatinib and provide data supporting a framework for its use in the care of patients with *HER2*-mutant lung cancers.

9072 Poster Session (Board #398), Sat, 8:00 AM-11:30 AM

***BRAF* fusions in clinically advanced non-small cell lung cancer: An emerging target for anti-*BRAF* therapies.** *First Author: Venkataprasanth P. Reddy, Shawnee Mission Cancer Center, Westwood, KS*

Background: Although far less common than *BRAF* V600E base substitutions (subs) classically associated with melanomas and colorectal carcinomas, *BRAF* subs occur in 1-2% of non-small cell lung cancer (NSCLC). *BRAF* fusions are emerging treatment targets for Spitzoid melanomas and other solid tumors. The frequency of *BRAF* fusions and targeting potential in NSCLC has not been widely described. **Methods:** Hybridization capture-based comprehensive genomic profiling (CGP) was performed on 17,128 NSCLC FFPE samples sequenced to a mean coverage depth of > 550X for up to 315 cancer-related genes plus 37 introns from 19 genes frequently rearranged in cancer. Genomic alterations (GA) included short variant (SV) base subs and insertions/deletions, copy number alterations, and rearrangements/fusions. Tumor mutational burden (TMB; mut/Mb) was calculated on up to 1.1 Mb of sequenced DNA. **Results:** *BRAF* fusions were identified in 42/17,128 (0.2%) NSCLC profiled. Median patient age was 67 (range 44-93 yrs). Of the *BRAF* fusion positive NSCLC, 55% were female. Biopsies were obtained from primary lung tumor (48%) and metastatic sites (52%). The most frequent 5' partners were *AGK*, *DOCK4*, and *TRIM24*. Multiple novel *BRAF* fusions were identified. The genes most frequently co-altered with *BRAF* fusions were *TP53* (67%), *CDKN2A* (31%), *EGFR* (29%) and *CDKN2B* (26%). Overall TMB in the *BRAF* fusion positive cohort was low (median 3.8 mut/Mb), although 3/42 cases (7%) had > 20 mut/Mb. Of the *BRAF* fusion driven NSCLC, 10 cases (24%) featured *EGFR* SV alterations. Two *BRAF* fusion/*EGFR* SV cases featured primary exon 19 deletion and T790M mutation. Examples of *BRAF* fusion driven NSCLC responding to a combination of *BRAF* and MEK inhibitors (MEKi) will be presented. **Conclusions:** NSCLC *BRAF* fusions are a rare GA that may be associated with acquired resistance in a subset of *EGFR*-mutated NSCLC progressing on anti-*EGFR* TKI therapies. Given clinical evidence for the activity of targeted therapy approaches, molecular eligibility for clinical trials of MEKi should include these variants. The clinical evidence for responsiveness of *BRAF* fusion driven NSCLC provides an opportunity to personalize treatments and improve clinical outcomes for patients.

9073 Poster Session (Board #399), Sat, 8:00 AM-11:30 AM

Targeted therapy for non-small cell lung cancer (NSCLC) with HER2, BRAF, or hedgehog alterations: Interim data from MyPathway. *First Author: John D. Hainsworth, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: Treatments targeting critical molecular alterations (EGFR, ALK, and ROS1) in NSCLC are highly effective. MyPathway (NCT02091141) is an ongoing, phase 2, multi-basket study evaluating the efficacy of targeted treatment in non-indicated tumor types harboring alterations in the HER2, BRAF, Hedgehog (Hh), or EGFR pathways. Interim results in NSCLC are presented. **Methods:** Patients with previously treated advanced NSCLC and alterations in the HER2 (amplification and/or mutation), BRAF (V600E or other mutations), Hh (SMO or PTCH-1 mutations), or EGFR (mutations other than known activating mutations) pathways received standard doses of pertuzumab + trastuzumab, vemurafenib, vismodegib, or erlotinib, respectively, until disease progression or unacceptable toxicity. The HER2, BRAF, and Hh cohorts are included in this analysis. The primary endpoint is investigator-assessed objective response rate (ORR, defined as complete response [CR] + partial response [PR]) by RECIST v1.1. **Results:** As of November 30, 2016, 61 patients with NSCLC and HER2 (n = 36), BRAF (n = 22), or Hh (n = 3) alterations have been treated (median age of 64 years, 49% male, 85% adenocarcinoma, and a median of 2 previous regimens). Median treatment duration was 1.8 (range, 0–21.4) months. Efficacy in the 55 patients with the minimum required follow-up for efficacy analysis is summarized in the table. **Conclusions:** Targeted therapy is active in patients with previously treated NSCLC harboring BRAF V600E mutations or HER2 alterations (amplifications and/or mutations). These cohorts have been expanded as MyPathway accrual continues. Additional efficacy data and details regarding molecular alterations will be presented. Clinical trial information: NCT02091141.

	Patients, n	ORR, n (%)	Clinical benefit rate[a], n (%)	Durations of objective responses, months
HER2 alterations[b]	31	6 (19)	10 (32)	< 1+, 3+, 5+, 6, 8, 10
BRAF V600E	14	6 (43) (1 CR)	8 (57)	4, 4, 5, 5+, 10+, 14
BRAF other	7	0	1 (14)	NA
Hh	3	0	1 (33)	NA

+ indicates response is ongoing. [a]CR + PR + stable disease > 4 months. [b]HER2 amplified and/or mutated.

9074 Poster Session (Board #400), Sat, 8:00 AM-11:30 AM

Efficacy of vemurafenib in patients (pts) with non-small cell lung cancer (NSCLC) with *BRAF*^{V600} mutation. *First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *BRAF*^{V600} mutations occur in 1–2% of pts with NSCLC. We previously reported the efficacy of vemurafenib, a selective BRAF^{V600} inhibitor, in *BRAF* mutation-positive non-melanoma tumors (VE-BASKET study). We now present final data for the expanded NSCLC cohort. **Methods:** This open-label, histology-independent, phase 2 study included 6 prespecified cohorts (including NSCLC) plus one 'all-others' cohort. Pts received vemurafenib (960 mg bid) until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (RECIST v1.1). Secondary endpoints included best overall response rate, duration of response (DoR), progression-free survival (PFS), and overall survival (OS). Because the pre-specified clinical benefit endpoint was met in the initial NSCLC cohort, the cohort was expanded. ClinicalTrials.gov identifier NCT01524978. **Results:** Database lock was 12 Jan 2017. Of 208 pts enrolled at 25 centers worldwide, 62 pts had NSCLC: median age 65 years; 56% male; 13% had no prior systemic therapy; 50% had ≥2 prior therapies. Responses were seen in previously treated and untreated pts (Table). The most common all-grade adverse event (AE) was nausea (40%); grade 3–5 AEs included keratoacanthoma (15%) and squamous cell carcinoma of the skin (15%). Six pts discontinued vemurafenib due to AEs; two had non-treatment-related fatal AEs. **Conclusions:** Vemurafenib showed evidence of encouraging efficacy in pts with NSCLC with *BRAF*^{V600} mutation, with prolonged PFS in previously untreated pts; median OS was not estimable due to ongoing responses. The safety profile of vemurafenib was similar to that seen in melanoma studies. Our results suggest a role for BRAF inhibition in NSCLC with *BRAF* mutations. Clinical trial information: NCT01524978.

	Previously untreated (n=8)	Previously treated (n=54)	All (n=62)
Confirmed response, n (%) 95% CI	3 (38) 9–76	20 (37) 24–51	23 (37) 25–50
Stable disease, n (%)	5 (63)	21 (39)	26 (42)
Missing/not evaluable, n (%)	0	5 (9)	5 (8)
Median DoR, months (95% CI)	NE (7.2–NE)	6.1 (5.5–18.4)	7.2 (5.5–18.4)
Median PFS, months (95% CI)	12.9 (4.0–NE)	6.1 (5.1–8.3)	6.5 (5.2–9.0)
Median OS, months (95% CI)	NE (6.0–NE)	15.4 (8.2–22.6)	15.4 (9.6–22.8)

NE: not estimable (insufficient progression and death events)

9075 Poster Session (Board #401), Sat, 8:00 AM-11:30 AM

Updated survival of patients (pts) with previously treated *BRAF* V600E–mutant advanced non-small cell lung cancer (NSCLC) who received dabrafenib (D) or D + trametinib (T) in the phase II BRF113928 study. *First Author: David Planchard, Gustave Roussy, Villejuif, France*

Background: *BRAF* V600E mutations occur in 1% to 2% of lung adenocarcinomas and act as oncogenic drivers. Initial cohorts of the BRF113928 (NCT01336634) trial evaluated efficacy and safety of D monotherapy (cohort A; n = 78) or D + T (cohort B; n = 57) in pts with previously treated *BRAF*V600E–mutant metastatic NSCLC. At primary analysis, overall response rates (ORRs) were 33.3% and 63.2% in pts who received D or D + T, respectively. Furthermore, durable response (median duration of response [DOR], 9.0 mo) was observed in D + T pts. Here, we present an updated survival analysis based on additional follow-up. **Methods:** In this phase 2 trial, 2 cohorts (A and B) of pts with previously treated metastatic *BRAF*V600E–mutant NSCLC were enrolled sequentially. The primary endpoint was investigator-assessed ORR. Secondary efficacy endpoints included progression-free survival (PFS), DOR, and overall survival (OS). D and T were dosed orally at the established phase 2 dose of D 150 mg twice daily and T 2 mg once daily. **Results:** This updated analysis had a median follow-up of 16.2 mo, which represented an additional 10 mo of follow-up. Median OS was 12.7 mo (95% CI, 7.3-16.3) with 57 deaths reported for pts treated with D monotherapy and 18.2 mo (95% CI, 14.3-not estimable [NE]) with 33 deaths reported for pts treated with D + T. Detailed efficacy results are presented in the table. Investigator-assessed ORR, DOR, and PFS were supported by independent review committee assessments. No new safety signals were observed for D + T. **Conclusions:** This update of the BRF113928 study confirms that durable responses and encouraging survival were achieved with combination D + T in pts with *BRAF*V600E–mutant NSCLC. Clinical trial information: NCT01336634.

	D (n = 78)	D + T (n = 57)
ORR, n (%)[a]	25 (32.1)[b]	38 (66.7)
95% CI	21.9-43.6	52.9-78.6
DOR, median, mo[a]	9.6[b]	9.8
95% CI	5.4-15.2	6.9-16.0
PFS, median, mo[a]	5.5[b]	10.2
95% CI	2.8-7.3	6.9-16.7
12-mo PFS, %	26	43
95% CI	15.9-36.6	29.8-55.7
24-mo PFS, %	14	22
95% CI	7.2-24.1	11.4-35.6
OS, median, mo	12.7	18.2
95% CI	7.3-16.3	14.3-NE
12-mo OS, %	52	66
95% CI	39.7-62.3	52.4-77.1
24-mo OS, %	31	39
95% CI	20.8-42.0	25.5-52.1

[a]Investigator assessment. [b] Data cutoff, November 21, 2014.

9076 Poster Session (Board #402), Sat, 8:00 AM-11:30 AM

Immune marker profiling and PD-L1, PD-L2 expression mechanisms across non-small cell lung cancer mutations. *First Author: Maria Toki, Yale School of Medicine, New Haven, CT*

Background: PD-1/PD-L1 axis inhibitors have been proven effective, especially in patients expressing Programmed Death Ligand 1 (PD-L1). Their clinical efficacy in patients with epidermal growth factor receptor (EGFR) activating mutations is still unclear, while KRAS mutations seem to be associated with high response rates. In this study we investigated the expression of PD-L1, PD-L2 and Tumor Infiltrating Lymphocyte (TIL) status as a function of mutation status in Non-Small Cell Lung Cancer (NSCLC). **Methods:** We used the AQUA method of quantitative fluorescence (QIF) to compare PD-L1 and PD-L2 expression and to characterize TILs populations and their activation status in over 150 NSCLC patient tumors with known mutation status. EGFR activation was assessed in situ using the proximity ligation assay (PLA) for EGFR and GRB2 and T cell activation was assessed using a novel multiplexed QIF assay including CD3, Granzyme B and Ki67. **Results:** PD-L1 tumor and stroma expression was significantly lower in EGFR mutant compared to KRAS mutant ($p = 0.009$) and EGFR/KRAS Wild Type ($p < 0.0001$) tumors, while they had a higher frequency of PD-L2 expression. Conversely, KRAS mutants had significantly lower PD-L2 tumor and stroma expression but they were also more inflamed with higher CD4+, CD8+ and CD20+ TILs. Subgroup analysis of patients by their TILs activation status revealed that EGFR mutants had a very high frequency of inactive TILs even though lymphocytes were present in the tumor microenvironment. In contrast, in KRAS mutants, when TILs were present, they were almost always active. Finally, we find that PLA-defined activated EGFR correlated with increased PD-L1 expression in EGFR mutants but not in EGFR WT, while TIL activation was associated with higher PD-L1 in EGFR/KRAS WT. **Conclusions:** Our findings are consistent with the unique biology of EGFR mutant tumors. The high frequency of inactive TILs could explain the low immune therapy response rates in this patient group. Similarly, in this group, the reason PD-L1 expression fails to predict response may be due to expression as a result of constitutive oncogenic signaling rather than immune signaling, which would be associated with high PD-L1 levels and TILs activation.

9077 Poster Session (Board #403), Sat, 8:00 AM-11:30 AM

Nivolumab-induced interstitial lung disease (ILD) in Japanese patients with non-small cell lung cancer: A study on risk factors for fatal outcome. *First Author: Terufumi Kato, Kanagawa Cancer Center, Yokohama, Japan*

Background: We investigated case reports of nivolumab-induced ILD in patients with non-small cell lung cancer to identify risk factors for poor prognosis of ILD. **Methods:** Among data obtained during post-marketing surveillance of nivolumab, case reports of ILD with detailed clinical course and chest imaging (CT) findings were assessed by the ILD Expert Review Committee, which consists of respiratory medicine specialists and expert chest radiologists. The imaging findings were examined and classified into those with typical or atypical patterns. Atypical patterns included shadows limited to surrounding tumors designated as "peritumoral infiltration", relapse of radiation pneumonitis, worsening of underlying infection, and predominant shadow in diseased side. CT pattern was classified as DAD (diffuse alveolar damage) or non-DAD. Data were analyzed using a multivariate stepwise logistic regression analysis. **Results:** Among 160 reported cases of ILD, 140 cases were considered to be induced by nivolumab. Imaging findings showed typical patterns in 92 patients, and 23 (25.0%) died of ILD. Atypical patterns were noted in 48 patients, and 5 (10.4%) died of ILD. The following table summarizes the results of univariate and multivariate analyses of risk factors for poor prognosis of ILD. See table. DAD pattern was observed in 20, 14 (70%) among them showed fatal outcome, whereas non-DAD pattern showed it in 14/120 (11.7%). Male and pretreatment CRP level were significant risk factors for fatal outcome. **Conclusions:** Nivolumab-induced ILD may show some atypical pattern that was not seen in conventional chemotherapy or EGFR-TKI. Outcome of patients with atypical patterns was better than those with typical patterns. DAD pattern at CT, male, and pretreatment level of CRP were identified as risk factors of fatal outcome.

Factors	Category	N	Death due to ILD N (%)	Univariate analysis Odds ratio [95% confidence interval]	Multivariate analysis P value
Gender	Male	117	25 (21.4)	1.8	0.0135
	Female	23	3 (13.0)	[0.5, 6.6]	
ILD image pattern	DAD pattern	20	14 (70.0)	17.7	<0.0001
	Non-DAD pattern	120	14 (11.7)	[5.8, 53.4]	
Baseline CRP (mg/dL)	<5	78	13 (16.7)	2.8	0.0162
	≥5	31	11 (35.5)	[1.1, 7.1]	

9078 Poster Session (Board #404), Sat, 8:00 AM-11:30 AM

Nivolumab-induced interstitial lung disease (ILD) in Japanese patients with non-small cell lung cancer: A study on risk factors using interim results of post-marketing all-case surveillance. *First Author: Hirotsugu Kenmotsu, Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

Background: We investigated case reports of ILD in patients receiving nivolumab for the treatment of unresectable, advanced or recurrent non-small cell lung cancer to identify risk factors for the occurrence of nivolumab-induced ILD. **Methods:** In Japan, post-marketing all-case surveillance of nivolumab is currently underway in patients with non-small cell lung cancer who received nivolumab from December 17, 2015 to March 31, 2016. The data were retrospectively analyzed using a multivariate stepwise logistic regression analysis with a level of significance of 5% to identify risk factors for the occurrence of nivolumab-induced ILD. **Results:** A total of 3,648 patients received nivolumab during the surveillance period, and data from 1,005 patients whose case report forms were available by November 30, 2016 were analyzed. Among them ILD was reported in 58 (5.8%). The median time to onset in 42 patients who were recovering or recovered from ILD was 50 days (range: 2 to 246 days). Eleven patients died of ILD. The following table summarizes univariate and multivariate analyses of risk factors for the occurrence of ILD. **Conclusions:** In this interim analysis of Japanese lung cancer patients treated with nivolumab, incidence of ILD as immune-related AE was 5.8%. Age, abnormal findings of chest CT, and treatment line were identified as risk factors for the occurrence of ILD during treatment with nivolumab.

Factors	Category	N	patients with ILD N (%)	Univariate analysis Odds ratio [95% confidence interval]	Multivariate analysis P value
Age (years)	<75 years	854	44 (5.2)	1.9	0.0215
	≥75 years	151	14 (9.3)	[1.0, 3.5]	
Chest imaging (CT)	Present	178	20 (11.2)	2.6	0.0005
Abnormal findings other than lung cancer	Absent	779	36 (4.6)	[1.5, 4.6]	
Treatment line	2nd	223	19 (8.5)	1.8	0.0353
	3rd or subsequent	773	39 (5.0)	[1.0, 3.1]	

9079 Poster Session (Board #405), Sat, 8:00 AM-11:30 AM

Immune-related adverse events (IRAEs) in metastatic lung cancer patients receiving PD-1/PD-L1 inhibitors and thoracic radiotherapy. *First Author: William L. Hwang, Massachusetts General Hospital, Boston, MA*

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but are associated with unique IRAEs, including pneumonitis (PNS). Thoracic radiotherapy (TRT) is also associated with PNS but it is unknown whether TRT+ICI increases the risk of PNS or other IRAEs. Furthermore, low serum LDH levels are associated with better response/survival to ICI but its potential role as a biomarker for IRAEs is unexplored. **Methods:** We retrospectively reviewed 164 pts with metastatic lung cancer (95% NSCLC, 5% SCLC) consecutively treated at our institution from 2013-2016 with PD-1/PD-L1 inhibitors and a minimum of one month follow-up, except in cases of rapid death from an IRAE (n =4). Pts were grouped according to TRT received (+ vs -). IRAE grades were assigned using NCI CTCAE v4.0. Outcomes were compared using Fisher's exact test and two-sided Student's t-test. **Results:** Baseline characteristics such as age, gender, smoking status, supplemental oxygen requirement, median number of chemotherapy lines prior to ICI (1 vs 1), median ICI cycles (5 vs 3), and median follow-up after ICI initiation (8 vs 7 months) were similar in the +TRT (n = 73) and -TRT (n =91) groups. Rates of grade ≥ 2 IRAEs (18.1 vs 14.4%, p = 0.67), all-grade PNS (8.2 vs 5.5%, p= 0.54), and grade ≥ 2 PNS (4.1 vs 3.3%, p = 1) were not significantly different between the +TRT and -TRT cohorts. Mean TRT dose was similar between those pts who developed PNS and those who did not (55.8 vs 55.9 Gy). In the +TRT group, 85% received TRT a median of 8.6 months before ICI. Among 7 pts (10%) who had concurrent TRT+ICI, none developed symptomatic PNS. Patients who developed grade ≥ 2 IRAEs (n= 26) had significantly higher mean serum LDH before initiation of ICI than patients who did not (283 vs 214, ref 98-192 IU/L, p= 0.03). **Conclusions:** TRT in lung cancer pts receiving ICI was not associated with increased risk of PNS in this series. LDH may be a negative predictive biomarker as pts who suffered grade ≥ 2 IRAEs had significantly higher baseline LDH than those who did not. Larger cohorts and prospective studies would be helpful to validate these findings.

9080 Poster Session (Board #406), Sat, 8:00 AM-11:30 AM

Impact of immune-related adverse events (irAE) on overall survival (OS) in patients treated with immunotherapy for non-small cell lung cancer (NSCLC). *First Author: Dwight Hall Owen, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Immunotherapy (IO) has brought dramatic clinical benefit to patients with NSCLC. Most patients tolerate IO, but serious irAE have been reported. In melanoma, a correlation between development of irAE and clinical benefit has been suggested. For NSCLC, the risk of irAE including pneumonitis has been described in clinical trials but not for the wider population. Risk factors for irAE and the impact of irAE on OS are unknown. **Methods:** A retrospective review of patients with NSCLC treated with single-agent IO between September 2014 and June 2016 was carried out at The Ohio State University. Patients had confirmed pathologic disease and received IO either on clinical trial or as standard of care. IrAE were assessed based on the treating physician diagnosis. OS was calculated from the date of initiation of IO to death from any cause or date or last follow-up. **Results:** A total of 90 patients met criteria. Median age was 67. Histology was nonsquamous in 58 (64%) and squamous in 32 (35%). Most patients received nivolumab (n = 87). Median months of IO was 2.6 (95% CI 1.9 – 4.2). IrAE occurred in 24 patients (26.67%). The most common irAE were pneumonitis (n = 8), thyroid dysfunction (n = 6), and rash/pruritus (n = 5). Other irAE included colitis in 2 patients and new onset diabetes and autoimmune hepatitis in 1 patient each. Development of pneumonitis did not have a statistically significant impact on overall survival (median OS 5.8 vs 8.1 months, p = 0.11). Prior thoracic radiation (TR) was not associated with pneumonitis (11.54% vs 8.33%, p = 0.69), but was associated with shorter survival (median OS 3.9 vs 8.7 months, p = 0.018). Development of irAE was not associated with histology (p = 1.00), KRAS mutation (p = 0.10), TP53 mutation (p = 0.09), or recent flu vaccination (p = 1.00). Patients with irAE had longer median OS (13.2 vs 5.8 months, p = 0.018). **Conclusions:** The incidence of irAE and pneumonitis match that seen in published clinical trials. The development of irAE was associated with better prognosis, whereas patients with prior TR had worse outcomes. Further prospective research is warranted to investigate the correlation of irAE with clinical benefit from IO in patients with NSCLC.

9081 Poster Session (Board #407), Sat, 8:00 AM-11:30 AM

Use of PD-1 pathway inhibitors among patients with non-small cell lung cancer (NSCLC) and preexisting autoimmune disorders. *First Author: Giulia Costanza Leonardi, Dana-Farber Cancer Institute, Boston, MA*

Background: Since patients (pts) with NSCLC and autoimmune (AI) disease were largely excluded from immune checkpoint inhibitor clinical trials, we aimed to determine the safety of PD-1 inhibitors in NSCLC pts with a history of AI diseases. **Methods:** As part of a multi-center, retrospective study, we collected clinicopathologic data from pts with advanced stage IIIB or stage IV NSCLC with a history of AI disease and who received treatment with a PD-1 inhibitor as monotherapy. Qualifying AI disorders included but were not limited to: thyroiditis (excluding hypothyroidism without clear autoimmune etiology), inflammatory bowel disease, as well as rheumatologic, neurologic and dermatologic conditions. **Results:** We identified 46 pts with NSCLC treated with a PD-1 inhibitor who also had a history of AI disease. At the time of PD-1 inhibitor treatment initiation, 13% of pts had active AI symptoms and 19% were receiving immunomodulatory agents for their AI condition. The median period of follow up after initiation of anti-PD-1 therapy was 17.4 weeks (range 0.6-72.1 weeks). Exacerbation of the underlying AI condition occurred in 8 pts (17%). Two of these pts required steroid treatment (both for rheumatoid arthritis), and three of these pts required temporary interruption of treatment due AI disease flare. Overall, twelve (26%) pts developed at least one immune-related adverse event (irAE) unrelated to the underlying AI condition (8 grade 1-2, 4 grade 3); there were no cases of grade 4-5 irAEs. PD-1 therapy was permanently discontinued in 3 cases due to the development of an irAE (1 for grade 1 pneumonitis, 1 for grade 3 transaminitis, 1 for grade 3 diabetes insipidus). **Conclusions:** In pts with NSCLC and a history of AI conditions treated with PD-1 blockade, symptomatic flare of underlying AI disease was uncommon. The rate of immune-related toxicities in this population appears similar to published studies in pts without baseline AI conditions. Further analysis of pts with active AI conditions is needed to clarify the safety profile in this population.

9082 Poster Session (Board #408), Sat, 8:00 AM-11:30 AM

Clinical outcomes of patients with non-small cell lung cancer (NSCLC) receiving chemotherapy after immune checkpoint blockade. *First Author: Claud Grigg, Columbia University Medical Center, New York, NY*

Background: Objective response rates (ORR) to chemotherapy beyond the first-line for advanced NSCLC are low (5-10%). Pre-clinical studies suggest that some chemotherapies may act, in part, through immune mediated mechanisms. Additionally, results from phase I/II studies of chemotherapy combined with immune checkpoint inhibitors (ICIs) suggest high response rates ($>$ 50%) and potential synergy. It is unknown whether chemotherapy is more efficacious when given after ICIs. **Methods:** We reviewed demographics, imaging, treatment history, and clinical course for all patients at our institution with a diagnosis of metastatic NSCLC who received at least one dose of nivolumab, pembrolizumab, atezolizumab, or durvalumab prior to December 8, 2016. Patients who received any subsequent chemotherapy were included for analysis. Objective response was determined by RECIST v1.1, and date of progression was determined radiographically or clinically (treatment discontinuation with documented clinical deterioration). **Results:** 145 patients received at least one dose of any ICI, and 38 patients received subsequent chemotherapy. The median age was 68 years (range 44-88). Six chemotherapy-naïve patients received carboplatin + pemetrexed +/- bevacizumab. There were 3 partial responses (PR) including one exceptional response that is ongoing after 2 years. Among 32 chemotherapy non-naïve patients, the median number of prior chemotherapy regimens was 2 (range 1-6). Post-ICI chemotherapy included docetaxel + ramucirumab (n = 12), vinorelbine (n = 7), gemcitabine-based chemotherapy (n = 6), carboplatin doublets (n = 4), pemetrexed + bevacizumab (n = 2), and paclitaxel (n = 1). Six patients had documented poor performance status and died within 1 month of starting treatment. The ORR was 25% (1CR, 7PR), median time to progression was 116 days, and 9 patients (28%) experienced stable disease (SD) or better lasting $>$ 150 days. Exceptional responses occurred across regimens. Nine patients received a further line of chemotherapy, with 3 ongoing PR or SD lasting $>$ 100 days. **Conclusions:** For NSCLC, chemotherapy response rates may be higher when administered after an ICI.

9083 Poster Session (Board #409), Sat, 8:00 AM-11:30 AM

Response to single-agent (SA) chemotherapy (CTx) after immunotherapy exposure in non-small cell lung cancer (NSCLC). *First Author: Gustavo Schvartsman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Overall response rates (ORR) to 2nd-line SACTx in NSCLC have consistently not exceeded 15%. Exploratory analysis of clinical trials in various tumor types have demonstrated potential improvements in ORR to CTx after exposure to vaccine-based immunotherapy. The objective of this retrospective study was to determine if SACTx (3rd-line or beyond) would yield improved ORR when given after exposure to programmed-death-(ligand)1 inhibitors (PD1i) in metastatic NSCLC. **Methods:** Eligibility criteria - patients registered in the Thoracic GEMINI database of MD Anderson treated between 06/12 and 11/16 who received at least one SACTx as 3rd-line or beyond, following progression after platinum-based CTx and PD1i. We computed efficacy outcomes to each therapy, including ORR by RECIST v1.1, progression-free survival (PFS) and overall survival (OS). **Results:** Of 306 PD1i-treated patients registered in the database, 28 met eligibility criteria - 54% were male, median age 66 years, 82% adenocarcinoma, 29% never smokers. The PD1i and SACTx most commonly used were nivolumab (82%) and docetaxel (54%). ORR to SACTx after exposure to PD1i was 39% (11/28 patients, 8 confirmed). In contrast, ORR to 1st-line CTx in this cohort was 30% (Table). Liver metastasis and pembrolizumab as the PD1i of choice were the only factors associated with response to SACTx on univariate analysis ($p < 0.05$). **Conclusions:** In NSCLC patients, ORR to SACTx after immunotherapy exposure was higher compared to historical data from the pre-PD1i era, and approached ORR to 1st-line platinum-based CTx. Further investigation of a possible chemosensitization effect by immunotherapy is warranted.

	1st Line CTx n = 27*	At least 2nd Line PD1i n = 28	At least 3rd Line SACTx n = 28
Complete response	0	0	1 (3.6%)
Partial response	10 (37%)	0	10 (35.7%)**
Stable disease	15 (55.6%)	14 (50%)	10 (35.8%)
Progressive disease	2 (7.4%)	14 (50%)	7 (25%)
Median duration of response, months	7.8		4.1**
Median PFS, months (95% CI)	7.3 (4.9-8.4)	2.6 (1.9-3.7)	4.6 (2.8-6.3)
Median OS from start of therapy, months (95% CI)	37.8 (25.9-47.8)	13.9 (10.2-2836)	8.9 (7.7-24.2)

*1 patient inevaluable for response, 3 patients received chemoradiation; **3 unconfirmed

9084 Poster Session (Board #410), Sat, 8:00 AM-11:30 AM

Response to salvage chemotherapy following exposure to immune checkpoint inhibitors in patients with non-small cell lung cancer. *First Author: Paul Denis Leger, Vanderbilt University Medical Center, Nashville, TN*

Background: Immune checkpoint inhibitors are active for patients with stage IV NSCLC who have progressed following platinum-based chemotherapy. We evaluated responses to chemotherapy in patients who had progressed on a checkpoint inhibitor. **Methods:** Eligible patients were adults with NSCLC who received salvage chemotherapy following PD-1/PD-L1 inhibitors (cases) versus no PD-1/PD-L1 inhibitors (controls). CT-imaging was done within 4 weeks of initiation of salvage chemotherapy and every 6 weeks thereafter. Revised RECIST guidelines were used to define response. Clinical and imaging data were abstracted from review of electronic medical records. Multivariate logistic regression analysis was used to calculate probability of response. **Results:** Three-hundred and fifty patients' charts were reviewed and 82 patients met eligibility criteria. Among evaluable patients, 46 were males. Sixty-seven patients were cases versus 15 controls. Fifty-six patients received nivolumab, 7 pembrolizumab and 4 atezolizumab. Sixty-three (77%) had adenocarcinoma, 18 (22%) squamous cell carcinoma and 1 (1%) large cell carcinoma. The mean number of chemotherapy regimens prior to salvage chemotherapy was 2.37 (95% C.I. 2.10-2.64)) in cases versus 1.93 (95% C.I: 1.32-2.54) in controls. Salvage drugs included docetaxel (62%), pemetrexed (20%), gemcitabine (12%), paclitaxel (6%). Eighteen (27%) cases had partial response to chemotherapy versus 1(7%) controls. Fifteen (22%) cases had progressive disease versus 6 (40%) controls. Thirty-four (51%) cases had stable disease versus 8 (53%) controls. The odd ratio for achieving a partial response was 0.30 (95% CI: 0.18 to 0.50, P = 0.000). In multiple logistic regression model, age, gender, number of prior chemotherapy regimens, tumor histology, smoking status, different salvage chemotherapy regimens were not associated with the likelihood of achieving a partial response. **Conclusions:** The odds of achieving a partial response to salvage chemotherapy were more than 3 times higher inpatients with prior exposure to PD-1/PD-L1 inhibitors. Ongoing investigations include the duration of response as well as evaluation of toxicity.

9085 Poster Session (Board #411), Sat, 8:00 AM-11:30 AM

Updated safety and clinical activity of durvalumab monotherapy in previously treated patients with stage IIIB/IV NSCLC. *First Author: Ani Sarkis Balmanoukian, The Angeles Clinic and Research Institute, Los Angeles, CA*

Background: Preliminary analyses of an ongoing Phase 1/2 study of single-agent durvalumab showed antitumor activity and a tolerable safety profile in advanced NSCLC, with higher ORR and longer OS in pts with high vs. low/negative PD-L1 tumor expression. Here we present updated safety analyses (primary endpoint) for all NSCLC pts and clinical activity based on investigator-assessed RECIST v1.1 in pts who had received prior treatment for advanced NSCLC. **Methods:** Durvalumab (10 mg/kg q2w) was given until unacceptable toxicity or disease progression, or for up to 12 mos; retreatment was permitted upon disease progression after completion of 12 mos of treatment. PD-L1 expression was assessed using the Ventana PD-L1 (SP263) Assay (PD-L1 high = ≥25% and PD-L1 low/negative = <25% of tumor cells with membrane staining). **Results:** As of 24 Oct 2016, 245 pts with previously treated NSCLC (53% squamous) received durvalumab and were followed for a median of 29.2 (range 0.3–40.5) mos; 142 pts (58%) had treatment-related adverse events (AEs), most frequent: fatigue (18%), decreased appetite (9%), and nausea, rash, and diarrhea (each 8%). 25 pts (10%) had treatment-related Grade 3/4 AEs, most frequent: fatigue and hyponatremia (each 2%); there were no treatment-related deaths. 4% had treatment-related serious AEs including colitis and pneumonitis (each 2%). In the overall population, 12 mo OS rate was 47% (95% CI 40–53) and 18 mo OS rate was 38% (95% CI 31–45). Antitumor activity and survival by PD-L1 status are shown in the table. **Conclusions:** Consistent with earlier reports, durvalumab had a manageable safety profile in Stage IIIB/IV NSCLC, with encouraging clinical activity as 2L+ therapy. Higher tumor PD-L1 expression enriched clinical benefit of response rate and survival endpoints. Clinical trial information: NCT01693562.

	PD-L1 high	PD-L1 low/neg
Responses[a]	n=109	n=108
Confirmed ORR, % (95% CI)	25 (17–34)	6 (2–12)
Disease control rate (CR/PR + SD ≥24 weeks), % (95% CI)	36 (27–46)	21 (14–30)
PFS	n=116	n=110
Median PFS, mos (95% CI)	2.8 (2.0–4.7)	1.5 (1.3–2.6)
OS	n=116	n=111
Median OS, mos (95% CI)	15.4 (9.7–22.4)	7.6 (5.6–10.0)
12 mo OS, % (95% CI)	56 (45–65)	37 (27–47)

Note: 17 patients had unknown PD-L1 expression. [a]Response evaluable population.

9086 Poster Session (Board #412), Sat, 8:00 AM-11:30 AM

Exposure-response and PD-L1 expression analysis of second-line avelumab in patients with advanced NSCLC: Data from the JAVELIN Solid Tumor trial. *First Author: James L. Gulley, Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Avelumab is a fully human anti–PD-L1 IgG1 antibody showing promising efficacy and safety in patients (pts) with non-small cell lung cancer (NSCLC) and other tumors. Here, we present exposure–response (E–R) and PD-L1 expression analyses of second-line (2L) avelumab treatment in pts with NSCLC from a phase 1 trial (NCT01772004). **Methods:** Pts with NSCLC received 2L avelumab 10 mg/kg IV every 2 weeks (Q2W) until progression or unacceptable toxicity. Serum samples were taken at various time points for pharmacokinetic (PK) analysis. Trough concentrations after first dose ($C\text{trough}_{\text{first-dose}}$) were predicted using an identified linear 2-compartment population PK (popPK) model without covariates other than pt body weight. Objective response rate (ORR) was evaluated (RECIST v1.1), and correlated with tumor cell (TC) PD-L1 expression (clone 73-10). Pooled safety data from various tumors in the large phase 1 trial were assessed. **Results:** In 184 avelumab-treated pts, unselected for PD-L1 expression, ORRs were 8.7%, 10.9%, 19.6%, and 17.4% for increasing quartiles of $C\text{trough}_{\text{first-dose}}$ (Q1–4). Using ≥1%, ≥5%, ≥50%, and ≥80% PD-L1 staining cutoffs, pts in the upper half of exposure ($C\text{trough}_{\text{first-dose}}$ Q3–4 [n = 92]), had ORRs of 25% (n = 59), 26% (n = 39), 33% (n = 21), and 43% (n = 14), respectively. Higher avelumab exposure was associated with a modest increase in immune-related adverse events (irAEs). PopPK modeling suggested $C\text{trough}_{\text{first-dose}}$ could be optimally increased with alternate avelumab dosing (10 mg/kg weekly vs Q2W, or 20 mg/kg Q2W [simulated median $C\text{trough}_{\text{first-dose}}$ 48 μg/mL vs 18 μg/mL, or 36 μg/mL]). **Conclusions:** Avelumab has shown clinical activity and acceptable safety in multiple tumors similar to other agents in class. Preliminary analysis of a cohort of pts with 2L advanced NSCLC shows a trend for higher ORR with increasing avelumab $C\text{trough}_{\text{first-dose}}$ quartiles and with higher levels of TC PD-L1 expression. Although this apparent E–R observation may be confounded by single-dose testing or other factors, this analysis provides rationale for studies of more intensive avelumab dosing regimens to assess further clinical benefit in pts with advanced NSCLC. Clinical trial information: NCT01772004.

9087 Poster Session (Board #413), Sat, 8:00 AM-11:30 AM

Tumor response dynamics of advanced non-small-cell lung cancer (NSCLC) patients (pts) treated with commercial PD-1 inhibitors in the clinical setting. *First Author: Mizuki Nishino, Dana-Farber Cancer Institute, Boston, MA*

Background: PD-1 inhibitors have shown promising activity in advanced NSCLC, with increasing clinical use. We evaluated tumor burden dynamics in advanced NSCLC pts treated with commercial PD-1 inhibitors to identify imaging markers for clinical benefit. **Methods:** The study included 160 advanced NSCLC pts (79 males; median age: 65) treated with commercial nivolumab or pembrolizumab monotherapy at DFCI as a part of routine clinical care. Tumor burden dynamics were assessed on serial CT scans during therapy by irRECIST1.1, which uses unidimensional measures and includes new lesions in tumor burden [Clin Cancer Res. 2013;19:3936-43]. **Results:** Tumor burden change at best overall response (BOR) ranged from -100% to +278% (median: +3.5%). Objective response rate (ORR) was 18% (29/160). Current and former smokers had higher ORR than never smokers (ORR:14% (8/58), 25% (20/79), 4% (1/23); Fisher p = 0.04). Durable disease control with tumor burden < 20% increase from baseline for at least 6 months was noted in 27 pts (17%), which included 11 pts with stable disease as their irBOR. Using an 8-week landmark analysis, pts with < 20% tumor burden increase from baseline at 8 weeks had longer OS than pts with ≥20% increase (median OS: 12.4 vs. 4.6 months, p < 0.001). In Cox models using a time varying covariate, pts with < 20% tumor burden increase during therapy had significantly reduced hazards of death (HR = 0.24, p < 0.0001) after adjusting for smoking (HR = 1.77, p = 0.016) and baseline tumor burden (HR = 1.66, p = 0.032). Two pts (1.3%) had atypical response pattern or "pseudoprogression", where tumor burden showed initial increase and subsequent decrease, which was noted after confirmed irPD on consecutive scans in both pts. **Conclusions:** An objective response or durable disease control was noted in 25% of advanced NSCLC pts treated with PD-1 inhibitors in the clinical setting. Tumor burden increase of < 20% from the baseline during therapy was associated with longer OS, proposing a practical marker of clinical benefit. Pseudoprogression was uncommon, with tumor decrease noted after confirmed irPD, indicating a limitation of the current strategy for immune-related response evaluation.

9089 Poster Session (Board #415), Sat, 8:00 AM-11:30 AM

Baseline-derived neutrophil-to-lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH) to predict the benefit of immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (NSCLC) patients. *First Author: Laura Mezquita, Department of Cancer Medicine, Gustave Roussy Cancer Campus, Paris-Sud University, Villejuif, France*

Background: dNRL (Neutrophils/Leucocytes-Neutrophils) and LDH were recently correlated to ICI benefit in melanoma. We tested if dNLR and LDH could have the same role in NSCLC patients. **Methods:** Baseline dNLR and LDH were collected in 234 patients treated with PD1/PDL1 inhibitors from Nov. 2013 to Dec. 2016, in a discovery (D) cohort (N = 161) from Gustave Roussy and an independent validation (V) cohort (N = 73) from 2 centers. ICI benefit was analyzed according to overall survival (OS), progression free survival (PFS) and response rate (RR) by RECIST 1.1. Kaplan-Meier and Cox regression were performed. **Results:** In the D cohort, 100 patients (62%) were males, 136 (85%) smokers and PS ≤1, with median age 61.5; 133 patients (81%) stage IV; 100 (62%) had adenocarcinoma and 46 (29%) squamous cells carcinoma; 35 (22%) were *KRAS*mut, 13 (8%) *EGFR*mut and 3 (2%) *ALK*positive. PDL1 expression was positive in 43 (75%), negative in 14 (25%) and unknown in 78. 132 (82%) patients received PD1 inhibitors; the median of prior lines was 1 (1-11). dNLR > 3 and LDH > upper normal limit (UNL) were independent factors for poor OS (HR 4,67, p = 0.011 and HR 2,65, p = 0.002, respectively) and poor PFS (HR 4,71, p = 0.001 and HR 1,68, p = 0.042 respectively). The median follow-up (FU) was 12 months (m) [95% CI 11-14], the median PFS 3m [2-4] and the median OS 10m [8-13]. In the V cohort, with a median FU of 11m [8-14], dNLR > 3 and LDH > UNL were significantly associated with poor OS (both p = 0.001), with a trend toward association with PFS (p = 0.06, p = 0.08, respectively). A Lung Immune Predictive Index (LIPI) was tested considering dNLR > 3 and LDH > UNL, with three groups. In D cohort, the median OS for good (no factor), intermediate (one factor) and poor (two factors) was 34m [17-NR], 10m [8-NR], 3m [1-NR], respectively (p = 0.0001), and PFS was similarly correlated (p = 0.001). Same results were demonstrated in the V cohort. **Conclusions:** Baseline dNLR > 3 and LDH > UNL can predict the benefit of ICI in advanced NSCLC patients. The LIPI at baseline is an easy tool to identify the candidates to immunotherapy. Confirmation cohorts are ongoing to validate the predictive role of the LIPI.

9090 Poster Session (Board #416), Sat, 8:00 AM-11:30 AM

Factors associated with better overall survival (OS) in patients with previously treated, PD-L1–expressing, advanced NSCLC: Multivariate analysis of KEYNOTE-010. *First Author: Roy S. Herbst, Yale Cancer Center, New Haven, CT*

Background: We identified factors associated with better OS for previously treated, PD-L1–expressing advanced NSCLC using data from KEYNOTE-010 (NCT01905657; Herbst et al. *Lancet.* 2016;387:1540-50), in which pembrolizumab had superior OS over docetaxel. **Methods:** 1033 patients were randomly assigned 1:1:1 to pembrolizumab 2 or 10 mg/kg every 3 weeks (Q3W) or docetaxel 75 mg/m^2 Q3W. Response was assessed per RECIST v1.1 by independent central review. Multivariate analyses were performed using a Cox proportional hazards regression model on OS in the pembrolizumab arms. A set of variable selection methods was applied to 19 baseline demographic and disease characteristics, including smoking status, and identified 7 factors that contributed to OS. Data cut was September 30, 2016. **Results:** Adjusted hazard ratios (HRs) for the factors in the pembrolizumab arm from the model are shown in the Table. Updated OS with an additional 6 months of follow-up from this data lock for KEYNOTE-010 will be presented. **Conclusions:** While the overall result of KEYNOTE-010 revealed improved OS with pembrolizumab compared with docetaxel in previously treated patients with PD-L1–positive advanced NSCLC, exploratory, post hoc multivariate analyses showed that some laboratory and tumor characteristics such as nonsquamous histology, normal baseline lactate dehydrogenase (LDH), PD-L1 TPS ≥50%, and wild-type *EGFR* mutation status were associated with better OS among patients treated with pembrolizumab. Clinical trial information: NCT01905657.

Characteristics (nonreference vs reference)	Pembrolizumab n = 690 HR (95% CI); *P* value
Race (Asian vs non-Asian)	0.70 (0.54-0.91); 0.0067
Baseline tumor size (≤80 mm vs > 80 mm)	0.71 (0.59-0.87); 0.0007
ECOG performance status at screening (0 vs ≥1)	0.79 (0.65-0.97); 0.0265
Histology (nonsquamous vs squamous)	0.55 (0.43-0.70); < 0.0001
Baseline LDH (normal vs elevated)	0.61 (0.49-0.76); < 0.0001
PD-L1 status (TPS ≥50% vs TPS 1%-49%)	0.64 (0.52-0.77); < 0.0001
EGFR mutation status (wild type vs mutant)	0.65 (0.46-0.91); 0.0122

9091 Poster Session (Board #417), Sat, 8:00 AM-11:30 AM

Efficacy, safety, and immune activation with pegylated human IL-10 (AM0010) in combination with an anti-PD1 in advanced NSCLC. *First Author: Deborah Jean Lee Wong, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: Although IL-10 has anti-inflammatory properties, it stimulates cytotoxicity and proliferation of intratumoral antigen activated CD8+ T cell at higher concentrations. AM0010 is anticipated to activate antigen stimulated, intratumoral CD8 T cells while PD-1 inhibits them, providing the rationale for combining AM0010 and anti-PD-1 antibody. **Methods:** We treated a cohort of 34 NSCLC pts with AM0010 (10-20mg/kg QD, SC) and a PD-1 inhibitor [pembrolizumab (2mg/kg, q3wk IV; n=5) or nivolumab (3mg/kg, q2wk IV; n=29)]. Tumor responses were assessed by irRC every 8 weeks. Immune responses were measured by analysis of serum cytokines (Luminex), activation of blood derived T cells (FACS) and peripheral T cell clonality (TCR sequencing). Tumor PD-L1 expression was confirmed by IHC (22C3). **Results:** Pts had a median of 2 prior therapies. Median follow-up is 9.6 mo (range 0.5-77.3) in this fully enrolled cohort. AM0010 plus anti-PD-1 was well-tolerated. TrAEs were reversible and transient, with most being low grade, most commonly fatigue and pyrexia. G3/4 TrAEs were thrombocytopenia (7), anemia (6), fatigue (4), rash (3), pyrexia (2), hypertriglyceridemia (1) and pneumonitis (1). As of Jan. 31 2017, 22 pts had at least 1 tumor assessment. Partial responses (PRs) were observed in 8 pts (36.4%). 17 of these 22 pts had tissue for analysis of percent of tumor cells with PD-L1 expression (22C3): 58.8% had <1%, 17.7% had 1-49% and 23.5% had >50%. Best response data stratified for PD-L1 are shown in the table. Median PFS and OS for the entire cohort have not been reached. Updated outcome data that includes all enrolled pts will be available at the meeting. AM0010 plus anti-PD1 increased serum Th1 cytokines (IL-18, IFNγ), the number and proliferation of PD1+ Lag3+ activated CD8+ T cells and a de-novo oligoclonal expansion of T cell clones in the blood while decreasing TGFβ. **Conclusions:** AM0010 in combination with anti-PD1 is well-tolerated in advanced NSCLC pts. The efficacy and the observed CD8+ T cell activation is promising. Clinical trial information: NCT02009449.

PD-L1 (22C3 IHC) (n=22)	<1% (n=10)	1-49% (n=3)	>50% (n=4)	Not available (5)
PR, n (%)	3 (30%)	1 (33%)	3 (75%)	1 (20%)
SD, n (%)	7 (70%)	1 (33%)	1 (25%)	3 (60%)
PD, n (%)	0 (0%)	1 (33%)	0 (0%)	1 (20%)

9092 Poster Session (Board #418), Sat, 8:00 AM-11:30 AM

Atezolizumab (atezo) plus platinum-based chemotherapy (chemo) in non-small cell lung cancer (NSCLC): Update from a phase Ib study. *First Author: Stephen V. Liu, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Platinum-based chemo is a standard first-line (1L) therapy for NSCLC lacking actionable gene alterations. Preclinical evidence suggests that chemo can play an immunomodulatory role and induce tumor antigen release, supporting combining chemo with immunotherapy. Atezo is a humanized and Fc-region-modified monoclonal anti-programmed death-ligand-1 (PD-L1) antibody that blocks interaction with PD1 or B7.1. The GP28328 study (NCT01633970) assessed safety and efficacy of atezo plus 1L chemo regimens in multiple tumor types. **Methods:** In this multicenter, multi-arm study, patients (pts) with locally advanced or metastatic NSCLC with no prior chemo for advanced disease received 15 mg/kg atezo IV q3w with standard doses of chemo (Arm C: carboplatin [carbo]+paclitaxel q3w; Arm D: carbo+pemetrexed q3w; Arm E: carbo+nab-paclitaxel qw) all for ≤6 cycles followed by atezo maintenance until loss of clinical benefit (+ pemetrexed maintenance until progression, Arm D). The primary endpoint was safety; secondary endpoints were overall response rate (ORR), PFS, and OS. **Results:** By the 30 Aug 2016 cut-off, 76 NSCLC pts were evaluable (n = 25, 25, 26 for Arms C, D, E, respectively). At this cut-off, the most common treatment-related grade 3–4 adverse events (AEs) were neutropenia (36% C, 36% D, 42% E) and anemia (16% C, 16% D, 31% E). Three potentially related grade 5 AEs were seen (arm C: pneumonia; arm D: systemic candida; arm E: autoimmune hepatitis). Confirmed ORRs were 36%, 64%, 46% for Arms C, D (1 CR), and E (4 CR). Median PFS (95% CI) was 7.1 months (4.2–8.3) for C, 8.4 months (4.7–11) for D, and 5.7 months (4.4–14.8) for E. Median OS (95% CI) was 12.9 months (8.8–not evaluable) for C, 19.3 months (14.7–27.4) for D, and 14.8 months (12.7–not evaluable) for E. **Conclusions:** Atezo was well tolerated when combined with various chemo regimens for advanced NSCLC. Clinical activity in terms of ORR was favorable supporting potential synergy between atezo and chemo. PFS and OS data show promising benefits, but are limited by small numbers and wide confidence intervals. Phase III studies that include chemotherapy and atezolizumab are currently ongoing. Clinical trial information: NCT01633970.

9093 Poster Session (Board #419), Sat, 8:00 AM-11:30 AM

Nivolumab (N) plus ipilimumab (I) as first-line (1L) treatment for advanced (adv) NSCLC: 2-yr OS and long-term outcomes from CheckMate 012. *First Author: Jonathan Wade Goldman, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: The fully human anti–PD-1 antibody N offers long-term OS benefit in patients (pts) with previously treated adv NSCLC. Adding I (anti–CTLA-4 antibody) to N has been shown to improve clinical activity vs either agent alone in multiple tumor types. We present long-term data for 1L N+I treatment of pts with adv NSCLC from CheckMate 012. **Methods:** In two cohorts in this phase 1 study, pts with recurrent stage IIIb/IV, chemotherapy-naive NSCLC and ECOG PS 0–1 received N 3 mg/kg Q2W combined with I 1 mg/kg Q12W (n=38) or Q6W (n=39) until disease progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was safety and tolerability. Secondary endpoints included investigator-assessed ORR (RECIST v1.1) and PFS. Exploratory endpoints included OS and efficacy by tumor PD-L1 expression. **Results:** In the N+I Q12W and N+I Q6W cohorts, respectively, 42% and 31% of pts experienced grade 3–4 treatment-related (TR) AEs; 18% in each cohort discontinued due to any-grade TRAEs. The most frequently reported any-grade TRAEs were pruritus (26%) and diarrhea (21%) with N+I Q12W, and fatigue (26%) and diarrhea (23%) with N+I Q6W. There were no TR deaths. N+I showed promising efficacy (table). While efficacy was enhanced with increasing PD-L1 expression, activity was noted in pts with <1% PD-L1 (table). Of 6 complete responses (CRs), 3 were in pts with <1% PD-L1. **Conclusions:** 1L therapy with N+I demonstrates a manageable safety profile and promising, durable efficacy (including pathological CRs) in adv NSCLC; efficacy was enhanced in pts with ≥1% PD-L1 tumor expression. Longer follow-up data, including 2-yr OS and characteristics of long-term survivors, will be presented. Clinical trial information: NCT01454102.

Cohorts	ORR, %	mDOR[a] (95% CI), mo	mPFS[a] (95% CI), mo	1-yr OS, %
N+I Q12W[b] (n=38)	47	NR (11.3, NA)	8.1 (5.6, 16.7)	83
N+I Q6W[c] (n=39)	38	NR (11.2, NA)	3.9 (2.6, 13.4)	69
Pooled (n=77)	43	NR (14.0, NA)	8.0 (4.1, 13.2)	76
≥50% PD-L1 (n=13)	92	NR (4.2, NA)	NR (7.8, NA)	100
≥1% PD-L1 (n=46)	57	NR (11.2, NA)	12.7 (7.8, 23.0)	87
<1% PD-L1 (n=19)	21	NR (NA)	3.3 (2.3, 5.3)	53

Based on Sept. 2016 database lock. [a]Kaplan−Meier method; [b]mFU 15.8 mo; [c]mFU 16.1 mo. Abbreviations: DOR = duration of response; FU = follow-up; m = median; NA = not available; NR = not reached.

9094 **Poster Session (Board #420), Sat, 8:00 AM-11:30 AM**

First-line carboplatin and pemetrexed (CP) with or without pembrolizumab (pembro) for advanced nonsquamous NSCLC: Updated results of KEYNOTE-021 cohort G. *First Author: Vassiliki Papadimitrakopoulou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Data from the randomized, phase 2 cohort G of KEYNOTE-021 (NCT02039674) showed that adding pembro to first-line CP in patients (pts) with advanced nonsquamous NSCLC significantly improved the primary end point of ORR (55% vs 29%, P = 0.0016) and the key secondary end point of PFS (HR 0.53, *P*= 0.0102) compared with CP alone and had a manageable safety profile (grade 3-4 treatment-related AEs, 39% vs 26%; treatment-related AEs leading to discontinuation, 10% vs 13%). We present updated efficacy for cohort G based on 5 mo additional follow-up. **Methods:** 123 pts with stage IIIB/IV, chemotherapy-naive, nonsquamous NSCLC and no *EGFR* mutation or *ALK* translocation were randomized to 4 cycles of carboplatin AUC 5 + pemetrexed 500 mg/m^2 Q3W ± 24 mo of pembro 200 mg Q3W; maintenance pemetrexed was permitted in both arms. Eligible pts in the CP arm who had radiologic progression could crossover to pembro monotherapy. Response was assessed per RECIST v1.1 by blinded, independent central review. All *P*values are nominal. **Results:** As of Dec 31, 2016, median follow-up was 14.5 mo (range, 0.8-24.0). 36 of 48 pts (75.0%) in the CP arm who discontinued CP received subsequent anti–PD-1 or PD-L1 therapy. There was 1 additional response in each arm, and ORR was 56.7% (95% CI 43.2%-69.4%) with pembro + CP vs 30.2% (95% CI 19.2%-43.0%) with CP (*P*= 0.0016). Median DOR was not reached for pembro + CP (range, 1.4+ to 18.6+ mo) and was 16.2 mo (range, 2.8 to 20.7+) for CP alone. PFS remained longer with pembro + CP (HR 0.49, 95% CI 0.29-0.83, *P* = 0.0035; median [95% CI] NR [9.7 mo-NR] vs 8.9 mo [6.2-10.3]; 12-mo estimate, 56% vs 34%). With 16 deaths in the pembro + CP arm and 23 deaths in the CP arm, HR for OS was 0.69 (95% CI 0.36-1.31, *P*= 0.13). Median OS was not reached in either arm; at 12 mo, estimated OS was 76% in the pembro + CP arm and 69% in the CP alone arm. **Conclusions:** With 5 mo additional follow-up, first-line pembro + CP continues to provide a substantial, clinically relevant improvement in efficacy over CP alone in pts with advanced nonquamous NSCLC, including an almost doubled ORR, halved risk of progression or death, and a trend toward improved OS despite a 75.0% crossover rate in the CP arm. Clinical trial information: NCT02039674.

9095 **Poster Session (Board #421), Sat, 8:00 AM-11:30 AM**

Nivolumab (nivo) + *nab*-paclitaxel (*nab*-P) + carboplatin (C) in patients (pts) with non-small cell lung cancer (NSCLC): Interim results from a multicenter phase I study. *First Author: David Michael Waterhouse, Oncology Hematology Care, Inc., Cincinnati, OH*

Background: Despite success of single-agent immune checkpoint inhibitors, an unmet therapeutic need remains in pts with NSCLC. Chemotherapy and immunotherapy may have synergistic antitumor activity, but safety and efficacy need to be established. Here, we present interim results for pts with NSCLC (Arm C) from the phase I safety trial of nivo + *nab*-P in pancreatic cancer (± gemcitabine), NSCLC (+ C), and metastatic breast cancer. **Methods:** Part 1 evaluated potential dose-limiting toxicities (DLTs) before Part 2 expansion. Chemotherapy-naive pts with histologically/cytologically confirmed stage IIIB/IV NSCLC received 4 cycles of *nab*-P 100 mg/m^{2}d 1, 8, 15 + C AUC 6 d 1 + nivo 5 mg/kg d 15 of each 21-d cycle; in cycles 5+, nivo was continued as maintenance monotherapy. Primary endpoints: number of pts with DLTs (Part 1) and percentage of pts with grade 3/4 treatment-emergent adverse events (TEAEs) or treatment discontinuation due to TEAEs (Parts 1 and 2). DLT-evaluable pts included those who received ≥ 2 complete nivo cycles and remained on study for 14 d after the last nivo dose in cycle 2, received ≥ 1 nivo dose and discontinued due to DLT before completing 2 nivo cycles, or experienced equivocal DLT after ≥ 1 nivo dose. Secondary endpoints included safety, PFS, OS, DCR, ORR, and DOR. **Results:** All pts (n = 22) received *nab*-P/C; results for nivo-treated pts (n = 20) are presented. Of the nivo-treated pts, the median age was 66 y (55% ≥ 65 y), 75% were female, 80% were white, and 70% had ECOG PS 1. More pts had adenocarcinoma (50%) than squamous cell carcinoma (35%; 10% other, 5% data pending). No DLTs reported (5 DLT-evaluable pts). Most common grade 3/4 TEAEs were neutropenia (45%) and anemia (35%). No grade 3/4 immune-related colitis or pneumonitis reported. Best ORR (RECIST v1.1) was 50% (1 CR [unconfirmed, 5%] and 9 PRs [45%]; 6 pts had SD [30%]; 4 pts had PD [20%]). Best ORR by histology: squamous, 71%; nonsquamous, 54%. Median PFS was 10.5 months (squamous, 10.5 months; nonsquamous, not evaluable). **Conclusions:** Results demonstrated safety of the nivo + *nab*-P/C combination in NSCLC with no unexpected safety signals. Preliminary efficacy results are promising. (NCT02309177) Clinical trial information: NCT02309177.

TPS9097 **Poster Session (Board #422b), Sat, 8:00 AM-11:30 AM**

NIVORAD: A randomised phase 2 trial of nivolumab and stereotactic ablative body radiotherapy in advanced non-small cell lung cancer, progressing after first or second line chemotherapy. *First Author: Paul Mitchell, Austin Health, Heidelberg, Australia*

Background: Recent data has demonstrated improvements in overall survival in patients with advanced non-small cell lung cancer (NSCLC) treated with nivolumab. Radiation may augment the immune response through abscopal effects - evidence of tumour control at sites other than those irradiated. We hypothesize that the addition of stereotactic ablative body radiotherapy (SABR) to immunotherapy with nivolumab will improve progression free survival (PFS) compared with nivolumab alone. **Methods:** DESIGN: Open label, randomised phase II trial with 25 sites across Australia and New Zealand. ELIGIBILITY: Metastatic NSCLC progressing after 1 or 2 lines of chemotherapy with an extrapulmonary metastasis suitable for SABR. STRATIFICATION: Age, lines of chemotherapy, histology and treating institution. TREATMENT: A single dose of SABR (18-20Gy) plus nivolumab or nivolumab alone (240mg 2-weekly) given until disease progression or prohibitive adverse events. ENDPOINTS: PFS at 6 months (PFS6; primary), objective tumour response rate, adverse events, overall survival, PFS at 1 and 2 years. Tertiary correlative objectives include associations between possible prognostic/ predictive biomarkers and outcomes (including PD-L1 expression). STATISTICS:Total sample size of 120 participants allocated in a ratio of 2:1, 80 to nivolumab + SABR and 40 nivolumab alone to provide 80% power, one-sided type I error rate of 5% for PFS6 of 50% (worthy of pursuit) vs 35% (not worthy of pursuit). BIOSPECIMENS: Tumour tissue and serial bloods (4 time points) will be collected for translational research. CURRENT ENROLLMENT (as of Feb 2017): 2 out of 20 sites are open. NIVORAD is an investigator-initiated, cooperative-group trial led by the ALTG in collaboration with the NHMRC Clinical Trials Centre, University of Sydney and the Trans Tasman Radiation Oncology Group (TROG). Australian New Zealand Clinical Trials Registry: ACTRN12616000352404.

TPS9098 **Poster Session (Board #423a), Sat, 8:00 AM-11:30 AM**

Design of ALTA-1L (ALK in lung cancer trial of brigatinib in first-line), a randomized phase 3 trial of brigatinib (BRG) versus crizotinib (CRZ) in tyrosine kinase inhibitor (TKI)-naive patients (pts) with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). *First Author: Marcello Tiseo, University Hospital of Parma, Parma, Italy*

Background: BRG is an investigational, next-generation ALK inhibitor with potent preclinical activity against rearranged ALK and CRZ-resistant mutants. In an ongoing phase 1/2 trial, BRG has shown promising intracranial and whole-body activity in ALK+ NSCLC pts with or without prior CRZ therapy (*Lancet Oncol*. 2016;17:1683-96). In an ongoing pivotal randomized phase 2 trial (ALTA) evaluating 2 BRG regimens (90 mg qd and 180 mg qd with a 7-d lead-in at 90 mg), BRG has shown substantial objective response rates (ORRs) and robust progression-free survival (PFS) in pts with CRZ-resistant ALK+ NSCLC, particularly at 180 mg (with lead-in), and acceptable safety (*J Thorac Oncol*. 2017;12:S612-3). Based on these results, the ALTA-1L trial was designed to assess the efficacy and safety of BRG vs CRZ in pts with advanced ALK+ NSCLC naive to TKI therapy (including ALK inhibitors). **Methods:** ALTA-1L (NCT02737501) is an open-label, multicenter, randomized phase 3 trial. Pts (≥18 y of age) are required to have locally advanced or metastatic ALK+ NSCLC, no prior TKI therapy, and ≤1 prior systemic anticancer regimen in the advanced setting. Approximately 270 pts will be stratified by presence of brain metastases at baseline and prior chemotherapy (yes/no) and randomized 1:1 to receive oral BRG (180 mg qd with a 7-d lead-in at 90 mg) or CRZ (250 mg bid). The primary endpoint is PFS per RECIST v1.1 assessed by a blinded independent review committee (BIRC); secondary endpoints include ORR, duration of response, overall survival, safety/tolerability, pt-reported outcomes, and intracranial ORR/PFS. The primary endpoint will be analyzed with the Kaplan-Meier method and a 2-sided stratified log-rank test after 198 events; 2 interim analyses are planned after approximately 50% and 75% of expected events. CRZ-treated pts may cross over to BRG (180 mg [with lead-in]) after BIRC-assessed disease progression. ALTA-1L was initiated in April 2016; 150 sites are planned in North America, Europe, and the Asia-Pacific region. 97 pts were enrolled as of February 6, 2017. Clinical trial information: NCT02737501.

TPS9099 Poster Session (Board #423b), Sat, 8:00 AM-11:30 AM

Deciphering antitumour response and resistance with intratumour heterogeneity (DARWIN II). *First Author: Crispin T. Hiley, King's College London, London, United Kingdom*

Background: The importance of intratumour heterogeneity (ITH) is increasingly recognised as a driver of cancer progression and survival outcome. However understanding how tumour clonal heterogeneity impacts upon therapeutic outcome is still an area of unmet clinical and scientific need. The TRACERx trial (NCT01888601), a prospective study of patients with radically resected primary non-small cell lung cancer (NSCLC), aims to define the evolutionary trajectories of lung cancer in both space and time through genetic analysis of multi-region and longitudinal tumour sampling. DARWIN II is an investigator initiated study for patients who are enrolled within the TRACERx trial, or who have multi-region sequencing of their primary disease, but subsequently relapse with metastatic disease. This study will examine the role of intra-tumour heterogeneity and predicted neoantigens on the anti-tumour activity of anti-PDL1 immunotherapy. **Methods:** This multicentre non-randomised phase II molecularly stratified umbrella study will examine how clonal dominance and ITH influence outcomes after treatment, offering a unique opportunity to decipher mechanisms of resistance to immunotherapy with anti-PDL1. These data will help improve future study design by developing greater understanding of patient selection for immunotherapies in patients with NSCLC. The relationship between ITH and cfDNA/CTCs will also be explored in DARWIN II. The study arms: Arm 1: Patients either -1) without an actionable mutation and PDL1 positive or 2) without an actionable mutation and PDL1 negative following first line cytotoxic chemotherapy - Atezolizumab. Arm 2: BRAFV600 - Vemurafenib. Arm 3: ALK/RET gene rearrangement - Alectinib. Arm 4: Her2 Amplification - Trastuzumab Emtansine. Primary Outcome Measures: Progression free survival (PFS), defined as the period between the date of registration to the date of subsequent progression or death will be assessed according to: Neo-antigen burden, mutational burden, ITH as assessed using an ITH ratio index and genomic instability as assessed using a weighted genome instability index (wGII). Trial Sponsor: University College London. Clinical trial information: NCT02314481.

TPS9100 Poster Session (Board #424a), Sat, 8:00 AM-11:30 AM

Early rebiopsy to identify mechanisms and biomarkers of tumor cell survival following epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy. *First Author: Caroline Elizabeth McCoach, University of Colorado School of Medicine, Aurora, CO*

Background: Significant advances in the clinical outcomes of lung cancer patients have been achieved in part due to the identification of targetable driver mutations. The success of targeting oncogenic drivers with TKIs has allowed for improvements in response rates, progression free survival and overall survival. Despite these improvements, patients ultimately relapse. Acquired resistance has been evaluated in post-progression tumor samples and is caused by a variety of mechanisms including secondary resistance mutations, gene copy number gains, gene amplification, or bypass pathway activation. Residual tumor burden with surviving cancer cells are the origin of the ultimate tumor progression. Studies analyzing signaling pathways and other markers of these tumor cells or microenvironmental cells in tumor samples before clinical resistance develops are needed to determine how best to target this compartment. **Methods:** Eligible patients will have a new diagnosis of advanced NSCLC with an EGFR TKI sensitizing mutation. Additional inclusion criteria include ECOG 0-2, a tumor measurable by RECIST 1.1 and at least 2cm in one dimension, and tumor site that is accessible and safe to biopsy. Patients will undergo a pretreatment target lesion biopsy, begin treatment with an EGFR TKI then receive a second biopsy of the same target lesion after two weeks of therapy. Our primary objective is to identify differences between pretreatment and early treatment tumor samples. To do this we will be using a combination of RNA seq, multiplex protein expression analysis and proximity ligation assays. Secondary objectives include identification of predictive markers that can be used to determine which tumors will undergo epithelial to mesenchymal transition or activate other survival pathways and determination of the success rate and adverse event rate of repeat biopsy. Patients are currently being enrolled at a single academic institution however, additional clinical site openings are pending. Our goal enrollment for this study is 47 patients to achieve 20 paired biopsy samples. We will present updated enrollment and demographic information. Clinical trial information: NCT03042221.

TPS9101 Poster Session (Board #424b), Sat, 8:00 AM-11:30 AM

IMpower132: A phase III clinical program—1L atezolizumab plus platinum-based chemotherapy in chemo-naive advanced non-squamous NSCLC. *First Author: Howard Jack West, Swedish Cancer Institute, Seattle, WA*

Background: Platinum-based chemotherapy (chemo) is the current standard of care for patients (pts) with newly diagnosed advanced non-squamous NSCLC. The combination of platinum-based chemo and pemetrexed (pem) provides comparable benefit to pts as other standard platinum doublets commonly used and has a favorable toxicity profile. However, the survival benefit conferred by this combination leaves considerable room for improvement. The anti–PD-L1 mAb atezolizumab (atezo) inhibits the interaction of PD-L1 with its receptors PD-1 and B7.1, thereby restoring tumor-specific T-cell immunity. In the OAK trial, pts with 2L/3L advanced NSCLC had improved mOS in the atezo arm (13.8 mo) vs the docetaxel arm (9.6 mo), with a survival benefit observed across PD-L1 expression levels. The potential for chemo to further augment responses to atezo, with tolerable safety, has also been demonstrated. A global, Phase III, randomized, open-label trial, IMpower132 (NCT02657434), is being conducted to evaluate 1L atezo + platinum-based chemo + pem in chemo-naive pts with stage IV NSCLC. **Methods:** Eligibility criteria include stage IV NSCLC, measurable disease (RECIST v1.1), no prior chemo and ECOG PS 0-1. Exclusion criteria include tumors known to harbor *EGFR* or *ALK* driver mutations, untreated CNS metastases, autoimmune disease and prior exposure to immunotherapy. Pts will be enrolled regardless of PD-L1 expression status and randomized to the treatment arms. Pts will be stratified by sex, ECOG PS, type of chemo (carboplatin [carbo] vs cisplatin [cis]) and smoking status. Pts will receive four or six 21-day cycles of either atezo + carbo/cis + pem or carbo/cis + pem. Following the induction phase, pts will receive maintenance atezo + pem or pem alone, depending on their allocated treatment regimen. Pts receiving atezo may continue until loss of clinical benefit.Co-primary endpoints are investigator-assessed PFS and OS. Secondary endpoints include IRF-assessed PFS, investigator-assessed ORR and safety. Predictive biomarkers associated with efficacy will be evaluated. Approximately 568 pts will be enrolled. Clinical trial information: NCT02657434.

TPS9102 Poster Session (Board #425a), Sat, 8:00 AM-11:30 AM

Randomized, open-label phase Ib/II study of atezolizumab with or without daratumumab in previously treated advanced or metastatic non-small cell lung cancer (NSCLC). *First Author: Rathi Narayana Pillai, Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA*

Background: Daratumumab (DARA), a human CD38 monoclonal antibody, is approved for treatment of relapsed/refractory multiple myeloma (RRMM). DARA produces deep clinical responses in RRMM and induces T-cell expansion through reduction of immune suppressive cell populations ($CD38^+$ myeloid-derived suppressor cells and regulatory T and B cells). Atezolizumab (atezo) blocks programmed death-ligand 1 (PD-L1) and was recently approved for metastatic NSCLC that progressed on or during platinum therapy based on data showing improved overall survival (OS) in the atezo vs docetaxel treatment arm. A combination of DARA and atezo may improve clinical responses in NSCLC by enhancing anti-tumor T-cell responses facilitated by checkpoint inhibition. This study will assess the anti-tumor activity and safety profile of DARA plus atezo vs atezo alone in patients (pts) with previously treated advanced or metastatic NSCLC. **Methods:** This is an ongoing phase 1b/2 randomized, open-label, multicenter study of atezo (1200 mg intravenous [IV]; Day 2 of Cycle 1 and Day 1 of each 21-day cycle thereafter) alone or in combination with DARA (16 mg/kg IV weekly for 3 cycles [Days 1, 8, and 15] and then Day 1 of each 21-day cycle thereafter). Eligible pts (≥18 years) must have advanced or metastatic NSCLC and received standard platinum-based therapy with disease progression or intolerance to therapy. ECOG performance status of ≤1 and known PD-L1 tumor status are required. Pts previously treated with anti-CD38 therapy, including DARA, CD137 agonists, or immune checkpoint inhibitors are excluded. The primary endpoint is overall response rate. Secondary outcomes include safety, duration of response, clinical benefit rate (≥16 weeks duration), progression-free survival, OS, and pharmacokinetics and immunogenicity of DARA and atezo when given in combination. Approximately 96 pts will be enrolled; 6 pts will receive combination therapy in a safety run-in cohort for evaluation of dose-limiting toxicity followed by 90 pts randomly (1:1) assigned to the 2 treatments. Clinical trial information: NCT03023423.

TPS9103 **Poster Session (Board #425b), Sat, 8:00 AM-11:30 AM**

B-F1RST: Assessment of novel blood-based biomarkers in patients with first-line advanced or metastatic NSCLC receiving atezolizumab monotherapy. *First Author: Edward S. Kim, Levine Cancer Institute, Charlotte, NC*

Background: The anti–PD-L1 monoclonal antibody atezolizumab inhibits the interaction of PD-L1 with its receptors PD-1 and B7.1, thereby restoring T-cell immunity. In the Phase III OAK study, patients with previously treated advanced NSCLC had improved mOS in the atezolizumab arm (13.8 mo) vs the docetaxel arm (9.6 mo) (HR 0.73 [95%CI: 0.62, 0.87]; *P*= 0.0003), irrespective of PD-L1 expression or histology. A Phase III clinical trial of atezolizumab monotherapy for first-line, PD-L1–selected patients with NSCLC is underway; however, first-line atezolizumab monotherapy for NSCLC treatment in a biomarker-unselected population has not yet been investigated. Current assays to measure PD-L1 expression by IHC require tumor biopsies, which can be difficult to obtain in some patients. Novel blood-based biomarkers will be evaluated retrospectively in B-F1RST (Blood-First-Line Ready Screening Trial) in patients receiving atezolizumab monotherapy in first-line NSCLC. **Methods:** A Phase II, open-label, single-arm study, B-F1RST (NCT02848651), will evaluate the efficacy and safety of atezolizumab in PD-L1–unselected patients with first-line locally advanced or metastatic NSCLC. Eligibility criteria include stage IIIB-IVB NSCLC, ECOG PS 0-1, measurable disease per RECIST v1.1 and adequate hematologic and end-organ function. Exclusion criteria include the presence of *EGFR*mutations or *ALK*fusions, active CNS metastases and prior immunotherapy for NSCLC. Patients will receive atezolizumab 1200 mg IV q3w until disease progression or loss of clinical benefit. Prospective collection of blood samples is mandatory; collection of tissue biopsies is optional. The co-primary endpoints of the study are investigator-assessed ORR per RECIST v1.1 for the efficacy objective and PFS per RECIST v1.1 for evaluating blood-based predictive biomarkers for atezolizumab efficacy, including mutation status. Approximately 150 patients will be enrolled at 25 or more centers in the United States. Clinical trial information: NCT02848651.

TPS9104 **Poster Session (Board #426a), Sat, 8:00 AM-11:30 AM**

Detect T790M in cell free tumor DNA of Chinese advanced non-small cell lung cancer adenocarcinoma patients by different platforms and evaluate clinical outcomes of T790M positive patients with osimertinib monotherapy. *First Author: Zhiyong Liang, Peking Union Medical College Hospital, Beijing, China*

Background: EGFR T790M mutation occurs in approximately 50-60% of non-small cell lung cancer adenocarcinoma (NSCLC) patients with acquired EGFR-TKI resistance, based on tumor re-biopsies using an invasive clinical procedure. Recently, Cell free tumor DNA (ctDNA) has emerged as a specific and sensitive blood-based biomarker and studies have demonstrated ctDNA as a feasible and minimally invasive alternative to tissue biopsy. Data on different technology platforms used for EGFR T790M detection in blood in China is limited. We aim to compare the methods currently available in hospital practise, including cobas EGFR Mutation Test (Roche Molecular Systems), super-ARMS, digital PCR and NGS, to compare each platform and clinically validate each as companion diagnostic to osimertinib. **Methods:** This is an open-label, multi-center study in 250 locally advanced or metastatic NSCLC patients with documented EGFR sensitizing mutation and progression on previous EGFR-TKI. T790M mutation in plasma ctDNA will be tested by four methods: cobas, super-ARMS, digital PCR and NGS in order to evaluate the concordance, sensitivity and specificity of T790M testing in plasma between the cobas test and the other platforms. T790M positive patients by any of the four platforms will receive osimertinib treatment (administered orally as one 80 mg tablet once a day in ASTRIS study, NCT02474355) and the clinical outcomes (PFS, ORR, OS) will be followed. Patients will continue to receive osimertinib until disease progression (PD), as assessed by investigators. Digital PCR and NGS will be used to monitor the molecular evolution of T790M and C797S in plasma from NSCLC patients during osimertinib treatment. NGS will also be used to explore acquired resistance mechanisms before osimertinib treatment and after PD. 23 of planned 250 patients have been enrolled in the study as of January 2017. Clinical trial information: NCT02997501.

TPS9105 **Poster Session (Board #426b), Sat, 8:00 AM-11:30 AM**

Phase II clinical trial of atezolizumab (A) in advanced non-small cell lung cancer (NSCLC) patients (pts) previously treated with PD1-directed therapy. *First Author: Saveri Bhattacharya, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: While inhibition of the PD1 axis is associated with improved response rates vs cytotoxic therapy in pts with previously treated NSCLC, the majority of pts will not benefit from objective response. Anti-PD1 and PD-L1 antibodies block distinct inhibitory pathways, possibly resulting in different clinical outcomes. While anti-PD1 antibodies block PD1 binding to PD-L1 and PD-L2, they do not affect the inhibitory signal of the PD-L1/B7.1 interaction. This trial is critical to establishing the clinical activity of sequencing PD-L1 inhibition in pts previously treated with PD1 directed and identifying candidate biomarkers of response and resistance to PD1/PD-L1 directed therapies. **Methods:** In this phase II clinical trial, pts with advanced NSCLC with stable or progressive disease on anti-PD1 therapy (nivolumab or pembrolizumab) will be treated with A1200 mg day 1 of a 21-day cycle until disease progression, unacceptable toxicity or death. The kinetics of response to anti-PD1 therapy can be variable and in some cases characterized by pseudo-progression. In order to account for variable response kinetics to PD1 therapy, pts will be enrolled in 3 parallel cohorts based on best overall response (BOR) to PD1 therapy (stable disease; progressive disease; complete or partial response followed by progressive disease). The primary objective is BOR to A. Secondary endpoints include duration of response, progression free survival, overall survival, and safety. 37 pts will be enrolled per cohort. A Simon 2-stage design will be employed with a stopping rule for futility if 0 of the first 11 evaluable patients within a cohort have a confirmed objective response in Stage 1. A promising result would be if ≥3 responses are seen at the conclusion of stage 2. This design has 80% power to detect a true response rate of 15% in each cohort (null rate 2%; alpha 0.05). Mandatory biopsies at time of enrollment, archival tumor pre-PD1 directed therapy, and optional biopsy at the time of progression on A will be collected for exploratory studies of immune biomarkers of response and resistance. Clinical trial information: NCT03014648.

TPS9106 **Poster Session (Board #427a), Sat, 8:00 AM-11:30 AM**

METIS: A phase 3 study of radiosurgery with TTFields for 1-10 brain metastases from NSCLC. *First Author: Minesh P. Mehta, University of Maryland Medical Center, Baltimore, MD*

Background: Tumor Treating Fields (TTFields) are non-invasive regional anti-mitotic treatment modality, based on low intensity alternating electric fields. Efficacy of TTFields in non-small cell lung cancer (NSCLC) has been demonstrated in multiple *in vitro* and *in vivo* models, and in a phase I/II clinical study. TTFields treatment to the brain was shown to be safe and to extend overall survival in newly-diagnosed glioblastoma patients. **Methods:** 270 patients with 1-10 brain metastases (BM) from NSCLC will be randomized in a ratio of 1:1 to receive stereotactic radio surgery (SRS) followed by either TTFields or supportive care alone. Patients are followed-up every two months until 2nd cerebral progression. Patients in the control arm may cross over to receive TTFields at the time of 2st cerebral progression. Objectives: To test the efficacy, safety and neurocognitive outcomes of TTFields in this patient population. Endpoints: Time to 1st cerebral progression based on the RANO-BM Criteria or neurological death (primary); time to neurocognitive failure based on the following tests: HVLT, COWAT and TMT; overall survival; radiological response rate; quality of life; adverse events severity and frequency (secondary). Main eligibility criteria: Karnofsky performance status (KPS) of 70 or above, 1 inoperable or 2-10 brain lesions amenable to SRS, optimal standard therapy for the extracranial disease, no brain-directed therapy, no signs of significantly increased intracranial pressure, no electronic implantable devices in the brain. Treatment: Continuous TTFields at 150 kHz for at least 18 hours per day will be applied to the brain within 7 days of SRS. The treatment system is a portable medical device allowing normal daily activities. The device delivers TTFields to the brain using 4 Transducer Arrays, which may be covered by a wig or a hat for cosmetic reasons. Patients will receive the best standard of care for their systemic disease. Statistical Considerations: This is a prospective, randomized, multicenter study for 270 patients. The sample size was calculated using a log-rank test (based on Lakatos 1988 and 2002) and has 80% power at a two sided alpha of 0.05 to detect a hazard ratio of 0.57. Clinical trial information: NCT02831959.

TPS9107 Poster Session (Board #427b), Sat, 8:00 AM-11:30 AM

A phase II, noncomparative, open label, multicentre, study of AZD9291 in patients with locally advanced or metastatic EGFR mutated "T790M undetectable or unknown" non-small cell lung cancer (stage IIIB-IV) after no immediate prior EGFR TKI (OSIRIS study). *First Author: Hector J. Soto Parra, Medical Oncology, University Hospital Policlinico, Vittorio Emanuele, Catania, Italy*

Background: Osimertinib (OSI), is an oral, potent, irreversible inhibitor of both epidermal growth factor receptor (EGFR) sensitizing and resistance mutations (T790M) indicated for the treatment of pts with advanced EGFR T790M mutation-positive NSCLC. In the AURA study, OSI was associated with an ORR of 21% (13/61) among all patients with T790M negative mutation. Response rate broken down by immediate versus no immediate prior EGFR TKI was 11% (4/36 pts) versus 36% (9/25) respectively. This better activity with deferred OSI, drug able to inhibit also the EGFR sensitizing mutations, could be explained by a selection of sensitive tumor cells during chemotherapy (re-challenge strategy). Aim of the current study is prospective evaluate the efficacy of OSI in EGFR mutated, T790M "undetectable or unknown" patients as third-line therapy after a first-line EGFR TKI and a subsequent chemotherapy. **Methods:** OSIRIS study is a prospective single-arm, phase 2, open label, italian multicenter study. T790M "undetectable or unknown" is defined by the following conditions: inconclusive/negative tumor test result for T790M at the time of disease progression or medical inaccessible/contraindications/declined tumor biopsy or insufficient tumor tissue for testing. Pts are treated with OSI 80 mg once daily until disease progression or unacceptable toxicity. The single-arm design is appropriate, as there is no accepted standard therapy for these pts after chemotherapy. The primary endpoint is ORR according to RECIST version 1.1. The null hypothesis that the true response rate is 9% will be tested against a one-sided alternative. In the first stage, 32 pts will be accrued. If there are 3 or fewer responses in these 32 pts, the study will be stopped. Otherwise, 49 additional pts will be accrued for a total of 81. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 19%. Secondary endpoints are PFS, OS and safety. Exploratory: mutational analysis of a panel of genes involved in resistance to EGFR-TKIs is planned. Clinical trial information: 2016-002555-17.

9500 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A phase III randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma (U.S. Intergroup E1609): Preliminary safety and efficacy of the ipilimumab arms. *First Author: Ahmad A. Tarhini, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: In the U.S., 3 regimens have regulatory approval as adjuvant therapy for high-risk melanoma, including high-dose interferon-alfa (HDI) and ipilimumab 10 mg/kg (ipi10). Ipilimumab 3 mg/kg (ipi3) has regulatory approval for metastatic inoperable melanoma. The toxicity of ipi is dose- dependent, and following the recent approval of adjuvant ipi10, it has become urgent to evaluate the relative safety and efficacy of adjuvant ipi at the 2 dose levels that have been tested in E1609. **Methods:** E1609 randomized patients (pts) with resected high-risk melanoma (stratified by stages IIIB, IIIC, M1a, M1b) to ipi10 or ipi3 versus HDI. Co-primary endpoints were RFS and OS. The current analysis investigates the relative safety and preliminary, non-comparative RFS of the ipi arms as of 3/2/17. **Results:** E1609 was activated on 5/25/11 and completed adult pt accrual on 8/15/14. Accrual to ipi10 was suspended due to toxicity between 9/23-11/16/2013. Final adult pt accrual was 1670 including 511 ipi10, 636 HDI and 523 ipi3 pts. Treatment related adverse events (AEs) were reported among 503 ipi10 and 516 ipi3 pts. Worst degree (Gr 3+) AEs were experienced by 57% ipi10 and 36.4% ipi3 pts and were mostly immune related (Table 1). AEs led to discontinuation of treatment in 271 (53.8 %) of 503 ipi10 and in 180 (35.2 %) of 512 ipi3 pts during the initial 4 dose induction phase. Gr5 AEs considered at least possibly related were 8 with ipi10 and 2 with ipi3. At a median follow-up of 3.1 years, an unplanned RFS analysis of ipi3 and ipi10 on concurrently randomized pts showed no difference between the 2 arms. Three-year RFS rate was 54% (95% CI: 49, 60) with ipi10 and 56% (50, 61) with ipi3. **Conclusions:** Adjuvant therapy of pts with high-risk melanoma is associated with significantly more toxicity at ipi10 compared to ipi3. An unplanned RFS analysis of concurrently randomized pts on the 2 ipi arms showed no difference in RFS. Clinical trial information: NCT01274338.

Common treatment-related Gr3+ AEs by treatment arm.

	Ipi10 (%)	Ipi3 (%)
Diarrhea/colitis	19.5	13
Endocrine	10.7	5.4
Liver	8.2	3.5
Skin	8.8	5.8
Pancreas	5	3.7
Neurologic	1.8	1.2

9501 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Adjuvant bevacizumab as treatment for melanoma patients at high risk of recurrence: Final results for the AVAST-M trial. *First Author: Philippa Corrie, Cambridge Cancer Trials Centre, Cambridge, United Kingdom*

Background: Bevacizumab (Bev) is a recombinant humanised monoclonal antibody to vascular endothelial growth factor (VEGF) shown to improve survival in several advanced solid tumours. As VEGF is a relevant target in melanoma, AVAST-M aimed to evaluate the role of Bev in melanoma patients at high risk of recurrence. **Methods:** AVAST-M (ISRCTN81261306) is a randomised phase III trial evaluating single agent Bev (7.5mg/kg IV 3 weekly for 1 year) as adjuvant therapy after resection of AJCC stage IIB, IIC and III cutaneous melanoma compared to standard observation (Obs). 1320 patients were needed to detect 8% differences in 5 year overall survival (OS) rate from 40% to 48%; 85% power, 5% alpha level. Primary endpoint was OS; secondary endpoints included disease free interval (DFI), distant-metastasis free interval (DMFI). *BRAF* and *NRAS*mutation status were obtained in 682 patients in a translational sub-study. **Results:** From July 2007 to March 2012, 1343 patients were recruited (671 to Bev; 672 to Obs). 56% were male, median age was 56 years (range 18-88 years), 14% were stage IIIA and 59% were stage IIIB/C. With 6 years median follow-up, 505 (38%) patients had died (251 [37%] on Bev; 254 [38%] on Obs); 699 (52%) patients had recurred (335 [50%] on Bev, 369 [55%] on Obs). OS at 5 years was 64% on Bev versus 63% on Obs (Hazard ratio [HR] 0.99; 95% confidence interval [CI] 0.84-1.18, p=0.96). At 5 years, 51% were disease free on Bev versus 45% on Obs (HR 0.85; 95% CI 0.74-0.99, p=0.04) and 59% were distant metastasis free on Bev versus 54% on Obs (HR 0.91; 95% CI 0.77-1.07, p=0.24). A *BRAF*V600 mutation was found in 44% of tumours assessed; 20% were *NRAS* mutant. *BRAF* mutant patients treated with Bev tended to have better DFI (HR=0.79 95% CI 0.58-1.08, p=0.14) and OS (HR=0.79; 95% CI 0.55-1.13, p=0.20); this was not evident for *BRAF*WT. *NRAS* mutant patients tended to have worse DFI (HR=1.39; 95% CI 1.03-1.88; p=0.03) and OS (HR=1.18; 95% CI 0.85-1.62, p=0.20) than *NRAS*WT patients. **Conclusions:** This large, multi-centre trial of melanoma patients at high risk of recurrence has shown that adjuvant Bev improves DFI, but this does not translate into an overall survival benefit. Funding:Cancer Research UK; drug supplied by Roche Products Ltd. Clinical trial information: ISRCTN81261306.

9502 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A randomized multicenter phase 3 trial of adjuvant fotemustine versus surveillance in high risk uveal melanoma (UM) patients (FOTEADJ). *First Author: Sophie Piperno-Neumann, Medical Oncology, Institut Curie, Paris, France*

Background: Up to 30% of UM patients will develop metastases, with a median survival of 12 months in the metastating setting. Prognostic factors combine clinical features of the primary tumor (diameter, thickness, retinal detachment, extra-scleral extension) and genetic factors (monosomy 3, 8 q gain and class 1 /2 gene expression profiling).The genomic analysis is feasible by fine needle aspiration biopsies before radiotherapy for small UM or on enucleated eyes. **Methods:** Multicenter randomized phase 3 trial with adjuvant fotemustine, 6 cycles, 100 mg/m2 versus surveillance for 3 years (liver tests/3 months, liver MRI or CT/6 months, whole body CT/12 months) in patients with high risk of recurrence, defined by clinical criteria (diameter $>$ 15 mm with extra scleral extension and/or retinal detachment or diameter $>$ 18 mm) or genomic high risk signature by array-CGH (monosomy 3 or deletion of 3p associated with gain of chromosome 8). The primary objective was 5-year Metastasis Free Survival (MFS). With an expected increase of 5-year MFS from 50 to 70%, 302 patients and 99 events were required to achieve an 95%-power with a 5% type I error rate. Secondary objectives were overall survival (OS), safety (NCI-CTC v3), quality of life (QLQ-C30). Interim analyses were planned for safety and after 50 events, disclosed to an independent safety monitoring board. **Results:** The trial was stopped for futility after 244 patients had been recruited between June 2009 and January 2016. No unexpected toxicity was found in the chemotherapy group. The study was amended to go on with intensive surveillance in new high risk patients. Ninety-one metastases and 43 deaths were reported, with no treatment-related death. With a median follow-up of 3 years, the 3-year MFS is 60.3% in the chemo group and 60.7% in the surveillance group (HR 0.97 [0.64-1.47]). The 3-year OS is 79.4% [73.2-85.7], with no difference between the 2 groups of patients. **Conclusions:** FOTEADJ is the first adjuvant randomized phase 3 trial based on genomic analysis in high risk UM patients. Despite negative results, it shows the feasibility of multicenter adjuvant studies in this rare cancer and provides genomic data in small tumors for future trials. Clinical trial information: NCT02843386.

9503 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

REGN2810: A fully human anti-PD-1 monoclonal antibody, for patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC)—Initial safety and efficacy from expansion cohorts (ECs) of phase I study. *First Author: Kyriakos P. Papadopoulos, START, San Antonio, TX*

Background: There is no established standard of care for unresectable locally advanced or metastatic CSCC. UV-induced DNA damage causes hypermutation in most CSCCs. Therefore, these tumors may be responsive to PD-1 checkpoint blockade. In the dose escalation portion of the phase 1 study of REGN2810, a durable (19 + months) radiologic complete response was observed in a patient (pt) with metastatic CSCC (ASCO 2015, #3024). **Methods:** ECs enrolled pts with distantly metastatic (EC 7) and locally advanced (EC 8) CSCC. All patients received 3 mg/kg REGN2810 by intravenous infusion over 30 minutes every 2 weeks for up to 48 weeks. Research biopsies were performed at baseline and Day 29 (and at progression, if possible). Tumor measurements were performed every 8 weeks according to RECIST 1.1 to determine overall response rate (ORR). Data cutoff date was 31 Jan 2017. **Results:** 26 pts were enrolled (10 in EC 7 and 16 in EC 8): median age, 72.5 y (range, 56-88y); median PS 1 (range, 0 – 1); 21M:5F; median number of prior systemic therapy regimens, 1 (range, 0 – 2). Median exposure to REGN2810 was 7 doses (range, 1-22). The most common treatment-related adverse event of any grade was fatigue (19.2%). Each of the following $\geq$ Grade 3 related AEs occurred once: AST elevation, ALT elevation, arthralgia, and rash. ORR (PR + CR, including unconfirmed) and disease control rate (ORR+SD) were 52% (12/23; 4uPR, 5 PR, 2CR, 1 uCR) and 70% (16/23, including 4SD), respectively. Three patients are not yet evaluable. Median PFS and OS have not been reached, and only one patient has experienced PD during REGN2810 treatment after initial response. Correlative studies are in process, including PD-L1 status and whole exome tumor DNA sequencing. **Conclusions:** REGN2810 is well tolerated and produces antitumor activity in patients with advanced CSCC. A pivotal trial of REGN2810 for patients with advanced CSCC is enrolling patients (NCT02760498). Clinical trial information: NCT02383212.

9504 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Long-term outcomes in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab (pembro) treatment. *First Author: Caroline Robert, Gustave Roussy, Villejuif, France*

Background: Pembro demonstrated superior PFS and OS vs ipi in ipi-naive pts with advanced melanoma in the phase 3 KEYNOTE-006 study (NCT01866319). Here, we present long-term outcomes for all pts and in those pts who completed pembro therapy. **Methods:** Eligible pts (N = 834) were randomized 1:1:1 to pembro 10 mg/kg Q2W, pembro 10 mg/kg Q3W, or ipi 3 mg/kg Q3W for 4 doses. Treatment was continued for 2 yr (pembro only) or until disease progression, intolerable toxicity, or pt/investigator decision to discontinue. Per protocol, pts could interrupt pembro for ≤12 wk before discontinuation was required. Tumor imaging was performed at wk 12, then every 6 wk up to wk 48 and every 12 wk thereafter. After the prespecified final analysis, response assessments were per immune-related response criteria (irRC) by investigator review. **Results:** As of the data cutoff (Nov 3, 2016), median follow-up in the total population was 33.9 mo (range, 32.1-37.6). 33-mo OS rates were 50% in the pooled pembro arms (n = 556) and 39% in the ipi arm (n = 278); 33-mo PFS rates were 31% and 14%. ORR was 42% and 16%. Median duration of response was not reached for pembro (range 1.0+ to 33.8+ mo) or ipi (1.1+ to 34.8+ mo); 46 (68%) pembro-treated pts and 7 (58%) ipi-treated pts had a response lasting ≥30 mo. Among the 104/556 (19%) pts who completed pembro, median exposure to pembro was 24.0 mo (range 22.1-25.9). After a median follow-up of 9.0 mo after completion of pembro, 102 (98%) pts were alive. Responses were durable in pts who completed pembro; 9.7 mo after completion of pembro, estimated PFS (95% CI) was 91% (80-96) in all 104 pts, 95% (69-99) in pts with complete response (n = 24), 91% (74-97) in pts with partial response (n = 68), and 83% (48-96) in pts with stable disease (n = 12). **Conclusions:** Pembro provides durable efficacy after stopping the protocol-specified duration of treatment in pts with ipi-naive advanced melanoma in KEYNOTE-006. The estimated risk for progression or death nearly 10 mo after completing pembro is 9% and does not appear to differ by best response to pembro. Clinical trial information: NCT01866319.

9505 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Five-year overall survival (OS) update from a phase II, open-label trial of dabrafenib (D) and trametinib (T) in patients (pts) with *BRAF* V600–mutant unresectable or metastatic melanoma (MM). *First Author: Georgina V. Long, University of Sydney, Sydney, Australia*

Background: D (BRAF inhibitor) + T (MEK inhibitor) combination therapy is associated with rapid clinical responses and has improved clinical outcomes in pts with *BRAF*V600–mutantMM, but long-term (˃ 3 y) clinical efficacy and safety data are limited. The longest follow-up to date of a randomized trial evaluating D+T at the approved dose (150 mg BID/2 mg QD [150/2]) was of the phase II study BRF113220 (part C; median, 45.6 mo) in which durable outcomes were achieved in some pts with *BRAF*V600–mutantMM (3-y OS, 38%). Here, we report updated 5-y landmark analyses to further characterize the impact of D+T in MM. **Methods:** Pts with *BRAF*V600–mutant mm enrolled in BRF113220 part C (NCT01072175) were randomized 1:1:1 to receive monotherapy D (150 mg BID), D+T (150 mg BID/1 mg QD), or D+T (150/2). Pts who progressed on D alone could cross over to the D+T 150/2 arm. Pt disposition, pt demographics, and 4- and 5-y efficacy and safety were analyzed for both the D-alone and D+T (approved 150/2 dose) arms. **Results:** This updated analysis represents an additional ≈ 2 y of follow-up (D and D+T arms; n = 54 each). As of 13 Oct 2016, 45 pts (83%) on D alone had crossed over to D+T. 20 pts were ongoing (D, n = 7 [13%]; D+T, n = 13 [24%]); 80% of D pts and 70% of D+T pts had died. D+T OS remained superior to D alone. The 4- and 5-y OS rates with D+T were 30% and 28%, respectively, demonstrating a stabilization of the OS curve. The PFS curve for D+T also remained stable (4- and 5-y: both 13%). Consistent with earlier results, the best OS for pts who received D+T was seen in pts with normal LDH (5-y, 45%) and normal LDH with disease in < 3 organ sites (5-y, 51%). At the 5-y landmark, 1 additional pt who received D+T improved from a partial to a complete response. Additional follow-up revealed no new safety signals with D+T. Detailed analyses of D crossover pts, responders, and post-progression therapy will be presented. **Conclusions:** This longest follow-up to date of BRAF + MEK inhibitor combination therapy in pts with *BRAF*V600–mutant mm revealed stable OS and PFS lasting ≥ 5 y with consistent tolerability. These results demonstrate that some pts with mm can achieve durable benefit with D+T therapy. Clinical trial information: NCT01072175.

9506 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

COMBI-MB: A phase II study of combination dabrafenib (D) and trametinib (T) in patients (pts) with *BRAF* V600–mutant (mut) melanoma brain metastases (MBM). *First Author: Michael A. Davies, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: CNS metastases are common and associated with very poor prognosis in pts with metastatic melanoma (MM). In the phase II BREAK-MB trial, D had clinical activity in *BRAF* V600–mut MBM. D + T has shown superiority over D alone in pts with *BRAF* V600–mut mm without MBM; however, efficacy of this regimen on MBM has not been characterized. Here, we report results from a phase II trial of D + T in *BRAF*V600–mut MBM (COMBI-MB; NCT02039947). **Methods:** This open-label, phase II study evaluated D 150 mg BID + T 2 mg QD in 4 MBM cohorts: (A) *BRAF*V600E, asymptomatic MBM, no prior local treatment (Tx); (B) *BRAF*V600E, asymptomatic MBM, prior local Tx; (C) *BRAF*V600D/K/R, asymptomatic MBM, with or without prior local Tx; and (D) *BRAF*V600D/E/K/R, symptomatic MBM, with or without prior local Tx. The primary objective was intracranial response rate (IRR) in cohort A (null hypothesis, IRR ≤ 35%). Secondary endpoints included IRR in cohorts B, C, and D; extracranial (ERR) and overall (ORR) response rates; intracranial (IDCR), extracranial (EDCR), and overall (ODCR) disease control rates; duration of IR, ER, and OR; PFS; OS; and safety. **Results:** 125 pts were enrolled (A, n = 76; B, n = 16; C, n = 16; D, n = 17). In cohort A, median age was 52, 53% were male, and 37% had LDH > ULN. At data cutoff (28 Nov 2016; median f/u, 9.0 mo), in cohort A, investigator-assessed IRR was 58% (IDCR, 78%), ERR was 55% (EDCR, 80%), and ORR was 58% (ODCR, 80%). Median duration of IR, ER, and OR was 6.5 mo (95% CI, 4.9-10.3), 10.2 mo (95% CI, 6.5-13.0), and 6.5 mo (95% CI, 4.9-10.3), respectively. Median PFS was 5.6 mo (95% CI, 5.3-7.4). Independent review supported these results. 6-mo OS was 79%; with 31 pts (41%) still in f/u, preliminary median OS was 10.8 mo (95% CI, 8.7-19.6). Efficacy in cohorts B, C, and D will be reported. AEs across cohorts (any, 98%; grade 3/4, 48%) were consistent with prior D + T studies; 10% of pts (8% in cohort A) discontinued due to AEs. **Conclusions:** In this first report of a phase II trial evaluating a BRAF and MEK inhibitor combination in *BRAF*V600–mut MBM, the primary endpoint was met. Promising IRR and IDCR were seen with D + T, but responses appear less durable than reported for mm without MBMs. No unexpected safety issues were observed. Clinical trial information: NCT02039947.

9507 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204. *First Author: Hussein Abdul-Hassan Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Brain metastases (BMts) are a major cause of morbidity/death in MEL. We report the first efficacy data in MEL patients (pts) with BMts who received NIVO+IPI in study CheckMate 204. **Methods:** In this multicenter US trial (NCT02320058), MEL pts with ≥1 measurable BMt 0.5-3.0 cm and no neurologic symptoms or steroid Rx received NIVO 1 mg/kg + IPI 3 mg/kg Q3W x 4, then NIVO 3 mg/kg Q2W until progression or toxicity. Pts with severe adverse events (AEs) during NIVO+IPI could receive NIVO when toxicity resolved; stereotactic radiotherapy (SRT) was allowed for brain oligo-progression if an assessable BMt remained. The primary endpoint was intracranial (IC) clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD] > 6 months). The planned 90-pt accrual is complete; we report efficacy and updated safety for 75 pts with disease assessment before the Nov 2016 database lock. **Results:** Median age was 59 yrs (range 22–79). Median number of induction doses was 3; 26 pts (35%) received 4 NIVO+IPI doses and 38 pts (51%) began NIVO maintenance. Response data are reported at a median follow-up of 6.3 months (Table). The IC objective response rate (ORR) was 56% (95% CI: 44–68); 19% of pts had a complete response. IC and extracranial responses were largely concordant. Rx-related grade 3/4 AEs occurred in 48% of pts, 8% neurologic, including headache and syncope. Only 3 pts (4%) stopped Rx for Rx-related neurologic AEs. One pt died of immune-related myocarditis. **Conclusions:** In CheckMate 204, prospectively designed to investigate NIVO+IPI in MEL pts with BMts, NIVO+IPI had high IC antitumor activity with objective responses in 56% of pts, CR in 19%, and no unexpected neurologic safety signals. The favorable safety and high anti-melanoma activity of NIVO+IPI may represent a new Rx paradigm for pts with asymptomatic MEL BMts and could change practice to avoid or delay whole brain RT or SRT. Clinical trial information: NCT02320058.

	Global	Intracranial	Extracranial
Best overall response, n (%, 95% CI)			
CR	2 (3, 0–9)	14 (19, 11–29)	4 (5, 1–13)
PR	40 (53, 41–65)	28 (37, 26–49)	33 (44, 33–56)
SD >6 months	5 (7, 2–15)	6 (8, 3–17)	2 (3, 0–9)
ORR, n (%, 95% CI)	42 (56, 44–68)	42 (56, 44–68)	37 (49, 38–61)

9508 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases (mets): The Anti-PD1 Brain Collaboration (ABC). *First Author: Georgina V. Long, University of Sydney, Sydney, Australia*

Background: Nivolumab (nivo) and the combination of nivo + ipilimumab (ipi) improve response rates (RR) and progression-free survival (PFS) compared with ipi alone in clinical trials of metastatic melanoma pts, but pts with untreated brain mets were excluded. Brain mets are a major cause of morbidity and mortality in melanoma and their management is critical. We sought to determine the antitumour activity and safety of nivo and nivo+ipi in pts with active melanoma brain mets (NCT02374242). **Methods:** This open-label, ph II trial enrolled 3 cohorts of pts naïve to anti-PD1/PDL1/PDL2/CTLA4 from Nov 2014 - Feb 2017. Pts with asymptomatic melanoma brain mets with no prior local brain therapy were randomised to cohort A (nivo 1mg/kg + ipi 3mg/kg, Q3W x4, then nivo 3mg/kg Q2W) or cohort B (nivo 3mg/kg Q2W). Cohort C (nivo 3mg/kg Q2W) had brain mets 1) that failed local therapy (new +/- progressed in previously treated met), 2) were neurologically symptomatic and/or 3) with leptomeningeal disease. Prior BRAF inhibitor (BRAFi) was allowed. The primary endpoint was best intracranial response (ICR) ≥ wk12. Secondary endpoints were best extracranial response (ECR), best overall response (OR), IC PFS, EC PFS, overall PFS, OS, and safety. **Results:** A total of 66 pts (med f/u 14 mo) were included in this analysis of total 76 planned; median age 60y, 77% male. For cohorts A, B and C: elevated LDH 48%, 58% and 19%; V600BRAF 44%, 56% and 81%; prior BRAFi 24%, 24%, 75%. Table shows RR, PFS and OS. ICR in cohort A treatment naïve vs prior BRAFi was 53% vs 16%. Treatment-related gd 3/4 toxicity in cohorts A, B and C were 68%, 40% and 56%, respectively. There were no treatment-related deaths. **Conclusions:** Nivo monotherapy and ipi+nivo and are active in melanoma brain mets. Ipi +nivo had reduced activity in pts who progressed on BRAFi. Pts with symptomatic brain mets, leptomeningeal mets or previous local therapy responded poorly to nivo alone. Clinical trial information: NCT02374242.

	A N = 25 nivo+ipi	B N = 25 nivo	C N = 16 nivo
ICR % (95% CI)	44 (24, 65)	20 (7, 41)	6 (0, 30)
ICR Complete Response	16 (24, 65)	12 (7, 41)	0
ECR % (95% CI)	38 (18, 62)	26 (10, 48)	21 (5, 50)
6-mo PFS % (95% CI)	50 (33, 75)	29 (15, 56)	0
6-mo OS % (95% CI)	76 (59, 97)	59 (41, 86)	44 (25, 76)

9509 Poster Discussion Session; Displayed in Poster Session (Board #117), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Primary results from a randomized (1:1), open-label phase II study of talimogene laherparepvec (T) and ipilimumab (I) vs I alone in unresected stage IIIB- IV melanoma. *First Author: Jason Alan Chesney, University of Louisville, Louisville, KY*

Background: T is a HSV-1-based oncolytic virus designed to selectively replicate in tumors and produce GM-CSF to stimulate antitumor immune responses. I is an anti-CTLA-4 Ab that blocks inhibition of activated T cells. This is the first randomized study to evaluate the addition of an oncolytic virus to a checkpoint inhibitor. **Methods:** The 1° endpoint was ORR by immune-related response criteria. Key 2° endpoints: duration of response, disease control rate (DCR), PFS, OS, and safety. Prior treatment was allowed but not required. Pts had unresected stage IIIB-IV melanoma with measurable/injectable tumor(s) and no evidence of immunosuppression. T was given at approved dosing until no injectable tumors, disease progression (PD), or intolerance. I was started at w6 in T+I and at w1 in I at 3 mg/kg IV q3w x 4. Primary analysis occurred 6 m after last pt enrolled. **Results:** 198 pts were randomized: 98 T+I; 100 I. Characteristics were similar: 54% stage IIIB-IVM1a, 46% IVM1b/c. Median follow up time was 68 w (T+I) and 58 w (I). ORR was 38.8% (T+I) and 18.0% I, $P = 0.002$, Odds ratio (OR) 2.9. 89% T+I and 83% I pts remain in response. Unconfirmed visceral lesion response was 35.5% T+I vs 13.6% I. OS is immature. Of 190 pts (safety set: 95 T+I, 95 I), most common adverse events (AEs) for T+I, I (%) were fatigue (59, 42), chills (53, 3), and diarrhea (42, 35). 28% T+I and 18% I pts had gr ≥3 tx-related AE. There were 3 deaths (all unrelated) in T+I: 1 myocardial infarction and 2 PD. **Conclusions:** The study met the 1° endpoint. ORR was significantly higher for T+I vs I; responses were not limited to injected lesions. Toxicity of T+I combination was tolerable with no unexpected AEs. Clinical trial information: NCT01740297.

	T+I N = 98	I N = 100
ORR[a] – n (%)	38 (38.8)	18 (18.0)
(95% CI)	(29.1, 49.2)	(11.0, 26.9)
OR (95% CI)	2.9 (1.5, 5.5), $P = 0.002$[c]	
CR – n (%)	13 (13.3)	7 (7.0)
PR – n (%)	25 (25.5)	11 (11.0)
DCR – n (%)	57 (58.2)	42 (42.0)
(95% CI)	(47.8, 68.1)	(32.2, 52.3)
DRR[b] – n (%)	29 (29.6)	13 (13.0)
(95% CI)	(20.8, 39.7)	(7.1, 21.2)
PFS, events/N (%)	52/98 (53.1)	51/100 (51)
Median (95% CI) - m	8.2 (4.2, 21.5)	6.4 (3.2, 16.5)

[a]CR/PR required confirmation ≥ 4 w apart [b]Durable response rate = response ≥ 6 m; descriptive $P = 0.007$[c] [c]Chi-square test with continuity correction

9510 Poster Discussion Session; Displayed in Poster Session (Board #118), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Final results of a phase II multicenter trial of HF10, a replication-competent HSV-1 oncolytic virus, and ipilimumab combination treatment in patients with stage IIIB-IV unresectable or metastatic melanoma. *First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: HF10 is a bioselected replication-competent oncolytic virus derived from HSV-1. Herein, we report the safety and efficacy data of HF10 + ipilimumab (ipi) combination treatment in a Phase II trial in melanoma. **Methods:** Key entry criteria: age ≥ 18 yrs, ECOG ≤ 2, Stage IIIB, IIIC, or IV unresectable melanoma, ipi naïve (IV administration) and measurable non-visceral lesion(s) suitable for injection. HF10 injected into single or multiple tumors (1×10^7 $TCID_{50}$/mL/dose, up to 5mL depending on tumor size and number); 4 injections q1wk; then up to 15 injections q3wk. Four ipi IV infusions (3 mg/kg; concurrent with HF10) were administered q3wk. AEs assessed per CTCAE 4.0. Tumor responses were assessed per mWHO and irRC at 12, 18, 24, 36 and 48 wks for patients (pts) continuing on HF10 monotherapy. Primary endpoint was Best Overall Response Rate (BORR) at 24 wks. Dose limiting toxicity (DLT) defined as ≥ G3 non-hematologic/hematologic toxicity, ≥ G2 neurologic toxicity, or allergic event occurring within 1st 3wks of therapy. **Results:** Of 46 pts enrolled and treated: 59% men, median age 67 yrs (range 28 to 91); disease stage 20% IIIB, 43% IIIC and 37% IV; 57% were treatment naïve and 43% with ≥ 1 prior cancer therapy for unresectable/metastatic melanoma. Most HF10-related AEs were ≤G2, similar to HF10 monotherapy. No DLTs were reported. 37% had ≥G3 AEs, the majority due to ipi. HF10-related ≥G3 AEs (n=3) were embolism, lymphedema, diarrhea, hypoglycemia, and groin pain. Of the 44 efficacy evaluable pts per irRC, BORR at 24 weeks was 41% (16% irCR and 25% irPR); disease stability rate was 68% (16% irCR, 25% irPR and 27% irSD). As of Feb 06, 2017, median PFS was 19 months and median overall survival was 21.8 months. **Conclusions:** The combination HF10 and ipilimumab treatment demonstrated a favorable benefit/risk profile and encouraging antitumor activity in pts with stage IIIB, IIIC, or IV unresectable or metastatic melanoma. Clinical trial information: NCT02272855.

9511 Poster Discussion Session; Displayed in Poster Session (Board #119), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

STREAM: A randomized discontinuation, blinded, placebo-controlled phase II study of sorafenib (S) treatment of chemonaïve patients (pts) with metastatic uveal melanoma (MUM). *First Author: Max E. Scheulen, Innere Univ Klinik Und Poliklinik, Essen, Germany*

Background: There is no established systemic treatment for pts with MUM. The STREAM study evaluated the efficacy of the oral multikinase inhibitor S in chemonaïve pts with MUM with the primary endpoint progression-free survival (PFS). **Methods:** During the initial 56d run-in period all pts received oral S 400 mg bid with concomitant monitoring by magnetic resonance imaging including diffusion weighted imaging (DWI-MRI). Pts with partial remission (PR) on d56 according to RECIST 1.1 were further treated with open-label S and monitored, pts with progressive disease (PD) were taken off study, and pts with stable disease (SD) were randomly assigned to blinded S or placebo (P) and were further monitored every 8 wks and unblinded in case of PD. Pts on S were taken off study and pts on P were offered S with further monitoring. **Results:** Altogether, 118 (79.2%) of 149 pts entering the run-in period were evaluable for response on d56. Two pts had PR (1.7%), 78 pts had SD (66.1%) and 38 pts had PD (32.2%), respectively. Median PFS from randomization was significantly longer with S (5.5 mths) than P (1.9 mths, HR = 0.527, p = 0.0079). S was readministered to 23 pts with PD under P (59.0%) with a median PFS of 2.0 mths (range 1.2-15.7 mths). Overall survival (OS) was not different between the S group (median 14.8 mths, range 3.7-38.3 mths) and the P group (median 14.4, range 3.3-37.3 mths). During the entire study there were 43 NCI-CTCAE grade 3 and 9 grade 4 adverse events requiring dose reduction of S to 200 mg bid or treatment discontinuation, respectively. No pt died from toxicity. The evaluation of the apparent diffusion coefficient (ADC) ratio derived from DWI-MRI in 47 pts of the run-in period showed a significant difference between pts with SD and pts with PD ($p < 0.05$). **Conclusions:** The primary endpoint of STREAM was reached. S is clinically active and tolerable in first-line treatment of pts with MUM with an increase of median PFS from 1.9 mths for P to 5.5 mths for S (p = 0.0079). The median OS of 14.8 mths compares favorably with previous findings in pts with MUM. Besides morphological MRI features, ADC ratio may be used as an additional functional response criterion. Clinical trial information: NCT01377025.

9512 Poster Discussion Session; Displayed in Poster Session (Board #120), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Re-challenge with BRAF-directed treatment: A multi-institutional retrospective study. *First Author: Sara Valpione, The Christie Hospital and University of Padova, Manchester, United Kingdom*

Background: Most patients treated with BRAF inhibitors (BRAFi) +/- MEK inhibitors (MEKi) eventually progress on treatment. Along with genetic acquired resistance, epigenetic mechanisms that could be reversed after BRAFi discontinuation have been described. The purpose of this study was to analyse outcomes for patients (pts) retreated with BRAF-directed therapy. **Methods:** 116 pts who received BRAFi based therapy and, after a break, were re-challenged with BRAFi +/- MEKi treated at 14 centres in Europe, US, and Australia were analysed for progression free survival (PFS) and response rate (RR), as well as factors predicting overall survival (OS) (demographics, disease stage, treatment, LDH level, duration of first BRAFi treatment, reason for first BRAFi discontinuation and interval between BRAFi stop and re-challenge). Multivariate Cox regression, regression trees and Kaplan Meier method were used. **Results:** Median duration of 1st BRAFi +/- MEKi treatment was 9.4 months (mts) and 7.7 mts for the subsequent treatment after discontinuation (immunotherapy 72%, other 17 %, drug holiday 11%). Brain metastases were present in 51 pts (44%). RR to re-challenge with BRAFi +/- MEKi was 43%: complete response (CR) 3%, partial response (PR) 39%, stable disease 24% and progressive disease (PD) 30%, 4% missing. Of 80 pts who previously discontinued BRAFi for PD, 31 (39%) responded (30 PR and 1 CR). Median OS from retreatment was 9.8 mts. Independent prognostic factors for survival at re-challenge included number of metastatic sites (HR = 1.32 for each additional organ with metastases, $p < .001$), LDH (HR = 1.37 for each multiple of the upper normal limit, $p < .001$), while combination of BRAFi+MEKi conferred a better prognosis vs BRAFi alone (HR = 0.5, p = .006). Pts with < 3 metastatic sites treated with BRAFi and MEKi had a better survival (median OS not reached) and pts with ≥ 3 metastatic sites and raised LDH treated with BRAFi alone had the worse outcome (median OS 4 mts). Number of metastatic sites (HR = 1.44, $p < .001$) and combination of BRAFi and MEKi (HR = 0.45, $p < .001$) were independent prognostic factors for PFS (median 5.0 mts). **Conclusions:** Re-challenge with BRAFi +/- MEKi induces a clinically significant response and should be considered for selected cases.

9513 Poster Discussion Session; Displayed in Poster Session (Board #121), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Incidence, features and management of radionecrosis (RN) in melanoma patients (pts) treated with cerebral radiotherapy (RT) and anti-PD-1 antibodies (PD1). *First Author: Ines Esteves Domingues Pires Da Silva, Melanoma Institute Australia, Sydney, Australia*

Background: Melanoma brain metastases confer poor prognosis, with various treatments used including RT and PD1. While RT and PD1 may have a synergistic effect to improve efficacy, RN may complicate RT, and whether PD1 potentiates this is unknown. We examined the incidence and features of RN and other neurotoxicities in melanoma pts treated with PD1 and whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS). **Methods:** Pts treated with PD1 who received WBRT/SRS during or within 1 year (y) of PD1 who survived > 1y were examined for short and long term neurotoxicity. 2 cohorts were included: (A) consecutive pts fulfilling eligibility criteria from 8 melanoma centers, (B) additional cases of RN from 3 centers. Pt demographics, disease features, treatment details, neurotoxicity, and outcome data were collected. **Results:** Cohort A included 118 pts, with median follow-up of 24.3 months (mo). Median age was 56yo, 51% had mutant BRAF, 41% elevated LDH and 65% were ECOG 1-2 at PD1 start. 58% had prior ipilimumab and 43% prior MAPK inhibitors. 85% were treated with pembrolizumab, 10% nivolumab and 5% combination ipilimumab/nivolumab. Most pts (82, 69%) had SRS, 22 (19%) had WBRT alone and 14 pts (12%) had both. Median PFS was 24mo and OS was 45.8mo. 21 pts (18%) developed RN, (14/82) 17% after SRS, (2/22) 9% after WBRT and (5/14) 36% after both. With 13 further cases from cohort B (total 34), all had radiological signs on MRI, 78% had neurological symptoms and 56% had pathological confirmation of RN. Median time to symptom onset and to first radiological sign was 9.8mo and 10.8mo, respectively. 52% were treated with steroids and 30% had bevacizumab, with clinical improvement in 64% and 100%, respectively. Updated analysis including clinical variables associated with RN development will be presented, including RT dose and schedule. **Conclusions:** RN is a significant toxicity in melanoma pts with brain metastases treated with RT and PD1, particularly in long term survivors. Further research to identify those at risk of RN, those who do not require RT, and studies exploring RT and PD1 schedules are required.

9514 Poster Discussion Session; Displayed in Poster Session (Board #122), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

The demand for psycho-oncological support in 820 melanoma patients: What are the determinants for the development of distress? *First Author: Andrea Forschner, Department of Dermatology Eberhard-Karls University of Tuebingen, Tuebingen, Germany*

Background: There is limited data about the impact of melanoma on the psychological burden of patients. Despite some known predictors for distress like female gender or younger age, melanoma stages have not been found being related to distress in melanoma patients and there is no data concerning distress in melanoma patients under systemic treatment for metastases. **Methods:** Between July and September 2016, 820 melanoma patients at the outpatient clinic at the Department of Dermatology at the University of Tuebingen underwent psycho-oncological screening. The patients routinely completed the distress thermometer (DT), supplemented by a problem list, before consulting the physician. DT scores ≥ 5 are above-threshold, indicating the need for psycho-oncological support. We matched psycho-oncological data with tumor and patient specific data to examine tumor or patient specific influence on distress using logistic regression. **Results:** 406 (49.5%) men and 414 (50.5%) women were included, mean age was 62.35 years (IQR 52-75), mean time since primary diagnosis of melanoma was 54.84 months (IQR 15-76). 359 (44%) of the patients suffered from advanced melanoma (stage III n = 182, stage IV n = 177). 120 patients (14.6%) received systemic treatment for metastases: 90/120 (75%) checkpoint inhibitors, 27/120 (22.5%) targeted therapy and 3/120 (2.5%) chemotherapy. 338/820 (41.2%) of the patients met the cut-off score for distress. Significant influencing factors ($p < 0.05$) for DT values of ≥ 5 were: female gender, younger age, melanoma stage III and IV. Interestingly we found a lower risk for values above-threshold for patients under systemic treatment, although this was not significant (p = 0.252). **Conclusions:** This is the first analysis to demonstrate the impact of advanced melanoma stages on DT scores above-threshold. Our study is also the first to indicate a lower risk for distress in patients under systemic treatment. This might be due to the closer contact between these patients and their physicians. Nevertheless, more than 40% of our patients needed psycho-oncological support. Departments that care for melanoma patients should therefore be fitted by a sufficient number of psycho-oncologists.

9515 Poster Discussion Session; Displayed in Poster Session (Board #123), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Association of distinct baseline tissue biomarkers with response to nivolumab (NIVO) and ipilimumab (IPI) in melanoma: CheckMate 064. *First Author: Scott Rodig, Brigham and Women's Hospital, Boston, MA*

Background: CheckMate 064 (open label, phase 2) randomized advanced melanoma pts to NIVO 3 mg/kg Q2W for 6 doses then IPI 3 mg/kg Q3W for 4 doses (n = 70; cohort A), or the reverse (IPI then NIVO; n = 70; cohort B). More cohort A than cohort B pts had complete or partial response (54% and 31%, respectively). We sought to determine whether common or distinct baseline biomarkers were associated with response for each cohort. **Methods:** Protein expression of biomarkers identifying a broad array of cell lineages and immunoregulatory factors was determined by IHC and evaluated by 2 pathologists, with concordance. Global transcript expression was determined by RNAseq from frozen tissue. An elastic net predictor was trained on cohort A ($\alpha = 0.1$, $\lambda = 0.05$) using leave-one-out cross-validation. RECIST v1.1 was used to assess tumor response. **Results:** Patients with tumors showing a pro-inflammatory transcriptional signature at baseline had superior overall response in cohort A, but not cohort B. Consistent with this observation, a parsimonious classifier of 10 immune/IFNγ-related genes predicted BOR (AUC 0.87) and OS (CPH log-likelihood $P = 0.0003$) for patients in cohort A, but not cohort B. In contrast, low baseline expression of MHC class I protein by malignant cells (< 50% positive) was associated with disease progression (MHCI < 50% vs ≥50%: 12/13 vs 16/28 progressed) and inferior OS for patients in cohort B (MHCI < 50%: 6.42 mo [2.20, 9.66]; MHCI ≥50%: mOS 18.02 mo [7.98, not reached]: $P = 0.0021$, log-rank test), but not cohort A. **Conclusions:** Different pre-treatment biological characteristics of melanoma are associated with clinical response to NIVO followed by a planned switch to IPI (cohort A) and clinical response to IPI followed by NIVO (cohort B). Improved outcome with initial NIVO is strongly associated with a pro-inflammatory signature enriched for IFNγ targets. Inferior outcome with initial IPI is associated with reduction/loss of MHC I antigen presentation machinery. These data imply that NIVO broadly activates innate and adaptive immunity, whereas IPI is reliant upon CD8/MHC class I mediated adaptive immunity to effect clinical response. Clinical trial information: NCT01783938.

9516 Poster Discussion Session; Displayed in Poster Session (Board #124), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Metagenomic shotgun sequencing to identify specific human gut microbes associated with immune checkpoint therapy efficacy in melanoma patients. *First Author: Arthur E. Frankel, The University of Texas Southwestern, Dallas, TX*

Background: Immune checkpoint inhibitor therapy, ICT, achieves durable remissions in 30-50% of patients (pts) with metastatic melanoma (Larkin et al. *NEJM* 2015). It is still unclear what host factors modulate response to ICT. Preclinical mouse studies with B16 melanoma demonstrated that ICT response was dependent on the presence of specific commensal gut bacteria (Vetizou et al. *Science* 2015; Sivan et al. *Science*2015). These specific gut bacteria induced the maturation of dendritic cells (DCs) and T-cells needed for effective ICT. We sought to determine whether specific gut microbiota are associated with improved response to ICT in melanoma patients. **Methods:** 37 melanoma pts treated with ICT (nivolumab plus ipilimumab or pembrolizumab alone) at UTSW Medical Center were enrolled. Fecal samples were collected prior to ICT. Genomic DNA was extracted, and metagenomic shotgun sequencing (MSS) performed on an Illumina HiSeq 2500 PE-100. Taxonomic (MetaPhlAn) and functional (HUMAnN) analysis was performed on MSS data. Disease status was assessed by CT scans and physical exams every two months. **Results:** Among the 23 evaluable pts, 8 were classified as RECIST responders, 5 with stable disease and 10 with progression. RECIST responder microbiomes were significantly enriched with *Methanobrevibacter smithii* ($p = 0.03$; LDA coupled with effect size measurements, LEfSe; Kruskal-Wallis test), *Bacteroides thetaiotamicron*($p = 0.03$), *Lactobacillus plantarum* ($p = 0.04$), and *Eubacterium limosum*($p = 0.01$) compared to those with progressive disease. **Conclusions:** MSS identified 4 specific gut microbiota associated with improved response to ICT therapy in melanoma pts. All of these bacteria have been shown to modulate host immune response (Bang *PLoS One* 2014; Hickey *Cell Host Microbe* 2016; Rigaux *Allergy* 2009; Kaunachi *World J Gastroent*ertol 2006). To gain mechanistic insight and confirm causality, shotgun metabolomics on the same fecal specimens used for MSS, *in vitro*immune cell assays using the gut microbiota identified, and preclinical modeling in a mouse melanoma model with ICT are underway. These studies may lay the foundation for optimizing the host response to ICT.

9517 Poster Discussion Session; Displayed in Poster Session (Board #125), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Quantitative spatial profiling of PD-1/PD-L1 interaction and HLA-DR/IDO1 to predict outcomes to anti-PD-1 in metastatic melanoma (MM). *First Author: Douglas Buckner Johnson, Vanderbilt University Ingram Cancer Center, Nashville, TN*

Background: Although PD-1/L1 axis directed therapies induce durable responses in some mm patients (pts), biomarkers of response remain elusive. We hypothesized that quantifying key immune suppression mechanisms within the tumor microenvironment would provide superior predictors of response to anti-PD-1 compared with single marker assessment. **Methods:** Pre-treatment tumor biopsies from 124 mm pts treated with anti-PD-1 at 7 academic centers were fluorescently stained with multiple immune markers in discovery ($n = 24$) and validation ($n = 100$) cohorts. Selected biomarker signatures, PD-1/PD-L1 interaction score (proportion of PD-1+ cells co-localized with PD-L1) and IDO1/HLA-DR co-expression were evaluated for anti-PD-1 treatment response and survival. Slides were imaged using Vectra; biomarker positive cells and their co-localization were objectively quantified in pathologist-selected regions using novel Automated Quantitative Analysis (AQUA) algorithms. **Results:** In the discovery cohort, high levels of PD-1/PD-L1 interaction score and/or IDO1/HLA-DR coexpression was strongly positively associated with response to anti-PD-1 ($p = 0.0005$). In contrast, other individual biomarkers (PD-1, PD-L1, CD8) were not associated with response or survival ($p > 0.10$). This finding was replicated in the validation cohort: pts with high PD-1/PD-L1 and/or IDO1/HLA-DR were more likely to respond to treatment ($p = 0.009$). These pts also experienced a three-fold increase in progression free survival (hazards ratio (HR) = 0.33; $p = 0.003$) and overall survival (HR = 0.34; $p = 0.004$). Multivariate analyses revealed that these findings were independent of BRAF mutation, stage, LDH and prior therapy. In the combined cohort ($n = 124$), 80% of responding pts had higher levels of PD-1/PD-L1 interaction scores and/or IDO1/HLA-DR. In contrast, PD-L1 expression alone ($\geq$1% or $\geq$50%) was not predictive of PFS or OS ($p > 0.1$). **Conclusions:** This novel multiplexed method profiling key tumor-immune suppression pathways identified mm pts likely to respond to anti-PD-1 therapy. This method could help stratify patients for PD-1 monotherapy and be useful in guiding future clinical trials.

9518 Poster Discussion Session; Displayed in Poster Session (Board #126), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase Ib/II dose-escalation study evaluating triple combination therapy with a BRAF (encorafenib), MEK (binimetinib), and CDK 4/6 (ribociclib) inhibitor in patients (Pts) with *BRAF V600*-mutant solid tumors and melanoma. *First Author: Paolo Antonio Ascierto, Istituto Nazionale Tumori "Fondazione G.Pascale"- IRCCS, Naples, Italy*

Background: The benefits of BRAF + MEK inhibition (dual combo) in pts with *BRAF V600*-mutant ($BRAF^{V600}$) melanoma are known. Preclinical data supports inhibiting CDK 4/6 and BRAF + MEK (triple combo) to improve antitumor activity. We report safety and preliminary efficacy from a phase 1b/2 study (NCT01543698) of encorafenib (ENCO; a selective BRAF kinase inhibitor), binimetinib (BINI; a MEK inhibitor), and ribociclib (RIBO; a CDK 4/6 inhibitor). **Methods:** Phase 1b of this open-label, multicenter study enrolled pts with confirmed $BRAF^{V600}$advanced solid tumors. Escalating doses of RIBO 100 mg-600 mg QD for 3 wk on/1 wk off were administered with ENCO 200 mg QD + BINI 45 mg BID in successive cohorts (6 pts each) until the maximum tolerated or recommended phase 2 dose (RP2D) was reached. Due to potential pharmacokinetic interactions with RIBO, the ENCO dose was lower than the dual combo RP2D (450 mg QD). Dose escalations followed an adaptive Bayesian model. In phase 2, the triple combo was tested in pts with $BRAF^{V600}$melanoma naïve to prior BRAF inhibitor treatment; the primary endpoint was objective response rate (ORR) per RECIST v1.1. **Results:** In phase 1b ($n = 21$), no dose-limiting toxicities were reported and the triple combo RP2D was ENCO 200 mg QD + BINI 45 mg BID + RIBO 600 mg QD. ENCO AUC was slightly lower than at the dual combo RP2D. In phase 2 ($n = 42$), 59.5% pts had an ECOG PS of 0 and 43% of pts had elevated lactate dehydrogenase. The most common ($\geq$5%) grade 3/4 toxicities were neutropenia (26.2%), increased alanine transaminase (14.3%), diarrhea (7.1%), and anemia (7.1%). Ten pts (23.8%) discontinued treatment due to an AE, of which 4 were increased transaminases.The confirmed ORR was 52.4%, including 4 complete responses, 18 partial responses, and 15 pts with stable disease. Median duration of exposure in phase 2 was 9.1 mo (range, 0.0-21.6). Median progression-free survival was 9.0 mo (95% confidence interval, 7.0-11.1). **Conclusions:** Triple therapy with ENCO + BINI + RIBO in this small trial of pts with high disease burden was associated with responses in over half of pts and some evidence of increased toxicity. Clinical trial information: NCT01543698.

9519 Poster Discussion Session; Displayed in Poster Session (Board #127), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase 1b/2 trial of ribociclib+binimetinib in metastatic *NRAS*-mutant melanoma: Safety, efficacy, and recommended phase 2 dose (RP2D). *First Author: Martin H. Schuler, West German Cancer Center, University Hospital, Essen, Germany*

Background: Simultaneous inhibition of MEK and CDK4/6 may suppress MAPK pathway activation and cell-cycle checkpoint dysregulation in *NRAS*-mutant melanoma, resulting in enhanced antitumor activity. Phase 1b data are reported. **Methods:** The phase 1b primary objective was to determine maximum tolerated dose (MTD)/RP2D. A 28-d cycle of oral ribociclib (RIBO) once daily (QD) for 21 d + oral binimetinib (BINI) twice daily (BID) for 28 d, and a 21-d cycle of RIBO QD + BINI BID, both for 14 d per cycle, were evaluated. Secondary objectives were to evaluate efficacy, safety and pharmacodynamics. **Results:** Based on dose escalation (van Herpen, ESMO 2015), MTD was 600mg RIBO/45mg BINI for the 21-d and 200/45 for the 28-d regimens. Due to promising activity, the 28-d cycle was selected as RP2D(unconfirmed partial response [PR] with limited follow-up occurred in 35% of pts). This finding was supported by comparable and manageable safety and the Bayesian logistic regression model.As of Jan 2017, the RP2D was received by 16 pts in phase 1b (ECOG PS 0/1/2, 63%/31%/6%; elevated lactate dehydrogenase, 44%; stage IVM1c disease, 50%; prior ipilimumab [ipi], 44%; prior anti–programmed death [PD]-1/PD-L1, 31%). Median (range) exposure was 4 (0–13) mo. Common adverse events (AEs) were increased blood creatine phosphokinase, elevated AST, peripheral edema, acneiform dermatitis, diarrhea and fatigue. Common grade 3/4 AEs were elevated AST and ALT (19%/6%), nausea (19%/0%), rash (19%/0%), vomiting (6%/6%) and neutropenia (12%/0%). Confirmed PR (cPR) occurred in 4 pts (25%; time to response, 48–168 d), stable disease in 7 pts (44%), disease progression in 3 pts (19%); 2 pts (12%) were not evaluable. Among cPR pts, 3 had prior ipi and/or anti–PD-1/PD-L1. Median progression-free survival (mPFS) was 6.7 (95% CI, 3.5–9.2) mo. Sequence analysis of synchronous non-*RAS* genetic alterations will be presented. **Conclusions:** Combined RIBO/BINI at the selected RP2D had a manageable safety profile and favorable efficacy (based on mPFS) for *NRAS*-mutant melanoma in phase 1b. Based on these promising data, the phase 2 expansion is underway to assess antitumor activity at the RP2D. Clinical trial information: NCT01781572.

9520 Poster Discussion Session; Displayed in Poster Session (Board #128), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Initial efficacy of anti-lymphocyte activation gene-3 (anti–LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti–PD-1/PD-L1 therapy. *First Author: Paolo Antonio Ascierto, Istituto Nazionale Tumori "Fondazione G.Pascale"- IRCCS, Naples, Italy*

Background: Signaling via LAG-3 and other T-cell inhibitory receptors (eg, PD-1) can lead to T-cell dysfunction and tumor immune escape. Simultaneous blockade of LAG-3 + PD-1 may synergistically restore T-cell activation and enhance antitumor immunity. In a phase 1/2a study, BMS-986016 (IgG4 mAb targeting LAG-3) ± nivo (IgG4 mAb targeting PD-1) demonstrated tolerability, peripheral T-cell activation, and preliminary clinical activity (NCT01968109; Lipson E, et al. *J Immunother Cancer.* 2016;4[s1]:173 [P232]). Here we describe preliminary efficacy of BMS-986016 + nivo in pts with MEL whose disease progressed on/after prior anti–PD-1/PD-L1 therapy, along with updated safety from all dose expansion pts. **Methods:** Pts with MEL must have had prior anti–PD-1/PD-L1 (± anti–CTLA-4 or BRAF/MEK inhibitors) and progressive disease (PD). Pts received BMS-986016 80 mg + nivo 240 mg IV Q2W. Primary objectives were safety and objective response rate (ORR; complete [CR] + partial [PR] response), disease control rate (DCR; CR + uCR + PR + uPR + stable disease [SD] > 12 wk), and duration of response (RECIST v1.1). **Results:** At data cutoff, 43 pts with MEL had been treated with BMS-986016 + nivo following PD on/after prior anti–PD-1/PD-L1 with known prior best responses of 1 CR, 9 PR, 12 SD, and 16 PD. Of the 43 pts, 30 (70%) also had prior anti–CTLA-4, 20 (47%) had ≥ 3 prior therapies, and 15 (35%) had *BRAF*mutations.In the 31 efficacy-evaluable pts to date, ORR was 16% (confirmed/unconfirmed) and DCR was 45% with benefit observed even in some pts refractory to prior anti–PD-1. Evaluations are ongoing for most pts, with median treatment duration of 10 wk for all 43 pts. Immunopathologic (eg, PD-1/PD-L1 and LAG-3 expression) and clinical characteristics of responders vs nonresponders will be presented. Any grade and grade 3/4 treatment-related AEs occurred in 46% and 9%, respectively, across all dose expansion pts (n = 129). **Conclusion:** Addition of BMS-986016 to nivolumab demonstrates encouraging initial efficacy in pts with MEL whose disease progressed on/after prior anti–PD-1/PD-L1 therapy, and a safety profile similar to nivolumab monotherapy. Clinical trial information: NCT01968109.

9521 Poster Session (Board #129), Sat, 1:15 PM-4:45 PM

Immune-related tumor response dynamics in melanoma patients (pts) treated with pembrolizumab: Identifying markers for clinical outcome and treatment decisions. *First Author: Mizuki Nishino, Dana-Farber Cancer Institute, Boston, MA*

Background: PD-1 inhibitors have shown marked efficacy in advanced melanoma and are associated with unique response patterns. We aimed to characterize the tumor burden dynamics and identify quantitative imaging markers for overall survival (OS) in melanoma pts treated with pembrolizumab. **Methods:** The study included 107 advanced melanoma pts (63 males; median age: 63) treated with pembrolizumab monotherapy at DFCI. Tumor burden dynamics were assessed on serial CT scans during therapy by irRECIST, which uses unidimensional measurements and includes new lesions in tumor burden [Clin Cancer Res. 2013;19:3936-43]. The relationships between tumor burden dynamics and OS were studied. **Results:** Among 107 pts, 96 pts had measurable tumor burden at baseline and 11 had non-target lesions alone at baseline. Among the 96 pts, maximal tumor shrinkage ranged from -100% to 567% (median:-18.5%). Overall response rate was 44% (42/96; irCR in 5, irPR in 37). Tumor burden remained < 20% increase from baseline throughout therapy in 57 pts (55%). Using a 3-month landmark analysis, pts with < 20% tumor burden increase from baseline at 3 months had longer OS than pts with ≥ 20% increase (12-month OS rate: 82 vs. 53%). In extended Cox models, pts with < 20% tumor burden increase during therapy had significantly reduced hazards of death (HR = 0.19, 95%CI: 0.08–0.43, p < 0.0001 univariate; HR = 0.18, 95%CI: 0.08-0.41, p < 0.0001, multivariable). Five pts (5%) experienced pseudoprogression; 3 pts had increase of target lesions with subsequent response, which was noted after confirmed irPD on consecutive scans. Two pts with no measurable tumor burden progressed with new/non-target lesions that subsequently regressed. **Conclusions:** Tumor burden increase of < 20% from the baseline during pembrolizumab therapy was associated with longer OS, proposing a practical prognostic marker to guide treatment decisions. Pseudoprogressors may experience response after confirmed irPD, indicating a limitation of the current strategy for immune-related response assessment. Evaluations of non-measurable tumor burden may require further attention in the clinical setting of immuno-oncology.

9522 Poster Session (Board #130), Sat, 1:15 PM-4:45 PM

Overall survival (OS) analysis from an expanded access program (EAP) of nivolumab (NIVO) in combination with ipilimumab (IPI) in patients with advanced melanoma (MEL). *First Author: David Hogg, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: NIVO (anti-PD-1) and IPI (anti-CTLA-4), alone and in combination, are approved for the treatment of MEL. Phase II and III trials showed improved efficacy for NIVO+IPI versus IPI alone, but with a higher frequency of adverse events (AEs). In the phase II CheckMate 069 trial, the 2-year OS rate was 63.8% for all patients (pts) in the NIVO+IPI group. We report the first OS analysis, as well as updated safety data, from a North American EAP of NIVO+IPI in pts with MEL (CheckMate 218; NCT02186249). **Methods:** CheckMate 218 included pts with MEL who could have progressed on other therapies, but were anti-CTLA-4 and anti-PD-1 treatment-naive. Pts received NIVO 1 mg/kg + IPI 3 mg/kg Q3W x 4, followed by NIVO 3 mg/kg Q2W until disease progression or a maximum of 48 weeks from the first monotherapy dose. We assessed OS in the US cohort (n = 580) and safety in all pts (n = 732). Pts were followed for a minimum of 1 year in the USA and 6 months in Canada. **Results:** Of 732 pts, 43% had a *BRAF*mutation, 84% stage IV MEL, 51% M1c disease, 31% LDH > ULN (9% LDH > 2x ULN), and 13% received ≥1 prior systemic therapy in the metastatic setting. All pts received a median of 3 doses each for NIVO (range: 1–4) and IPI (range: 0–4) in the induction phase; 34% of pts received at least 1 dose of NIVO maintenance. The 1- and 2-year OS rates were 78.6% (95% CI: 74.2–82.4) and 65.3% (95% CI: 56.1–73.0), respectively. AEs of any grade occurred in 717 pts (98%), with grade 3/4 AEs in 470 pts (64%). Immune-modulating medications were used to manage any grade AEs, including grade 1/2 skin and gastrointestinal AEs, in 538 of 717 pts (75%), and to manage grade 3/4 AEs in 279 of 470 pts (59%). The most common treatment-related AEs of any grade were diarrhea (39%), pruritus (26%), and an increase in aspartate aminotransferase level (23%). Treatment-related deaths in 2 pts were reported as drug-induced liver injury and myocardial infarction. **Conclusions:** In this EAP, which included pts who had received prior systemic therapies for MEL and pts with poor prognostic factors generally not included in clinical trials, NIVO+IPI treatment demonstrated survival outcomes and a safety profile consistent with clinical trial data. Clinical trial information: NCT02186249.

9523 Poster Session (Board #131), Sat, 1:15 PM-4:45 PM

Management of gastrointestinal (GI) toxicity associated with nivolumab (NIVO) plus ipilimumab (IPI) or IPI alone in phase II and III trials in advanced melanoma (MEL). *First Author: Jeffrey S. Weber, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY*

Background: NIVO and IPI are approved as monotherapy and in combination for treatment of MEL. These treatments are associated with select (potentially immune-related) adverse events (AEs) of the GI tract, most commonly diarrhea and colitis. We describe the management of GI toxicity in patients (pts) treated with NIVO+IPI or IPI from phase II (CheckMate 069) and III (CheckMate 067) trials. **Methods:** Pts received NIVO 1 mg/kg + IPI 3 mg/kg Q3W x 4, followed by NIVO 3 mg/kg Q2W until progression or unacceptable toxicity, or IPI 3 mg/kg Q3W x 4, followed by placebo. Minimum follow-up was 2 yrs for CheckMate 069 and 18 months for CheckMate 067. **Results:** Of 407 pts treated with NIVO+IPI, 195 (48%) experienced any grade select GI AEs, and of 357 pts treated with IPI, 132 (37%) experienced any grade select GI AEs. Grade 3/4 select GI AEs were reported in 67 (16%) pts treated with NIVO+IPI and in 41 (11%) pts treated with IPI; median time to onset was 7.1 weeks (range 0.9-48.9) with NIVO+IPI and 7.3 weeks (range 0.6-14.9) with IPI. To manage these AEs, immune-modulating medications (IMM) were used in 61/67 (91%) pts in the NIVO+IPI group and in 41/41 (100%) in the IPI group. Corticosteroids (CS) were used in 61/67 (91%) and 41/41 (100%) pts, and infliximab (IFX) was used in 21/67 (31%) and 14/41 (34%) pts in the NIVO+IPI and IPI groups, respectively. In the NIVO+IPI group, the resolution rate of grade 3/4 select GI AEs was 96%, 97%, and 95% with a median time to resolution of 3.3, 3.0, and 3.9 weeks in all treated pts, CS, and CS+IFX managed pts, respectively; 88%, 92%, and 79% resolved with a median time to resolution of 3.9, 2.4, and 7.8 weeks in the IPI group, respectively. Objective response rates (ORR) were unchanged in the presence of any grade select GI AEs, or by using CS or CS+IFX (Table). **Conclusions:** NIVO+IPI or IPI alone is associated with a high incidence of GI select AEs, but most are effectively managed by IMMs, which do not appear to inhibit tumor response. Clinical trial information: NCT01844505; NCT01927419.

	All treated pts		Any grade select GI AEs					
			All		High-dose CS		CS+IFX	
	NIVO+IPI N=407	IPI N=357	NIVO+IPI N=195	IPI N=132	NIVO+IPI n=72	IPI n=44	NIVO+IPI n=22	IPI n=16
ORR (%)	58	18	63	19	63	25	55	25
95% CI	53, 63	14, 23	56, 70	13, 27	50, 74	13, 40	32, 76	7, 52

9524 Poster Session (Board #132), Sat, 1:15 PM-4:45 PM

Efficacy and safety of nivolumab (NIVO) in patients with advanced melanoma (MEL) and poor prognostic factors who progressed on or after ipilimumab (IPI): Results from a phase II study (CheckMate 172). *First Author: Dirk Schadendorf, University Hospital Essen, Essen, Germany*

Background: In the phase III CheckMate 037 study, NIVO improved the objective response rate and progression-free survival with less toxicity vs chemotherapy in patients (pts) with MEL who progressed after prior IPI treatment. We report the first efficacy and updated safety data from pts with MEL in CheckMate 172, including those with rare melanoma subtypes (uveal, mucosal), brain metastases, or an ECOG performance status (PS) of 2. **Methods:** In this ongoing phase II, single-arm, open-label, multicenter study, pts with MEL who progressed on or after IPI were treated with NIVO 3 mg/kg Q2W for up to 2 years until progression or unacceptable toxicity (NCT02156804). We report efficacy and updated safety data from 734 treated pts with ≥1 year of follow-up (database lock: November 2016). **Results:** Of 734 pts, 50% had LDH>ULN, 7% ECOG PS 2, 66% M1c disease, 15% a history of brain metastases, and 23% received ≥3 prior therapies. Overall, 593 pts (81%) received more than 4 doses of NIVO. Overall, response rate at 12 weeks was 32%, with a complete response in 1% (Table). The 1-year overall survival (OS) rate was 63%. Any grade and grade 3/4 treatment-related adverse events (AEs) occurred in 66% and 17% of pts, respectively. Discontinuations due to treatment-related AEs occurred in 4% of pts. The most common treatment-related select (potentially immune-related) AEs were diarrhea (12%), hypothyroidism (9%), and pruritus (7%). **Conclusions:** CheckMate 172 is the largest study of NIVO efficacy and safety in pts with MEL who progressed on or after IPI. NIVO demonstrated a safety profile consistent with that of prior clinical trials. Efficacy outcomes were encouraging in some difficult-to-treat subgroups of pts with poor prognostic factors, such as mucosal melanoma and brain metastases. Clinical trial information: NCT02156804.

	Total pts (N=734)	ECOG PS 2(n=48)	Uveal (n=75)	Mucosal (n=52)	CNS (n=112)
Response rate at 12 wks, % (n)*	32 (123/386)	15 (2/13)	6 (2/34)	21 (5/24)	43 (20/47)
Median OS, mos (95% CI)	19 (17–NR)	2 (1–4)	11 (7–15)	13 (6–NR)	13 (9–NR)
1-year OS rate, % (95% CI)	63 (60–67)	14 (6–26)	47 (34-59)	53 (38–67)	51 (40–60)

*Assessed in evaluable pts on treatment for ≥12 weeks; NR=not reached.

9525 Poster Session (Board #133), Sat, 1:15 PM-4:45 PM

Glycemic disorders in melanoma patients treated with anti-PD1. *First Author: Quentin Magis, Dermatology and Skin Cancers Department, UMR911 CRO2 Timone Hospital, Aix-Marseille University, Marseille, France*

Background: Anti-PD1 are now the backbone of immunotherapy (IT) of metastatic melanoma (MM). Although they are overall well- tolerated, a number of severe immune-related adverse events (IRAE) have been described, among which type 1 diabetes. We observed 3 cases of fulminant diabetes (FD) in our center, and also had the impression that diabetics patients became more difficult to manage when receiving anti-PD1. **Methods:** Retrospective analysis of blood glucose samples collected before, during and after anti-PD1 treatment (trt) in all mm patients (pts) receiving anti-PD1 in our department over a 36-month period. Study of FD cases observed. **Results:** A total of 163 pts were treated with 1920 cures of anti-PD1 including 27 treated within clinical trials. Anti-PD1 was the 1st line of IT in 70% of cases. As a whole, 1470 glycaemia were available. There was no significant difference between the median pre and post-trt glycaemia (5.37 +/-1.6 vs 5.6 +/-1.3 mmol/L (p = 0.033)). In the 28 pts with a type I (n = 0) or II (n = 28) diabetes prior to trt, there was very slight drift toward an increase of glycaemia along with the successive trt infusions (+0.05mmol/L/Cure, p = 0.004 with linear regression tendency test). Three pts (1.84%) developed a FD revealed by a severe episode of ketosis with acute polyuria polydipsia, hyperglycaemia until 50mmol/L and weight loss. Two additional cases of FD were observed in pts treated within clinical trial comparing anti-PD1 with anti-CTLA4 in adjuvant and metastatic situation (imputability of anti-PD1 likely but uncertain until unblinding). None of these pts had any glucose increase in weeks prior to FD diagnosis. Four out of 5 FD cases had an HLA group at risk for type 1 diabetes development (HLA DRB3/4), a rare group in general population (1%). **Conclusions:** We could not document any systematic tendency to glycemic disorder in mm pts treated by anti-PD1. In diabetic pts prior to trt, a slight drift toward increase of glycaemia may be explained by other interfering factors (diet, metastatic disease itself, corticosteroids, anxiety etc). FD is not exceptional (2% of patients in our series) and does not seem to be announced by any minor preliminary glycemic disorder. Despite apparently stochastic onset, FD may be associated with HLA DRB3/4 subgroup.

9526 Poster Session (Board #134), Sat, 1:15 PM-4:45 PM

Updated 5-y landmark analyses of phase 2 (BREAK-2) and phase 3 (BREAK-3) studies evaluating dabrafenib monotherapy in patients with *BRAF* V600–mutant melanoma. *First Author: Paul B. Chapman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Prior analyses of phase 2 (BREAK-2; NCT01153763) and phase 3 (BREAK-3; NCT01227889) trials showed that durable clinical benefit and tolerability lasting ≥ 3 y are achievable with the BRAF inhibitor dabrafenib in some patients (pts) with *BRAF*V600–mutant metastatic melanoma. Here, we report 5-y landmark analyses for BREAK-2 and BREAK-3. **Methods:** BREAK-2, a single-arm, phase 2 study, evaluated dabrafenib 150 mg twice daily in pts with stage IV *BRAF* V600E/K–mutant MM. BREAK-3, an open-label, randomized (3:1), phase 3 study, assessed dabrafenib 150 mg twice daily vs dacarbazine 1000 mg/m^2 every 3 weeks in pts with previously untreated *BRAF*V600E–mutant unresectable stage III or stage IV MM. Updated analyses were performed to describe ≥ 5-y outcomes in each study. **Results:** BREAK-2 enrolled 92 pts (V600E, n = 76; V600K, n = 16), of whom most (90%) had prior systemic anticancer therapy. At data cutoff (17 Jun 2016), all pts had discontinued, mostly due to progression (84%). In V600E pts, 5-y progression-free survival (PFS) was 11%, and 5-y overall survival (OS) was 20%. Post-progression immunotherapy was received by 22% of enrolled pts. In BREAK-3 (data cutoff, 16 Sep 2016), median follow-up was 18.6 mo for the dabrafenib arm (n = 187) and 12.8 mo for the dacarbazine arm (n = 63). Follow-up for the 37 dacarbazine-arm pts (59%) who crossed over to receive dabrafenib was based on the initial assignment of dacarbazine. The 5-y PFS was 12% vs 3% and 5-y OS was 24% vs 22% for the dabrafenib and dacarbazine arms, respectively. A subset of pts in each respective arm received postprogression anti–CTLA-4 (24% vs 24%) and/or anti–PD-1 (8% vs 2%) therapy, whereas 31% vs 17% did not receive any further therapy following study treatment. No new safety signals were observed in either study with long-term follow-up. Additional characterization of pts using cfDNA analysis will be presented. **Conclusions:** These data provide the longest reported PFS and OS follow-up for BRAF inhibitor monotherapy in BRAF V600–mutant MM. Both BREAK-2 and BREAK-3 showed that 11%-12% of pts initially treated with single-agent dabrafenib remained progression free at 5 y. Clinical trial information: NCT01153763; NCT01227889.

9527 Poster Session (Board #135), Sat, 1:15 PM-4:45 PM

PD-L1 and CD8 expression and association with outcomes in patients (pts) with *BRAF* V600E/K-mutant metastatic melanoma (MM) who received dabrafenib + trametinib (D+T) in the randomized phase 3 COMBI-v study. *First Author: Dirk Schadendorf, University Hospital of Essen, Essen, Germany*

Background: The phase 3 COMBI-v study (NCT01597908) showed that D+T significantly improved outcomes vs vemurafenib inpts with *BRAF*V600E/K–mutant MM. Checkpoint inhibitors also provide clinical benefit in some pts with MM. To date, characterization of markers associated with response to anti–PD-1 therapy has identified positive associations with PD-L1 expression and immune cell infiltration. Here we describe expression of PD-L1 and the T-cell marker CD8 in tumor samples from pts randomized to receive D+T in COMBI-v and associations with clinical outcomes. **Methods:** Biopsies from 74 of 352 D+T pts (21%) in COMBI-v were assessed for expression of PD-L1 (PD-L1 IHC 22C3 pharmDx assay; Dako) and CD8 (anti-CD8 antibody, clone C8/144B; Dako). PD-L1 positivity was determined as a percentage of stained tumor cells and MEL score (staining on both tumor and mononuclear inflammatory cells; 0 or 1 [negative]: < 1% staining; 2-5 [positive]: ≥ 1% staining; Daud et al. *J Clin Oncol*. 2016). **Results:** Of 74 pts analyzed, 54 (73%) had PD-L1–positive tumors, and the largest MEL score subgroup was 2 (45%). A significant association ($P < .0001$) was observed between PD-L1 and CD8 expression. Overall response rate, tumor shrinkage, progression-free survival, overall survival (OS), and duration of response with D+T were not associated with PD-L1 (MEL score of ≥ 2) or CD8 positivity. However, a significant association ($P = .04$) with improved OS was observed in tumors with high PD-L1 expression (≥ 20% of cells PD-L1 positive), and a trend ($P = .06$) was seen in pts with a MEL score of ≥ 3. Among PD-L1–negative pts, improved OS was seen in those with high CD8 positivity ($P = .03$), particularly in the stromal compartment. **Conclusions:** These data, representing PD-L1 and CD8 expression profiles for a *BRAF*-mutant mm population in the context of outcomes following D+T, showed that clinical benefit was maintained regardless of immune phenotype. The results also suggest that an immune component has an impact on outcomes following targeted therapy. Clinical trial information: NCT01597908.

9528 Poster Session (Board #136), Sat, 1:15 PM-4:45 PM

Association of improved survival (OS) and tumor control (TC) with interleukin-2 (IL2) with development of immune-related events (IREs): Data from the PROCLAIM^{SM} registry. *First Author: Brendan D. Curti, Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR*

Background: IREs are associated with immunotherapy (IT) for cancer and while reports suggest improvement in TC and OS with induced IREs, the long-term impact is unclear. IL2 has been the major IT for patients (pts) with renal cell carcinoma (RCC) and melanoma (MM) since 1992. We evaluated IREs reports in the PROCLAIM^{SM} data base (2008-2016) of IL2-treated pts. **Methods:** Reports on 614 (MM) and 843 (RCC) pts were queried for IREs. IREs were categorized as occurring before, during, or after IL-2 and related to any checkpoint inhibitor (CPI). TC (CR+PR+SD) was compared between no IRE and IRE, using Fisher's exact test. OS curves were estimated by Kaplan-Meier method, and comparison of no IRE/before IL2 with during/after IL2, was analyzed by log-rank test. **Results:** With a median (med) follow-up of 3.5+ years (range 1-8+ year), 140 IREs were reported in 118 pts (9.6% of all PROCLAIM^{SM} pts): 93 (15%) in MM; 47 (5.6%) in RCC. 25 IREs were prior to IL2; 13 IREs were during IL2; 102 were after IL2. Of the latter 102, 31 were after IL2 and after subsequent CPI; 71 were attributed to IL2 only; and in 13, IREs were due to either IL2 or CPI. TC was 73% for IRE group vs 56% for no IRE group ($p = 0.0054$). OS was significantly greater for IRE group during/after IL2 compared to no IRE/before IL2 in MM, med 46 months (mo) vs 18 mo ($p = 0.0001$) and in RCC, med 61 mo vs 43 mo ($p = 0.0196$), independent of CPI IREs. Med # of IL2 doses was 19 in no IRE group, 39 in IRE during IL2 group, and 25 in IRE after IL2 group. IL2-related IREs were primarily vitiligo and thyroid dysfunction (70% of IL2 IREs), with limited further impact, while CPI-related IREs were often serious, requiring intervention (hypophysitis, colitis, hepatitis, uveitis) (52% of CPI IREs) and possibly chronic management. **Conclusions:** IREs following IL2 are associated with improved TC and OS. IREs resulting from IL2 and from CPIs are qualitatively different and likely reflect different mechanisms of action of immune activation and response.

9529 Poster Session (Board #137), Sat, 1:15 PM-4:45 PM

ENCORE 601: A phase II study of entinostat (ENT) in combination with pembrolizumab (PEMBRO) in patients with melanoma. *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: Entinostat is an oral, class I selective histone deacetylase inhibitor shown preclinically to enhance immune checkpoint inhibitor activity by regulation of immune suppressor cells in the tumor microenvironment. ENCORE 601 is designed to evaluate safety and efficacy of ENT in combination with PEMBRO. Phase 1b identified ENT 5 mg PO weekly and PEMBRO 200 mg IV every 3 weeks as the recommended Phase 2 dose for further investigation. **Methods:** Phase 2 of ENCORE 601 employs a Simon 2-stage design to assess activity across 3 cohorts: 1) NSCLC not previously treated with a PD-1/L1 blocking antibody, 2&3) NSCLC & melanoma previously progressing on or after a PD-1/L1 blocking antibody. Patients were enrolled irrespective of PD-L1 expression levels. The primary endpoint is ORR as assessed by irRECIST. Results of the first stage of Cohort 3 are reported. Criteria for advancing to Stage 2 are $\geq$2 responses out of 13 evaluable patients. **Results:** Stage 1 enrollment has been completed (n = 13). All patients received a prior PD-1 inhibitor; in addition, 7 patients received prior ipilimumab and 2 patients received a prior BRAF inhibitor. 9 patients are still on treatment; 4 patients have discontinued due to progression. To date, 1 confirmed and 1 unconfirmed objective response have been observed. The confirmed response (PR) was in a patient who was previously treated with ipilimumab/nivolumab for 6 months (best response of SD with subsequent progression on therapy). Treatment-related AEs occurred in 5 patients (most common being nausea and fatigue occurring in 2 patients); one patient experienced Gr3/4 events (fatigue and rash). Blood samples and pre-treatment biopsies were obtained in all patients along with paired post-treatment biopsies in 8 patients. Evaluation of PD-L1 expression, gene expression, myeloid and lymphoid compartments in blood and tumor samples is in progress. Of note, the patient with a confirmed PR converted from a PD-L1 negative, non-inflamed gene signature to PD-L1 positive, inflamed after 2 weeks of treatment. **Conclusions:** ENT combined with PEMBRO demonstrates acceptable safety and encouraging preliminary activity in melanoma patients refractory to checkpoint inhibitors. Clinical trial information: NCT02437136.

9530 Poster Session (Board #138), Sat, 1:15 PM-4:45 PM

First-line (1L) avelumab treatment in patients (pts) with metastatic Merkel cell carcinoma (mMCC): Preliminary data from an ongoing study. *First Author: Sandra P. D'Angelo, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: MCC is a rare, aggressive skin cancer. Avelumab is a fully human anti–PD-L1 antibody. In a phase 2 study in pts with distant mMCC who progressed after prior chemotherapy (JAVELIN Merkel 200; NCT02155647), avelumab showed a manageable safety profile and durable responses, including an objective response rate (ORR) of 31.8%, estimated 6-month durable response rate of 29%, and 6-month overall survival rate of 69%. Here, we report preliminary results from a separate cohort of pts with chemotherapy-naïve mMCC enrolled in the same study. **Methods:** Eligible pts with mMCC and no prior systemic treatment for metastatic disease received avelumab 10 mg/kg Q2W until confirmed progression, unacceptable toxicity, or withdrawal. Tumors were assessed every 6 weeks (RECIST v1.1). Adverse events (AEs) were assessed by NCI CTCAE v4.0. **Results:** As of Dec 30, 2016, 29/112 planned pts had been enrolled. Median age was 75.0 years (range 47–87). Median treatment duration was 8.1 weeks (range 2.0–37.9). Of 16 pts with $\geq$3 months of follow-up, unconfirmed ORR was 68.8% (95% CI 41.3–89.0) with CR in 18.8%; confirmed ORR was 56.3% (95% CI 29.9–80.2; 1 unconfirmed PR with discontinuation). Of 25 pts with $\geq$6 weeks of follow-up, unconfirmed ORR was 64.0% (95% CI 42.5–82.0). All responses were ongoing at last follow-up, including in 5/5 pts with $\geq$6 months of follow-up (potential to confirm responses). 20/29 pts (69.0%) had a treatment-related AE (TRAE), including grade 3–4 TRAE in 5 pts (17.2%). TRAEs led to discontinuation in 5 pts (17.2%): 2 pts with infusion-related reaction, and 1 pt each with elevated AST and ALT, cholangitis, and paraneoplastic syndrome. There were no treatment-related deaths. 21/29 pts (72.4%) remain on treatment. **Conclusions:** In initial results from a cohort of chemotherapy-naïve pts with mMCC, avelumab was associated with early responses and a manageable safety profile, consistent with findings for second-line or later avelumab treatment in a previous cohort. These results suggest that responses mature to become durable and the use of 1L avelumab may increase the probability of response vs later-line treatment. Enrollment and follow-up in this 1L cohort are ongoing. Clinical trial information: NCT02155647.

9531 Poster Session (Board #139), Sat, 1:15 PM-4:45 PM

Intra-patient escalation dosing strategy with IMCgp100 results in mitigation of T-cell based toxicity and preliminary efficacy in advanced uveal melanoma. *First Author: Takami Sato, Department of Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

Background: IMCgp100 is a bispecific biologic capable of redirecting T cells against the melanocyte-associated antigen gp100. In the first-in-human (FIH) clinical trial,preliminary efficacy of IMCgp100 in advanced uveal melanoma (UM) was observed; however, cases of severe T cell-mediated toxicities with the first 2 doses limited dosing to 50 mcg QW. This phase 1 study was designed to implement intra-patient escalation to mitigate toxicity and maximize exposure of IMCgp100. **Methods:** Using a 3+3 design, HLA-A2+ pts with metastatic UM were treated with low weekly (QW) dosing of IMCgp100 *iv* at Cycle 1, Day 1 (C1D1) (20 mcg) and C1D8 (30 mcg), followed by the escalated cohort dose administered at C1D15 and beyond. **Results:** Nineteen metastatic UM pts with a median of 3 prior lines of therapy (range 0 - 8) were treated across 4 target dose cohorts (60, 70, 80, and 75 mcg). Fifteen of 19 pts remain on treatment at the data cutoff (25Nov16). Enrollment completed 15Sep16. DLT was observed in 1 of 6 pts in the 70-mcg cohort (LFT elevation), and 2 of 4 pts treated at 80 mcg QW (LFT and bilirubin elevation). The 80 mcg dose level was not tolerated and a 75 mcg cohort was enrolled. Six pts were treated at 75 mcg without DLT; this dose was identified as the MTD and RP2D. All 3 DLT resolved without corticosteroids and all pts resumed IMCgp100. Frequent related AE included pruritus (84%), pyrexia (84%), fatigue (74%), hypotension (74%) and peripheral edema (63%). Gr 3/4 drug-related AE include AST increased (15%), erythema (15%) and hypotension (15%). Preliminary efficacy data (RECIST v1.1) from 17 evaluable pts (2 pts had insufficient follow-up) showed no objective responses; 12 pts had a BOR of SD (63%) including 4 pts (24%) with a $\geq$10% reduction in target lesions. With median follow-up of 1.8 mo, the disease control rate (16 wks) was 32%. **Conclusions:** The intra-patient escalation regimen of IMCgp100 results in a 50% increase in dose above the FIH Phase 1, acceptable safety profile, and preliminary efficacy in UM pts. Considering the dismal prognosis of metastatic UM, the PFS observed in this study is encouraging. A Phase 2 expansion cohort and separate pivotal trial of IMCgp100 in advanced UM are ongoing. Clinical trial information: NCT02570308.

9532 Poster Session (Board #140), Sat, 1:15 PM-4:45 PM

Incidence, patterns of progression and outcomes of melanoma brain metastasis (MBM) during programmed-death 1 inhibitor (PD1i) therapy. *First Author: Gustavo Schvartsman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MBM are common in patients (pts) with metastatic melanoma (MM) and represent a frequent site of treatment failure with current therapies. Little is known, however, about the incidence, patterns of progression and outcomes of MBM pts treated with PD1i and in conjunction with central nervous system (CNS) focused therapy. **Methods:** Outcomes of mm pts treated with PD1i at MD Anderson from 01/12 to 07/16 were reviewed. The association between clinical variables and development of MBM and overall survival (OS) were assessed using logistic regression and Cox regression analyses. **Results:** We identified 324 mm pts, including 77 pts (24%) who had MBM prior to first dose of PD1i. Median follow-up from start of therapy was 16.3 months, median OS for pts without MBM at the start of PD1i 3.37 years, as compared to 2.85 years in pts with prior MBM (p = 0.268). Of the 247 pts without prior MBM, 64 (26%) developed MBM after exposure to PD1i. Of those, 21 pts (8.5%) developed MBM during therapy or within 30 days of discontinuation, with 12 (4.5%) having CNS-only progression, while 9 (3.6%) had both systemic and CNS progression. Pts with MBM prior to PD1i (n = 77) had CNS-only progression in 22 pts (28.6%) during therapy. Progression occurred in systemic and systemic plus CNS in 12 pts (15.6%) and 19 pts (24.7%), respectively. 24 pts (31.2%) had stable disease (SD). On multivariate analysis, pts with lung metastases (OR, 2.16; 95% CI, 1.25 - 3.78; p = 0.006) and NRAS-mutated tumors (OR, 2.17; 95% CI, 1.14 - 4.18; p = 0.02) were more likely to develop MBM; pts who had liver metastases at the start of PD1i (HR, 1.77; 95% CI, 1.09 - 2.87; p = 0.002) and those who developed MBM during PD1i (HR, 4.81; 95% CI, 3.00 - 7.71; p < 0.0001) had increased risk of death. **Conclusions:** We found a 26% incidence of MBM after PD1i exposure. Pts that develop MBM are still at higher risk of death despite advances in systemic and local CNS therapy. CNS-only progression was substantially higher in patients with MBM prior to PD1i, supporting a change in the natural history of the disease after PD1i. These findings support the use of CNS imaging to monitor disease during PD1i therapy.

9533 Poster Session (Board #141), Sat, 1:15 PM-4:45 PM

Phase II multicenter, single arm, open label study of nivolumab (NIVO) in combination with ipilimumab (IPI) as first line in adult patients (pts) with metastatic uveal melanoma (MUM): GEM1402 NCT02626962. *First Author: Josep M. Piulats, Catalan Institute of Oncology, Barcelona, Spain*

Background: Uveal melanoma is the most common primary intraocular malignant tumor in adults. Overall Survival (OS) at 5 years(y) is 62% due high incidence of liver metastasis, fatal within 4-9 months(m) from diagnosis. No standard treatment exists for MUM. NIVO+IPI combination has shown efficacy in metastatic cutaneous melanoma. However, MUM pts were excluded in these trials. **Methods:** GEM1402 is a phase-2 trial evaluating NIVO+IPI in untreated adult pts with MUM; is being conducted in 10 centers in Spain, leading by the Spanish Melanoma Group. Eligible pts had histologically-confirmed MUM, ECOG-PS 0/1, and no prior systemic treatment for MUM. Treatment consisted in NIVO (1mg/kg, iv, q3 weeks [wk]) and 4 doses of IPI (3mg/kg iv q3wk) followed by NIVO (3mg/kg q2wk) until progressive disease (PD), toxicity or withdrawal. Primary endpoint is OS and secondary progression free survival (PFS), Overall Response Rate (ORR) (per RECIST 1.1) and safety. Radiologic evaluations q6wk. Interim analysis (n = 19) was planned per protocol to assess safety and ORR. Intention to treat analysis includes pts with PD at first radiological evaluation. Safety population includes all pts receiving at least one dose of study treatment. **Results:**19 pts enrolled from April to July 2016: Median age 62y (43y-82y), 63% male, liver M1 84% pts and extra-liver M1 42% pts, 31% elevated baseline LDH. 11 pts completed cycle 2 and 8 pts stopped after 1 dose (6 PD, 2 toxicity). Treatment-related adverse events were reported in 12 pts and lead to end of treatment in 2 pts. Grade ≥3 toxicities were seen in 7 pts (36.8%): diarrhea, transaminitis, dermatological events, anemia, acute thyroiditis. All G3/4 were resolved following the toxicity guideline. One G5 acute thyroiditis related to NIVO+IPI was reported. ORR was observed in 15.8% and disease stabilization in 47.4%. With a median follow-up of 4.6m, PFS was 4.99m. Median OS was not reached at time of this analysis. **Conclusions:** Combination of NIVO+IPI is feasible for MUM. In this INTERIM ANALYSIS, ORR did not reach yet 20%, but PFS seems promising. The clinical trial is ongoing. Final results will be updated. Clinical trial information: 2015-004429-15.

9534 Poster Session (Board #142), Sat, 1:15 PM-4:45 PM

Targeting EZH2 in acral lentiginous melanoma (ALM). *First Author: Allison Izsak, New York University School of Medicine, New York, NY*

Background: Efforts to identify targeted therapies that can improve treatment outcome in metastatic ALM have been unsuccessful. In a previous genomic screening, we identified copy number amplification of the histone methyltransferase EZH2 in 47% of ALM cases, a higher frequency than previously reported in cutaneous melanomas (CM) (5%). Here, we tested the hypothesis that increased EZH2 expression contributes to ALM progression and may confer selective sensitivity to EZH2 inhibition. **Methods:** EZH2 expression was examined by immunohistochemistry (IHC) in 51 primary (21 stage I, 13 Stage II and 17 Stage III) and 23 metastatic (11 in transit, 8 nodal and 4 visceral) ALM cases with extensive clinicopathological data and protocol-driven follow up. Colony formation and cell proliferation was assessed following treatment of ALM and CM cell lines with three EZH2 inhibitors, including GSK126, currently in clinical trials. The effect of GSK126 on H3K27me3 and downstream EZH2 targets was analyzed by western blotting. **Results:** EZH2 is commonly overexpressed in both primary (30/51; 65%) and metastatic (20/23; 87%) ALM cases, with a significant increase in mean IHC score between primary and metastatic tumors (1.9 vs. 2.7, respectively, p = 0.047). EZH2 expression increased in 6/10 metastatic ALM tumors compared to their matched primary tumors. ALM tumors with EZH2 gene amplification showed increased EZH2 protein expression; however more cases showed overexpression with no amplification suggesting a potential epigenetic component of EZH2 regulation. GSK126 significantly suppressed ALM colony formation at lower doses compared to CM (1 μM vs. 5 μM, respectively). EZH2 inhibition also increased expression of the downstream tumor suppressor E-cadherin in ALM but not in CM cell lines. Finally, ALM cell lines had significantly lower basal H3K27me3 levels than CM cell lines, suggesting an additional, histone methyltransferase-independent function of EZH2 in ALM. **Conclusions:** Our data demonstrate thatEZH2 upregulation is common in ALM, and suggest that it may play a role in ALM's metastatic progression that requires further investigation. Selective sensitivity of ALM cell lines to EZH2 inhibitors supports the therapeutic potential of EZH2-targeted therapy in ALM.

9535 Poster Session (Board #143), Sat, 1:15 PM-4:45 PM

Follow-up of patients with complete remission of locally advanced basal cell carcinoma treated with vismodegib after treatment discontinuation: A retrospective multicentric French study. *First Author: Florian Herms, CHU Saint Louis, Paris, France*

Background: Vismodegib is a Hedgehog Pathway inhibitor (HPI) indicated for treatment of inoperable locally advanced basal-cell carcinoma (laBCC). Previous studies showed an objective response (OR) rate of 67%, including 34% of complete response (CR). Discontinuation of vismodegib is very frequent, mostly due to intolerable side-effects. Long-term response and predictive factors of relapse after suspension of vismodegib have not yet been evaluated, but should play a crucial role in the management of laBCC patients. **Methods:** We conducted an observational retrospective study in 9 onco-dermatological French units. Medical charts of laBCC patients treated with vismodegib from March 2012 until June 2016 were reviewed and patients with CR who stopped treatment were selected. Relapse was diagnosed clinically and/or histologically. A survival analysis was conducted, and predictive factors, characterization and management of relapse were studied. **Results:** 119 laBCC patients achieved CR and stopped treatment. 21 were lost to follow-up and 6 died before relapse. Event-free survival median was 18.4 months (12.1 – 24.1) and cumulative incidence of relapse at 36 months was 59.04% (48.05 - 70.04), implying that more than 40% of patients do not relapse. Multiple BCC and BCC not localized on the head and neck were associated with a higher risk of relapse, independently of the existence of Gorlin syndrome (HR = 3.3 (IC95 = 1.6 - 6.7) and 2.01 (IC95 = 1.05 - 3.87) respectively). Total duration of treatment was not associated with relapse. 50% (n = 27) of patients who relapsed during follow-up were retreated with vismodegib, with an OR of 85.2% (n = 23). 42% (n = 24) were eligible to surgery only and other patients received local treatments. **Conclusions:** Long term responders after vismodegib treatment discontinuation are frequent independently of the time exposure to the drug before and after CR. Most patients who relapse are still responder to vismodegib rechallenge. Patients with multiple or laBCC not localized on the head and neck are more at risk of relapse after discontinuation. This study emphasizes the interest of treatment of laBCC with HPI.

9536 Poster Session (Board #144), Sat, 1:15 PM-4:45 PM

Landscape of genomic alterations (GA) and tumor mutational burden (TMB) in different metastatic melanoma (MM) subtypes. *First Author: Douglas Buckner Johnson, Vanderbilt University Ingram Cancer Center, Nashville, TN*

Background: MM is a highly targetable malignancy, with both kinase inhibitors and immunotherapies providing meaningful survival benefit. Different subtypes of mm harbor distinct GA that suggest targeted and immunotherapy options. **Methods:** Comprehensive genomic profiling was performed in 2,197 MMs for up to 315 cancer-related genes plus introns from 28 genes commonly rearranged in cancer on hybrid-capture, adaptor ligation-based libraries (mean coverage depth > 600X). TMB was calculated from ≥1.11 Mb sequenced DNA. We assessed base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes. **Results:** We assessed 6 subtypes: routine cutaneous (CT; 90%), desmoplastic (DM: 1%), acral lentiginous (AL; 1%), Spitzoid (SP; 1%), mucosal (MC; 2%) and ocular (OC; 5%). Each group harbored characteristic genomic signatures (Table). *BRAF* was mutated in 38% of CT of which 92% were SV GA and 8% were amplifications, fusions or cases with > 1 *BRAF* GA. High TMB in CT and DM is highly prevalent (42% and 83% with > 20 mut/Mb). *BRAF* GA were less common in AL (18%), MC (15%), and OC (2%). SP GA were dominated by fusions in *BRAF* (60%) and other kinases. *KIT* GA were prominent in MC and AL. TMB for MC and OC mm were very low. Key findings include novel drivers of BRAF inhibitor resistance including *BRAF* internal rearrangements and kinase domain duplications. **Conclusions:** In the largest cohort of mm with NGS to date, genomic profiles and TMB differ across mm subtypes. Highly prevalent BRAF GA (including in the SP variant) and high TMB in CT and DM mm permit effective use of targeted and immunotherapies. Although MC and OC have lower BRAF GA frequency and lower TMB, targetable GA can be present. Novel BRAF inhibitor resistance mechanisms were observed.

	Cutaneous	Desmoplastic	Acral-Lentiginous	Spitzoid	Mucosal	Ocular
Number	1991	12	22	22	44	105
Significant driver GA	*BRAF*(38%) *NF1*(21%) *PTEN*(12%)	*BRAF (0%)* *TP53 (75%)* *NF1 (50%)*	*BRAF*(18%) *NF1*(18%) *PTEN*(18%)	Fusions in: *BRAF*(60%) *ROS1*(3%)	*BRAF*(15%) *NF1*(32%) *KIT*(25%)	BRAF (2%) NF1 (2%) (GA in *BAP1, GNAQ, GNA11* or *MYC*in 100%)
	KIT (5%)		*KIT* (18%)	*RET*(3%) *NTRK1*(1%) *ALK* (1%)	*PTEN* (13%)	
TMB > 10 mut/Mb	61%	92%	NA	NA	3%	3%
High TMB > 20 mut/Mb	42%	83%	NA	NA	0	1%

9537 Poster Session (Board #145), Sat, 1:15 PM-4:45 PM

Outcomes following progression on BRAF/MEK inhibition in metastatic melanoma. *First Author: Robert Mason, Princess Alexandra Hospital, Brisbane, Australia*

Background: Restrictions in Australia dictate the prescription of BRAF/MEK inhibitors prior to immunotherapy in BRAF mutant metastatic melanoma (BRMM). We analysed patients (pts) with advanced BRMM after treatment with a BRAF/MEK inhibitor and use of second line immunotherapy (PD-1 inhibitor or CTLA4 inhibitor). **Methods:** Patients (pts) with BRMM from Princess Alexandra Hospital treated between June 2013 to June 2016 were identified retrospectively. Demographics, treatment pattern and survival were analysed. **Results:** 92 pts were identified. 50% had an elevated LDH at diagnosis. 30 pts had brain metastasis at diagnosis, of these pts 11 had cerebral progression on BRAF/MEK. 41 pts had radiotherapy, 50% had stereotactic/gamma knife and 50% WBRT. 68 pts progressed giving a median progression free survival (PFS) of 9 months (95% CI 6.4 – 11.6 m). The median PFS for pts with normal LDH was 14 months, opposed to 9 months if elevated. On progression 31 pts (36.5%) were not offered second line immunotherapy due to rapid deterioration or declining performance status. 26 (30.6%) were treated with PD-1 inhibitor; 7 (8.2%) had Ipilimumab, of these, 4 then had PD-1; 1 had combination therapy; 23.5% of pts continued on BRAF/MEK at analysis. Of the patients exposed to immunotherapy, 27 pts experienced disease progression, giving a median PFS survival of 2.5 months (95% CI 1.2 –3.6m). **Conclusions:** After BRAF/MEK inhibition, due to rapid disease progression and poor performance status a significant proportion of patients do not receive immunotherapy and received best supportive care. Disease control with single agent PD-1 is short after BRAF/MEK inhibitors. These patients may have benefited from first line immunotherapy. This cohort, while small, suggests further data is needed about optimal sequencing of targeted and immunotherapy.

9538 Poster Session (Board #146), Sat, 1:15 PM-4:45 PM

Micro- and macro-metastatic disease kinetics: Results from the French cohort Melbase. *First Author: Anais Vallet, Dermatology, Hôpital Saint-Louis, Paris, France*

Background: In the past decade, the prognosis of advanced melanoma has been greatly improved by new therapeutic agents such as immune and targeted therapies, which are now being evaluated as adjuvant therapies. Although the kinetic of metastatic disease is correlated to patient survival, the unfolding of the dormant disease remains hardly predictable and data from the literature on the topic is controversial (Karakousis, Francken). We hypothesized that the course of the advanced disease could be predicted from time to distant recurrence. **Methods:** Melbase is a French multicentric cohort dedicated to the prospective follow-up of adults with unresectable stage III or IV melanoma. Date of primary excision, time to recurrence, progression free survival (PFS) and overall survival (OS) of 298 patients treated in first line by immune therapies (IT, n = 148), targeted therapies (TT, n = 68) or within clinical trials (n = 73) were collected on September 5th, 2016. Patients with unknown primary or *de novo* metastatic melanoma were not included. Time to distant recurrence was analyzed as a continuous variable and as a categorical variable (< 12 months; 12 to 24 months; ≥ 24 months). **Results:** Patients' characteristics at baseline are: mean age 62 years, PS 0-1 84%, elevated LDH 32%, BRAF mutated 39%, brain metastases 18%. Time to recurrence studied as a continuous variable was not correlated to PFS (HR = 0.96; 95%CI: 0.85-1.07) or OS (HR = 0.89; 95%CI: 0.77-1.03). These results remained insignificant after stratification upon treatment or even when time to recurrence was analyzed as a categorized variable. **Conclusions:** Our data showed no correlation between the time from primary to distant recurrence and PFS or OS in patients treated with TT or IT. Therefore, kinetics of advanced disease cannot be predicted by the history of dormant disease. Dormancy and metastasis proliferation are thus probably driven by different molecular and cellular mechanisms.

9539 Poster Session (Board #147), Sat, 1:15 PM-4:45 PM

Real life outcome of advanced melanoma patients who discontinue pembrolizumab (PEMBRO) in the absence of disease progression. *First Author: Yanina Jansen, Vrije Universiteit Brussel (VUB), Brussels, Belgium*

Background: PEMBRO improves survival of patients (pts) with advanced melanoma. Optimal duration of treatment in responding pts hasn't been established. **Methods:** 12 European hospitals collected data from 509 pts treated with PEMBRO outside an interventional clinical trial. Outcome was evaluated for pts who discontinued PEMBRO in the absence of progressive disease [PD]. **Results:** After a median follow up of 56 wks [range 1-135], median PFS was 22 wks [95% CI 18-26] and median OS was 70 wks [95% CI 59-81] for the total population. PEMBRO is ongoing in 66 [13%] pts, 344 [68%] pts stopped PEMBRO because of PD, and 99 [19%] pts discontinued PEMBRO without evidence of PD (of which 65 [13%] pts upon pt/MD decision, 26 [5%] pts due to a PEMBRO-related AE of grade < 4 and 8 [2%] pts due to a grade 5 PEMBRO-unrelated AE). Pts discontinuing PEMBRO without PD had a significant [P <.005] better ECOG PS, less advanced tumor stage, less frequent brain metastases and more often a normal LDH at baseline. There was no significant difference between pts stopping due to AE or upon pt/MD decision. The median time on treatment for the 65 pts who stopped PEMBRO upon pt/MD decision was 55 wks [range 9-112].Their best objective response rate [BORR] was 80% [31 [48%] CR, 21 [32%] PR, 12 [18%]SD, 1[2%]NE]. After a median follow-up of 26 wks [range 1-75] after the last PEMBRO dose, 3 [5%] pts progressed (after 9, 14 and 15 wks). PEMBRO was reintroduced in 1 patient resulting in a CR. The median time on treatment of the 26 pts who stopped PEMBRO due to an AE in the absence of PD was 27 wks [range 1-103]. Their BORR was 77% [9 [35%] CR, 11 [42%] PR, 5 [19%] SD, 1 [4 %] NE]. After a median follow-up of 50 wks [range 12-109] following the last PEMBRO dose, 9 [35 %] pts progressed. Median time to PD was 26 wks [range 7-108]. PD was not correlated with BOR. PEMBRO was reintroduced in 4 pts resulting in 1 CR, 1 PD, 1 SD and 1 NE. **Conclusions:** In this real life experience, advanced melanoma pts who discontinue PEMBRO treatment upon pt/MD decision, in the absence of PD or AE, were at low risk for short-term recurrence. Pts stopping PEMBRO due to an AE in the absence of PD (having a shorter exposure to PEMBRO and longer FU after discontinuing treatment) seem to have a higher risk for subsequent PD.

9540 Poster Session (Board #148), Sat, 1:15 PM-4:45 PM

Association of concomitant use of acid reducing agents in full-dose vemurafenib users with risk of progression in BRAF V600 mutation-positive unresectable or metastatic melanoma patients: A retrospective cohort study. *First Author: Lotte Marieke Knapen, Department of Clinical Pharmacy and Toxicology, Care And Public Health Research Institute, Maastricht University Medical Center+ and Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Maastricht, Netherlands*

Background: Vemurafenib is used for the treatment of adult patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma. The approved fixed vemurafenib dose of 960 mg twice daily may result in overexposure. Concomitant use of acid reducing agents (ARAs) may result in underexposure. Both situations are likely to affect treatment outcome. Therefore, the aim of this study was to determine the association between the use of vemurafenib (full-dose versus reduced dose) and/or concomitant ARA use (yes versus no) and the risk of disease progression. **Methods:** A retrospective cohort study was conducted using data from the electronic health record software of the Radboudumc pharmacy and medical records of the Radboudumc (March 17th 2012 to March 17th 2016). Patients (N = 112) using vemurafenib as first line treatment for melanoma were included. Multivariable cox regression estimated adjusted hazard ratios (HRa) and 95% confidence intervals (CI) of progression in vemurafenib users (full-dose N = 67 versus reduced dose N = 45) and/or concomitant ARA users (N = 38). Adjustments were made for age and sex. **Results:** The mean follow-up time was 3.5 months and 41 patients (36.6%) developed progression on first line vemurafenib. Co-treatment of ARAs in patients using full-dose vemurafenib was associated with a 4.6-fold increased risk of progression (HRa 4.56; 95% CI 1.51-13.75) as compared to full-dose vemurafenib users not co-treated with ARAs. No increased risk was found for users of vemurafenib in a reduced dose, regardless of concomitant ARA use. **Conclusions:** Concomitant use of ARAs in full-dose vemurafenib users was associated with an increased risk of progression. Physicians should be cautious to prescribe ARAs to patients tolerating full-dose vemurafenib. The presence of considerable confounding by disease severity, the small number of events and the hypothesis generating character of this study emphasize the need to prospective validate these results.

9541 Poster Session (Board #149), Sat, 1:15 PM-4:45 PM

Distinct gene expression, mutational profile and clinical outcomes of V600E and V600K/R BRAF-mutant metastatic melanoma (MM). *First Author: Ines Esteves Domingues Pires Da Silva, Melanoma Institute Australia, Sydney, Australia*

Background: BRAF V600E and V600K/R mm have distinct clinicopathologic features suggesting different etiology. V600K/R mm appears less responsive to MAPK inhibitors (MAPKi) compared to V600E MM. We investigated potential mechanisms for this by comparing the gene expression and mutation profiles of these two melanoma subgroups. **Methods:** BRAF V600 mutant mm patients (pts) treated with MAPKi (BRAFi +/- MEKi) between July/2009 and July/2013 were selected. Demographics, clinicopathologic features and clinical outcomes were examined. Pre-treatment FFPE tumors underwent RNA expression profiling (795-gene nanostring panel) and DNA sequencing (239 gene NGS panel). Molecular results were validated using an independent cohort from the The Cancer Genome Atlas (TCGA). **Results:** 95 mm pts were included (78 V600E, 17 V600K/R), with median (med) follow-up of 18.4 months (mo). 74 (78%) had BRAFi, 21 (22%) had BRAF/MEKi. At MAPKi start, there were no differences between subgroups regarding age, gender, ECOG, AJCC stage or LDH level. V600K/R pts had a trend to less tumour regression by RECIST (med 30% vs 51%, $p = 0.08$) and shorter PFS (med 5.1 vs 7.1mo, $p = 0.08$) than V600E, with no difference in OS (20.8mo vs 17.9mo, $p = 0.64$). V600K/R had lower expression of the MAPK-pathway feedback regulator DUSP6 and glycosyltransferase GCNT1, compared to V600E ($p < 0.05$). Analysis of TCGA data (122 V600E, 21 V600K/R) confirmed these findings. There was a trend toward higher mutational load in V600K/R than V600E, confirmed with TCGA data ($p < 0.05$). V600K/R had a higher proportion of mutations in PIK3CA and several tumour suppressor genes (FBXW7, NF2, RB1 and SMAD4), with only FBXW7 confirmed using TCGA data. **Conclusions:** V600K/R mm has inferior response and shorter survival with MAPKi than V600E, potentially due to less reliance on MAPK pathway activation (lower DUSP6 expression) and greater use of alternative drivers of oncogenesis (higher mutational load, particularly in tumor suppressor genes). Further analyses will be performed, including comparison of MAPK and additional pathway signalling in cell models. Response to immunotherapy will also be examined.

9542 Poster Session (Board #150), Sat, 1:15 PM-4:45 PM

A randomized phase II study of ipilimumab at 3 (ipi3) or 10 mg/kg (ipi10) alone or in combination with high dose interferon-alfa (HDI) in advanced melanoma (E3611). *First Author: Ahmad A. Tarhini, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: Interferon-α (IFN) favors a Th1 shift in immunity. Combining CTLA4 blockade with IFN may downregulate CTLA4 suppressive elements. Prior data from a phase II of tremelimumab and HDI showed promising efficacy supporting the current study. **Methods:** E3611 had a 2x2 factorial design (A: ipi10 + HDI; B: ipi10; C: ipi3 + HDI; D: ipi3) to evaluate (i) no HDI vs. HDI (across ipi doses) and (ii) ipi3 vs. ipi10 (across HDI status). We hypothesized that median progression free survival (PFS) would improve from 3 to 6 months (mos) with HDI vs. no HDI and with ipi10 vs. ipi3. Based on the log-rank test for 80 patients (pts) these comparisons would have 82% power at 2-sided type I error of 0.10. **Results:** Median follow up 26.4 mos. PFS and overall survival (OS) (eligible and treated pts; N = 80: 18 III/M1a, 24 M1b, 38 M1c) are shown in Table 1. There were no significant differences in PFS or OS when evaluating HDI vs. no HDI or ipi10 vs. ipi3 (Table 1). Response (RECIST) among response evaluable pts (and 4 pts with early death) (N = 76) is shown in Table 1. Stable disease (SD) in 7 (A), 6 (B), 8 (C) and 6 (D). Adverse events (AEs) were consistent with the toxicity profiles of ipi and HDI and included 3 grade 5 AEs considered at least possibly related: 1 in A (suicide), 1 in B (lung infection and hemorrhage) and 1 in C (adult respiratory distress syndrome). One patient in B died of gastrointestinal bleed and cardiac arrest while on corticosteroids to treat temporal arteritis and vision loss. **Conclusions:** Within the limitations of the sample size, there were no significant differences in PFS with HDI vs. no HDI or ipi10 vs. ipi3. Response and PFS with ipi10 were superior to historical controls and similar to the combination. Correlative studies are ongoing. Clinical trial information: NCT01708941.

PFS (top) and OS: Median (95% CI) months.

	Ipi10	Ipi3
HDI	A 8.0 (2.8, 20.1) 20.1 (5.1, -)	C 5.7 (1.5, 11.1) 20.2 (1.9, -)
No HDI	B 6.2 (2.7, 25.7) 19.6 (6.5, 31.4)	D 2.8 (2.6, 5.7) 24.7 (12.1, -)
RR HDI	A 5/15 (33.3%)	C 3/18 (16.7%)
No HDI	B 7/22 (31.8%)	D 3/21 (14.3%)
HDI vs. no HDI	PFS: 6.7 (5.1, 11.0) vs. 5.0 (2.7, 8.2) OS: 20.1 (8.5, 33.6) vs. 23.5 (12.2, 35.6)	
Ipi10 vs. Ipi3	PFS: 6.5 (5.1, 13.5) vs. 4.1 (2.6, 7.5) OS: 20.1 (10.4, 31.4) vs. 23.5 (11.7,35.7)	

9543 Poster Session (Board #151), Sat, 1:15 PM-4:45 PM

Efficacy and safety of single agent pan-HER inhibitor dacomitinib in locally advanced unresectable or metastatic skin squamous cell cancer (sSCC). *First Author: Paolo Bossi, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: In recurrent/metastatic skin squamous cell cancer (sSCC) not amenable to radiotherapy (RT) or surgery, chemotherapy (CT) has a palliative intent and limited clinical responses. We investigated the role of pan-HER inhibitor dacomitinib within a phase II trial in this setting. **Methods:** Patients (pts) with diagnosis of sSCC not amenable to curative approaches were included. Oral dacomitinib was started at a dose of 30 mg daily for 15 days, followed by 45 mg daily. Primary endpoint was response rate (RR). Tumor samples were analyzed through Next Generation Sequencing methods (pgm, Ion torrent) using a custom panel targeting 36 genes associated with sSCC. **Results:** Forty-two pts (33 M, 9 F; median age 77 years, range 45-92) were treated. ECOG PS was 0 in 58%, 1 in 40% and 2 in 2%. One fifth of the pts had distant metastasis. Most pts (86%) received previous treatments consisting in surgery (86%), RT (50%) and CT (14%). Among evaluable pts, overall RR was 28% (complete response CR 2%, partial response PR 26%), disease control rate 86%. Median duration of response was 11 months (range 1-26+). Median treatment duration was 4 months (range 1-26+). Reason for discontinuation were disease progression in 69%, adverse events (AEs) in 19%, non drug-related death in 5%; 3 pts are still on treatment. Median PFS and OS were 6 and 12 months, respectively. Most pts (93%) had at least one AE, mainly consisting in diarrhea and skin rash (71% each), fatigue (36%) and stomatitis (31%). G3/G4 AEs occurred in 36% of pts (diarrhea and skin rash 17% each). Tumor material was available from 7 responding (R: 6 PR, 1 CR) and 15 non-responding (NR: 13SD, 2PD) pts. Frequent TP53 (60%), NOTCH1/2 (60%) and FAT1 (40%) mutations were observed. NR pts showed a higher occurrence of HRAS/BRAF/NRAS mutations (40%) than R ones (28%). Moreover, HER3 (27%) CASP8 (27%), KMT2C (33%) and DCLK1 (27%) mutations were restricted to NR pts. **Conclusions:** In sSCC dacomitinib showed activity, similar to what observed with anti-EGFR monoclonal antibody cetuximab and panitumumab (RR 28% and 31%); safety profile was comparable to previous experiences in other diseases. Molecular pt selection could improve therapeutic ratio. Clinical trial information: NCT02268747.

9544 Poster Session (Board #152), Sat, 1:15 PM-4:45 PM

Safety of resuming anti-PD-1 (aPD1) in patients (pts) with immune-related adverse events (irAEs) during combined anti-CTLA-4 (aCTLA4) and aPD1 in metastatic melanoma (MM). *First Author: Megan Pollack, Vanderbilt University Medical Center, Nashville, TN*

Background: Combination aPD1 and aCTLA4 has demonstrated greater response rates (RR) than aPD1 alone in MM. However, aPD1 + aCTLA4 also leads to more frequent and severe irAEs compared to aPD1. The safety of resuming aPD1 following these irAEs is not known. We characterized the safety and efficacy of resuming aPD1 following severe irAEs during aPD1 + aCTLA4 in pts with MM. **Methods:** We retrospectively reviewed mm pts from 3 academic centers who had a severe irAE with aPD1 + aCTLA4 (defined as CTCAE v4.03 G3-4 or leading to early discontinuation of aPD1 + aCTLA4) and who resumed aPD1 thereafter. We assessed for frequency, timing, and spectrum of irAEs as well as RR, progression free survival (PFS) and overall survival (OS). **Results:** We identified 64 pts who received aPD1 + aCTLA4 for a median of 2 doses (range, 1-4). The most frequent irAEs that led to aPD1 + aCTLA4 discontinuation were: colitis (36%), hepatitis (23%), hypophysitis (8%), pneumonitis (5%), nephritis (3%), neurologic complications (3%), and pancreatitis (3%); eight pts (13%) had >1 concurrent severe irAEs. aPD1 was resumed at a median of 55 days after last dose of aCTLA4 + aPD1 (range, 17-289); 23% experienced recurrence of the same irAE with aPD1 monotherapy, 16% experienced a distinct irAE, and 60% did not experience any severe irAE after resuming aPD1. Hepatitis recurred in 6 of 18 pts, pancreatitis in 2 of 2, dermatitis in 1 of 4, nephritis in 1 of 2, pneumonitis in 1 of 3, hypophysitis in 1 of 5, and colitis in 1 of 27; the grade of these recurrent irAEs was: 46% grade 1-2, 33% grade 3, 13% grade 4, and 7% grade 5 (n = 1). One death from irAEs occurred related to Toxic Epidermal Necrolysis (TEN). No difference was observed in time prior to resuming aPD1 in those that had recurrent irAEs vs. those without (median 56 days each). The RR in this cohort was 73% (30% CR; 44% PR); median PFS (range, 2.2-not reached (NR)) and OS (range, 2.4-NR) were not reached. **Conclusions:** In our experience, pts who resume aPD1 following irAEs with aPD1 + aCTLA4 exhibit variable toxicity profiles with most experiencing no irAEs, but a minority experiencing severe or life-threatening irAEs. We observed excellent efficacy in this cohort.

9545 Poster Session (Board #153), Sat, 1:15 PM-4:45 PM

KEYNOTE-029: Efficacy and safety of pembrolizumab (pembro) plus ipilimumab (ipi) for advanced melanoma. *First Author: Matteo S. Carlino, Westmead and Blacktown Hospitals and Melanoma Institute Australia, Sydney, Australia*

Background: We previously showed that standard-dose pembro plus reduced-dose ipi has manageable safety and robust antitumor activity in patients (pts) with advanced melanoma. Here, we present more mature data, including 1-y landmark PFS and OS estimates. **Methods:** In the phase 1 KEYNOTE-029 expansion cohort (NCT02089685), pts with advanced melanoma, ECOG PS 0-1, no active brain metastases, and no prior immune checkpoint inhibitor therapy received pembro 2 mg/kg Q3W + ipi 1 mg/kg Q3W for 4 doses, then pembro alone for up to 2 y. Primary end point was safety. Efficacy end points were ORR, PFS, and DOR per RECIST v1.1 by independent central review and OS. **Results:** 153 pts were enrolled between Jan 13, 2015, and Sep 17, 2015. Median age was 60 y, 66% were male, 25% had elevated LDH, 56% had stage M1c disease, 36% were $BRAF^{V600}$mutant, and 13% received ≥ 1 prior therapy. As of Oct 17, 2016, median follow-up was 17 mo, and 64 (42%) pts remained on pembro. 110 (72%) pts received all 4 ipi doses. There were no treatment-related (TR) deaths. TRAEs occurred in all pts, were grade 3/4 in 69 (45%), and led to discontinuation of pembro and ipi in 17 (11%), ipi alone in 11 (7%), and pembro alone after ipi completion or discontinuation in 19 (12%). PD occurred in 1/11 pts who discontinued ipi alone and 4/17 pts who discontinued ipi and pembro. Of the 11 pts who discontinued ipi alone for a TRAE, 0 experienced recurrence of the same TRAE during pembro monotherapy and 2 discontinued pembro for a different TRAE (both elevated lipase). Immune-mediated AEs occurred in 90 (59%) pts and were grade 3/4 in 39 (25%). With 7 mo additional follow-up, there were 6 additional responses for an ORR of 61% (95% CI, 53%-69%); the CR rate increased from 10% to 15%. Median DOR was not reached (range, 1.6+ to 18.1+ mo), with 86/93 responders (92%), including 23/23 (100%) with CR, alive and without subsequent PD at cutoff. Median PFS and OS were not reached; 1-y estimates were 69% for PFS and 89% for OS. **Conclusions:** Pembro 2 mg/kg plus 4 doses of ipi 1 mg/kg has a manageable toxicity profile and provides robust, durable antitumor activity in pts with advanced melanoma. Clinical trial information: NCT02089685.

9546 Poster Session (Board #154), Sat, 1:15 PM-4:45 PM

Analysis of circulating tumor DNA (ctDNA) in pseudoprogression in anti-PD1 treated metastatic melanoma (MM). *First Author: Jenny HJ Lee, Macquarie University, Sydney, Australia*

Background: We have previously shown that undetectable ctDNA either at baseline or during therapy predicted response in mm patients (pts) treated with anti-PD1 antibodies (aPD1). Pseudoprogression, defined as radiological progression prior to response, occurs in 8% of pts treated with aPD1. We sought to determine if ctDNA could differentiate pseudoprogression from true progression, defined as continued clinical or radiological disease progression. **Methods:** Between July 2014 and May 2016, pts receiving aPD1 had serial bloods for ctDNA. Included pts either had RECIST PD at first restaging or early clinical progression. Those with untreated brain metastases were excluded from the analysis. ctDNA was quantified using digital droplet PCR for mutations (BRAF/NRAS) at baseline and during the first 12 wks of treatment. Based on our prior studies, ctDNA results were grouped in to 'favorable' and 'unfavorable' ctDNA profiles (see Table), and these were compared in pts with true and pseudoprogression. **Results:** 29 pts were included, 28 with RECIST PD at first restaging and one with early clinical progression. 9 (31%) pts had a subsequent RECIST PR or SD and were considered pseudoprogression and 20 (69%) had true progression. Of the pseudoprogressors, 7/9 pts remained in response with a median follow-up of 20 months (mths). 2/9 pts had disease progression at 7 and 18 mths, with ctDNA that remained detectable with a >10-fold decrease during treatment in both patients. Of those with true progression and a favourable profile, 1 had a >10-fold decrease in ctDNA by wk 12 and was switched to MAPK therapy prior to further imaging, and the other had an undetectable ctDNA at wk 6 which increased again at wk 12. The latter pt had a new lesion on first restaging CT scan despite PR in all existing lesions with true PD on second restaging at wk 24. **Conclusions:** ctDNA in patients with mm at baseline and early on aPD1 treatment differentiates pseudo from true progression.

	ctDNA profile			
	Favorable (n = 11)			Unfavorable (n = 18)
ctDNA at baseline/ on treatment up to wk 12	Undetectable/ undetectable	Detectable/ undetectable	Detectable/ >10 fold decrease	Detectable/minimal change or increase
Pseudoprogression (n = 9)	2	4	3	0
True progression (n = 20)	0	1	1	18

9547 Poster Session (Board #155), Sat, 1:15 PM-4:45 PM

A phase I trial of panobinostat with ipilimumab in advanced melanoma. *First Author: Nikhil I. Khushalani, H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL*

Background: Immune checkpoint blockade is standard therapy for advanced melanoma (MEL), yet not all patients (pts) benefit. Panobinostat (PAN), a pan inhibitor of class I, II, and IV histone deacetylases (HDAC) is immunomodulatory, decreases tumor associated inhibitory cytokines and inhibition of effector T-cells. This dose finding study aimed to determine the safety and efficacy of escalating doses of PAN combined with ipilimumab (IPI) in advanced MEL. **Methods:** Eligible pts with unresectable stage 3/4 MEL, up to 3 prior lines of therapy, and adequate laboratory values were treated with oral PAN 5mg thrice weekly (TIW) plus IPI at 3mg/kg IV every 3 weeks X 4 doses, followed by maintenance PAN until progression or intolerance. Using a modified Ji design, PAN dose escalation by 5mg was planned in 3-12 pt cohorts up to a maximum dose of 20mg TIW, without intra-pt dose escalation. Dose limiting toxicity (DLT) was assessed up to day 84 from start of therapy. **Results:** Seventeen pts (M/F: 13/4), median age 66 yrs (48, 80) were treated with a median of 4 cycles of IPI (1,4). Of 6 pts treated at PAN 5mg TIW, there was one DLT (G3 hydronephrosis). Eleven pts received PAN 10mg TIW; of 9 evaluable for DLT, there were 3 DLTs (G3 rash, G3 diarrhea, G4 thrombocytopenia) preventing further dose escalation. Other G3 toxicities included anemia, hypophysitis, diarrhea, fatigue (all n = 2); rash, colitis, nausea, dehydration, dizziness, hypotension, ↑ lipase, ↓ sodium, & ↑ glucose (all n = 1). Three pts had previous anti-PD1 therapy. The response rate was 12% (2 PRs) with 35% stable disease. One pt remains on PAN >24m since start of therapy. Median progression free- and overall survival was 2.23m (95% CI,1.57, 5.8) and 20.97m (95% CI, 8.97, NR) respectively. Biomarker analysis from peripheral blood and limited tumor biopsies pre-and on treatment examining immunoregulatory markers, including EOMES promoter acetylation in T-cells from PAN are ongoing. **Conclusions:** At tolerated doses, PAN does not appear to increase response to standard IPI in advanced MEL. Biomarker analyses will inform if immunomodulation by PAM improves efficacy of IPI. Combinations with selective HDAC inhibitors may be more appropriate for future study. Supported by grant P50 CA168536, Moffitt Skin Cancer SPORE. Clinical trial information: NCT02032810.

9548 Poster Session (Board #156), Sat, 1:15 PM-4:45 PM

Outcomes of patients with melanoma who discontinue immunotherapy. *First Author: Samuel Rosner, Albert Einstein College of Medicine, Bronx, NY*

Background: The question of when to discontinue (d/c) anti-program death-1 (PD-1) monotherapy (mono) or nivolumab in combination with ipilimumab (combo) immunotherapy (IT) is unknown. **Methods:** After IRB approval, a single center (Memorial Sloan Kettering Cancer Center), retrospective study was performed of 162 pts with unresectable stage III or IV melanoma treated with either mono (n = 106) or combo (n = 56) IT. Objective response rate (ORR), progression free survival (PFS), and overall survival (OS) were calculated for all pts from the 1st dose of IT. For pts (n = 40; mono and n = 40; combo) who d/c IT due to reasons (Table) other than progression or death, starting from the last date of IT, we then reported PFS, time to treatment failure (TTF) defined as any subsequent surgery/radiation/systemic therapy, and OS. **Results:** For pts that were alive at time of analysis, the median follow up was 28 mos. For all 162 pts (demographics in Table), ORR was 38.7% (mono) and 60.7% (combo); median PFS and OS were 12 months (mos) and 25 mos for mono; 34 mos and not reached (NR) for combo, respectively. From the last dose of IT, the PFS, TTF, and OS for 40 mono pts and 40 combo pts who d/c IT for reasons other than progression/death are shown in Table. Reasons included CR, toxicity, or other (most commonly protocol completion or prolonged PR). **Conclusions:** Outcomes in this cohort of pts with long follow-up treated with mono or combo IT are similar to results from other clinical trials. Pts who d/c IT for reasons other than progression/death were a highly selected group. Nonetheless, favorable PFS, TTF, and OS were seen after IT d/c, even in pts who did not obtain a CR.

	Mono (n = 106)	Combo (n = 56)
Age (years)	60	60
Sex (% Female)	45	41
Unresectable Stage III (%)	2	11
Stage M1A (%)	19	11
Stage M1B (%)	24	21
Stage M1C (%)	56	57
Prior Therapy (%)	96	23
Brain Mets (%)	22	2
% with LDH above ULN	38	34
Median Duration of Treatment (mos)	5	7
CR (%)	10	16
PR (%)	28	45
SD (%)	15	25
PD (%)	46	14
D/c for Tox	n = 10	n = 27
Median PFS (mos)	10.5	NR
Median TTF (mos)	11	NR
Median OS (mos)	NR	NR
D/c for CR	n = 9	n = 4
Median PFS (mos)	NR	NR
Median TTF (mos)	NR	NR
Median OS (mos)	NR	NR
D/c for Other	n = 21	n = 9
Median PFS (mos)	16	NR
Median TTF (mos)	21.5	NR
Median OS (mos)	NR	NR

9549 Poster Session (Board #157), Sat, 1:15 PM-4:45 PM

A dose escalation phase 1 study of radiotherapy (RT) in combination with anti-cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody ipilimumab in patients (pts) with metastatic melanoma. *First Author: Celine Boutros, Gustave Roussy, Villejuif, France*

Background: Preclinical findings have shown a synergy between RT and anti-CTLA-4 monoclonal antibody in several tumor animal models for both local tumor control and distant effects. Preliminary clinical data suggest that it could be due to an abscopal effect of RT. The Mel-Ipi-Rx phase 1 study aimed to determine the maximum tolerated dose (MTD) and safety profile of RT combined with ipilimumab in pts with metastatic melanoma. **Methods:** A 3+3 dose escalation design was used with 9, 15, 18 and 24 Gy dose of RT (in 3 fractions) at week 4 combined with 10 mg/kg ipilimumab (every 3 weeks for 4 doses). Pts with evidence of clinical benefit at week 12 were eligible for maintenance ipilimumab at 10 mg/kg every 12 weeks starting at week 24 until severe toxicity or disease progression based on immune-related response criteria (irRC). **Results:** 19 pts with advanced melanoma received ipilimumab between August 2011 and July 2015. Nine pts received the 4 doses of ipilimumab and 2 pts received maintenance ipilimumab (1 and 2 cycles respectively). All pts received the combined RT at week 4 in 3 fractions. All pts presented at least one AE of any grade. The most common AEs were asthenia, diarrhea, desease-related pain and fever. Grade 3 AEs occurred in 8 pts. They included colitis (n = 3), hepatitis (n = 2), anemia (n = 2), asthenia (n = 1), thyroid disorders (n = 1) and nausea/vomiting (n = 1). Nine pts discontinued the study owing to treatment-related adverse events including colitis (n = 6), hepatitis (n = 2) and DRESS (Drug Rash with Eosinophilia and systemic syndrome) (n = 1). DLT occurred in 2/6 pts in the cohort receiving 15 Gy. No drug-related death occurred. According to irRC, 4 partial responses (ORR: 21%) and 4 stable diseases were observed at week 24. The MTD was 9 Gy dose. One pt out of 12 treated in the 9 Gy cohort presented a DLT (grade 3 colitis). The median progression-free survival [95% CI] was 7.2 months [2.4 – 16.8]. The median overall survival [95% CI] was 14.4 months [7.2 – 20.4]. **Conclusions:** When combined with ipilimumab at 10 mg/kg, in the present design, the MTD of RT was 9 Gy. This combination appears to be associated with antitumor activity. Clinical trial information: 2010-020317-93.

9550 Poster Session (Board #158), Sat, 1:15 PM-4:45 PM

Phase 1b/2, open label, multicenter, study of intratumoral SD-101 in combination with pembrolizumab in anti-PD1 naïve & experienced metastatic melanoma patients. *First Author: Abraham C.F. Leung, Dynavax Technologies, Berkeley, CA*

Background: SD-101 is a synthetic CpG-ODN agonist of TLR 9 that stimulates dendritic cells to release IFN-alpha and mature into antigen presenting cells to activate T cell anti-tumor responses. Pembro is a PD-1 inhibitor approved for the treatment of metastatic melanoma. This study, MEL-01 (NCT02521870), assesses the safety and preliminary efficacy of SD-101 in combination with pembro in stage IIIC-IV melanoma. **Methods:** A modified 3+3 design was used for SD-101 dose escalation of 1, 2, 4, and 8 mg injected in a single tumor lesion Q1W x 4 then Q3W x 7 in combination with pembro (200 mg IV Q3W). Tumor responses were assessed per investigator using RECIST v1.1. **Results:** In phase Ib, 22 pts were enrolled: median age 64 y/o, male 68%, white 82%, Stage IV/IIIc 86%/14%, LDH $>$ 1 ULN 27%, $\geq$ 3 prior lines therapy 36%, anti-PD-1 naïve (n = 9) and experienced (n = 13). There has been no dose limiting toxicity (DLT) to date. The most common ($\geq$20%) treatment-related AEs (TRAEs) were transient low-grade fatigue, myalgia, headache, chills and injection site reactions. Grade $\geq$ 3 TRAEs were observed in 59.1% pts (most common: myalgia 13.6% and injection site pain 13.6%). Immune-related AEs occurred in 2 pts. One had a G2 pneumonitis on Day 23 resulting in drug withdrawal and the other G3 hypophysitis (85 days after last treatment). No deaths occurred. Responses were observed at all doses in PD-1 inhibitor naïve pts, both at the injected and non-injected lesions. A response was seen at the 8 mg dose in PD-1 inhibitor experienced pts. With median f/u of 97 days (max 382), the ORR was 66.7% in the PD-1 inhibitor naïve patients with best overall response of CR 22.2% (n = 2), PR 44.4% (n = 4), SD 11.1% (n = 1), PD 11.1% (n = 1), and NE 11.1% (n = 1). In the PD-1 inhibitor experienced pts: PR 7.7% (n = 1) and SD 38.5% (n = 5). **Conclusions:** The combination of SD-101 and pembro was well tolerated and demonstrates no worsening of the expected toxicities of each of the individual monotherapies. These interim data support enhanced activity of adding SD-101 to pembro in anti-PD-1 naive metastatic melanoma as well as potential activity in anti-PD-1 experienced pts. Additional follow up data through May 15, 2017 will be presented. Clinical trial information: NCT02521870.

9551 Poster Session (Board #159), Sat, 1:15 PM-4:45 PM

Role of time to switch from ipilimumab to anti-PD1 in anti-PD1 efficacy within the French national cohort, MelBase. *First Author: Clara Allayous, Dermatology, Hôpital Saint-Louis, Paris, France*

Background: With increasing armamentarium in advanced melanoma management, the impact of various strategies remains to be determined including the importance of time to switch from one treatment to another. We report the impact of time to IPI/APD non-planned switch on APD efficacy in real life patients within MelBase (MB). **Methods:** MB is a French multicentric biobank dedicated to the prospective follow-up (FU) of unresectable stage III or IV melanoma with 1102 patients included since March 2013. Data were collected (Sept.2016) and analyzed (demography, overall survival (OS), progression-free survival (PFS), response rate, multivariate analysis, safety). **Results:** 71 patients were treated with IPI/APD sequence. 72% received 4 IPI injections. The median time to switch was 1.7 months (0.36-3). The characteristics at the initiation of APD are: mean age 64 yrs, PS 0-1 80%, elevated LDH 34%, BRAF WT 90%, brain metastasis 25%, $\geq$ 3 metastatic organ sites (MOS) 49%, median FU 11.9 months, OS 20 months (95%CI:12.6-NR), PFS 3.5 months (95%CI:2.9-6.2). The best overall response was 25%, disease control rate was 54% with a low toxicity profile (17% grade 3/4). In a multivariable analysis, longer time to switch was significantly associated with better OS (adjusted HR 0.38 per 1 more month, 95%CI:0.14-0.93), as well as ECOG 0-1 (aHR 3.11, 95%CI:0.99-9.72) and LDH $<$ ULN (aHR 3.32, 95% CI:1.26-8.75). In addition, the association of time to switch with OS vary significantly according to the number of MOS ($<$ 3 MOS aHR 0.25, 95%CI: 0.10-0.62; $\geq$3 MOS aHR 0.99 95%CI:0.41-2.39) and AJCC stage (M0/1a/1b aHR 0.06, 95%CI:0.01-0.43 ; M1c aHR 0.77, 95%CI:0.39-1.54). **Conclusions:** In patients who failed IPI treatment, longer survival after APD was associated to time to switch only in patients with favorable baseline factors. Such results are probably more related to the slow kinetics of the disease than to the delay itself. Our results are different from Blank *et al.* (ESMO 2016) who tested a planned switch, immediately after 2 IPI perfusions, and showed overall response rate close to IPI+APD association. We are currently conducting a similar study on the reverse sequence (APD/IPI) and the role on IPI efficacy.

9552 Poster Session (Board #160), Sat, 1:15 PM-4:45 PM

Safety and results of anti-PD1 combined with radiosurgery for the treatment of melanoma brain metastases. *First Author: Caroline Gaudy Marqueste, Dermatology and Skin Cancers Department, UMR911 CRO2 Timone Hospital, Aix-Marseille University, Marseille, France*

Background: Anti-PD1 are now pivotal in the treatment of metastatic melanoma (MM). Some concerns have emerged regarding the risk/benefit ratio of their combination with stereotactic radiosurgery. **Methods:** Retrospective assessment of the interaction between Gamma-Knife radiosurgery (GKRS) and anti-PD1 in terms of toxicity and OS in mm patients (pts) with BM. Patients were included if they were under anti-PD1 (PRE) at time of GKRS, or if they had started anti-PD1 concomitantly with GKRS (CO), or had received anti-PD1 within 3 months after GKRS (POST). **Results:** Among 47 pts who received GKRS and anti-PD1 during their disease course, 35 fulfilled PRE or CO or POST criteria (anti PD1 1st line therapy in 10 pts and 2^{d} or more in 25 pts). One pt died before radiological evaluation. GKRS targeted a single BM in 10 pts and multiple BMs in 24 (max 19 BMs). Out of the 128 BMs treated, 6 cases of increase of preexisting edema (4.7%) and 8 hemorrhages (6.25%) occurred in 12 pts, but only 5 events (5%) were regarded as Adverse Radiation effects (ARE), being symptomatic in 3 pts (8% of pts). One BM had to be resected because of the occurrence of a symptomatic hemorrhage with hemiparesis 9 month after treatment. Median follow- up from GKRS was 13.7 mths. Median overall survival (OS) from GKRS and 1st BM were 14.8 and 26.5 mths respectively, with 6 and 12 mths OS rates from GKRS of 65.7% and 57%, respectively. Local failure was observed in 5 pt. Median time to new BM was 12.6 mths. There was no significant difference in outcomes in pts, depending on PRE, CO and POST conditions. **Conclusions:** In this series, the largest to date of pts with BMs treated by GKRS and anti-PD1,ARE were within the expected range and survival rates appear promising. Given the natural propensity of MM-BMs for bleeding and edema our data do not support an increased risk with the combination of GKRS and anti-PD1. Regarding the timing between anti-PD1 administration and GKRS our data do not support a higher efficacy or higher toxicity among the 3 following potential mechanisms: immuno- sensitization to radiation (PRE), immuno-radio direct synergy (CO) or radiosensitization to immunotherapy (POST).

9553 Poster Session (Board #161), Sat, 1:15 PM-4:45 PM

A phase Ib study of napabucasin plus weekly paclitaxel in patients with advanced melanoma. *First Author: William Jeffery Edenfield, Greenville Health System Cancer Institute, Greenville, SC*

Background: Napabucasin is a first-in-class cancer stemness inhibitor, identified by its ability to inhibit STAT3-driven gene transcription and spherogenesis of cancer stem cells (Li et al PNAS 112 (6):1839, 2015). Synergistic anti-tumor activity with paclitaxel was observed in pre-clinical testing, and a favorable clinical safety profile was established in a phase I/II trial in patients (pts) with advanced solid tumors. A phase 1b trial was established to evaluate the safety and preliminary signs of anti-cancer activity of the combination regimen in pts with advanced melanoma. **Methods:** Pts with melanoma were enrolled after failure of standard therapies for advanced disease. Napabucasin 480 or 500 mg orally twice daily was administered with paclitaxel 80 mg/m2 IV weekly for 3 of every 4 weeks. Adverse events were evaluated using CTCAE v4.03 and objective tumor assessments were obtained every 8 weeks and evaluated per RECIST 1.1 criteria. **Results:** A total of 12 pts with advanced melanoma were enrolled after a median 3 prior lines of therapy (including immune checkpoint inhibitors, BRAF-inhibitor if presence of BRAF V600E mutation). Protocol therapy was well tolerated with grade 3 AEs including diarrhea (n = 3), abdominal pain (n = 1), and fatigue (n = 1). Partial response (PR) was observed in 1 pt. Stable disease of at least 24 weeks or more was achieved by 33% of patients (n = 4) and the median progression-free survival (mPFS) was 3.7 months. Prolonged survival of 1 year or more was achieved by 33% of pts (n = 4), with a median overall survival (mOS) of 10.4 months. **Conclusions:** Napabucasin plus weekly paclitaxel has shown clinical safety and encouraging anti-tumor activity in a cohort of pts with previously treated advanced melanoma. The RP2D in combination with weekly paclitaxel was established to 480 mg orally bid. The data suggest that targeting stemness pathways with napabucasin may be a novel therapeutic strategy for melanoma. Clinical trial information: NCT01325441.

9554 Poster Session (Board #162), Sat, 1:15 PM-4:45 PM

The safety and early efficacy of high-dose ipilimumab (IPI) and the combination nivolumab plus ipilimumab (NIVO + IPI) in patients (pts) with uveal melanoma (UM). *First Author: Sapna Pradyuman Patel, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: UM metastases occur in 50% of cases and high-risk pts are identified by a gene expression profile. High-dose IPI is approved for adjuvant (adj) treatment (tx) of cutaneous melanoma and NIVO + IPI for metastatic (met) melanoma, yet the safety and efficacy of high-dose IPI or NIVO + IPI has not been established in UM in the adj or met settings. **Methods:** We performed a phase I/II trial of IPI for the tx of high-risk & met UM (CA184-187). The study consisted of two arms: an adj arm (AA) & met arm (MA) with two dose levels, 3 mg/kg & 10 mg/kg. Dose-finding proceeded on each arm in a 3 + 3 fashion. Pts received IPI once every 3 weeks for four doses followed by maintenance IPI every 12 weeks (for up to one year in AA). The AA treated pts with a Class 2 gene expression profile. This score imparts a 3-year distant metastasis-free survival (DMFS) of 50%. The primary endpoint for the AA was maximum tolerated dose (MTD) and improvement in 3-year DMFS to 70%. The primary endpoint for the MA was MTD & overall survival. The study was later amended to include a cohort of UM pts treated with combination NIVO + IPI in the standard FDA approved schedule. **Results:** Ten pts were enrolled on AA, 18 on MA, and 20 on NIVO + IPI. Adverse events (AEs) of any Grade (Gr) related to tx occurred in 80% of pts on AA. Gr 3/4 related toxicities observed in more than one pt were: transaminitis (30%) & pruritus (20%). Of these, 10% of the elevated AST and ALT and 10% of the pruritus occurred during the dose-finding portion of the trial at 3 mg/kg. One pt developed biopsy-proven colitis, and one developed diarrhea. Both were treated with high-dose steroids. One pt developed vasculitis manifesting as temporal arteritis with resultant blindness. AEs of any Gr occurred in 44% of pts on MA. Gr 3/4 toxicities observed in more than one pt were: Fatigue (11%) and Hyperbilirubinemia (11%). Only 1 pt (5.6%) developed Gr 3/4 diarrhea, and this was at the 3 mg/kg dose. In the NIVO + IPI cohort, Gr 3 transaminitis & elevated TSH occurred in 10%. **Conclusions:** High-dose IPI in UM did not demonstrate new or unexpected toxicities. Similarly, the combination of NIVO + IPI was well-tolerated with no new toxicities. Efficacy data will be presented at the meeting. Clinical trial information: NCT01585194.

9555 Poster Session (Board #163), Sat, 1:15 PM-4:45 PM

Survival trends among patients with metastatic melanoma in the United States: A population based study. *First Author: Ranju Kunwor, MacNeal hospital, Berwyn, IL*

Background: Ipilimumab was approved by FDA in March 2011 for the treatment of Metastatic Melanoma. We conducted this study to compare survival outcome in patients with Metastatic Melanoma in pre- (1973-2010) and post- (2011-2013) ipilimumab era in the United States using U.S. Surveillance, Epidemiology, and End Result (SEER) registry database. **Methods:** We selected patients with metastatic melanoma age $\geq$ 20 years from the SEER database. We used SEER 18 registry database to evaluate relative survival (RS) rate during 1973-2010 and 2011-2013. The RS rate at 1year and 2 year were analyzed for cohorts by age (20-49 years, 50-74 and $\geq$75 years), race [White, African American (AA), and others] and gender. The RS rates (%) accompany standard error (SE). We used SEER Stat software for statistical analysis. **Results:** There were a total of 129,362 (106,516 and 22,846 in pre and post ipilimumab era) metastatic melanoma patients, male (n = 71,220), female (n = 58,142), white (n = 121,843), AA (n = 854) other (n = 1,315) reported in the registry. RS in pre vs post-ipilimumab era for age group 20-49 was: 96.50 $\pm$ 0.1% vs 97.20 $\pm$0.3%, P = 0.013; and 94.10 $\pm$ 0.1% to 95.60 $\pm$0.40, P = 0.0009; for age group 50-74 was: 94.10 $\pm$ 0.1% vs 95.30 $\pm$ 0.2%, P = 0.0001; and 90.70 $\pm$ 0.1%vs 92.90 $\pm$ 0.3%, P = 0.0001; and for age group $\geq$75 was 90.80 $\pm$ 0.3% vs 91.40 $\pm$ 0.7%, P = 0.23; and 85.0 $\pm$ 0.4% vs 88.10 $\pm$ 1.0%, P = 0.011 at 1 and 2 years respectively. Overall RS in pre and post ipilimumab era for white population was: 93.83 $\pm$ 0.16% vs 94.567 $\pm$ 0.4%, P = 0.017; and 90.0 $\pm$ 0.2% vs 92.033 $\pm$ 0.6%, P = 0.0008 at 1 and 2 years respectively. Similarly RS for AA was: 78.07 $\pm$ 2.93% vs 73.33 $\pm$ 8.23%, P = 0.37; and 65.87 $\pm$ 3.47% vs 65.33 $\pm$ 9.73%, P = 0.94; and for other race was: 85.2 $\pm$ 2.13% vs 77.97 $\pm$ 5.6%, P = 0.04; and 74.43 $\pm$ 5.2% vs 69.67 $\pm$ 6.7%, P = 0.1 at 1 year and 2 years. **Conclusions:** Our study showed that younger (20-74 years) patients with metastatic melanoma have improvement in 1 and 2-year RS rates in post ipilimumab era. Subgroup analysis by race showed no improvement in RS in AA and other races patients during this period. There was also no significant survival benefit seen in older ($\geq$ 75 years) patients of all races and gender in post ipilimumab era.

9556 Poster Session (Board #164), Sat, 1:15 PM-4:45 PM

Impact of gene expression profiles on clinical predictors of survival in patients (pts) with *BRAF*^{V600}-mutated metastatic melanoma (mM). *First Author: James M. G. Larkin, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: Treatment of *BRAF*^{V600}-mutated mm with V and C+V has clinical benefit. Prior analyses established PFS/OS prognostic models in pts with mm based on clinical variables. This exploratory analysis evaluated the impact of immune and cell cycle gene signatures (GS) from baseline mm (Wongchenko et al, *Pigment Cell Melanoma Res*2015;28:822) on survival outcomes and associated prognostic models. **Methods:** Data from all eligible pts with GS data in the BRIM-2, -3, -7, and coBRIM studies were pooled for analysis. The independent effect of GS on PFS/OS outcomes was tested by multivariate Cox proportional hazards models. Recursive partitioning (RP) for censored response variables in a conditional inference framework was performed in the pooled dataset to model relationships between prespecified covariates, GS, and PFS/OS. Prognostic subgroups identified by the model for all pooled pts were applied to pooled treatment cohorts (dacarbazine [D], V, and C+V). **Results:** GS data were available for 608 pts across pooled studies. Immune GS was associated with improved survival vs cell cycle for PFS (HR = 0.75, 95% CI 0.62–0.89, *P*= 0.0015) and OS (HR = 0.74, 95% CI 0.61–0.90, *P*= 0.0024) in multivariate models. HR point estimates were consistent across treatment cohorts. PFS RP models identified baseline LDH, tumor size, and GS as prognostic factors, giving 4 groups with distinct outcomes. GS was not identified as a prognostic factor in OS RP models. C+V improved PFS/OS outcomes vs V across prognostic subgroups. Immune GS was significantly (one-sided Cochran-Armitage trend test) more prevalent in the favorable prognostic groups previously defined for PFS and OS for the V (*P*< 0.0001 for both) and C+V cohorts (*P*= 0.0240 and *P*= 0.0269, respectively), but not the D cohort. **Conclusions:** PFS/OS was significantly improved for pts with immune GS. RP modeling confirmed the importance of GS as an independent prognostic factor for PFS but not OS. The preferential association of immune GS with favorable prognostic subgroups in the C+V and V but not D cohorts and known effects of MAPK signaling on immune response merit further exploration in prospective studies.

9557 Poster Session (Board #165), Sat, 1:15 PM-4:45 PM

Exploratory biomarker analysis in avelumab-treated patients with metastatic Merkel cell carcinoma progressed after chemotherapy. *First Author: Irina Shapiro, EMD Serono, Inc., Billerica, MA*

Background: Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer. Tumor oncogenesis is linked to Merkel cell polyomavirus (MCPyV) integration and UV exposure. PD-L1 is often expressed in MCC tumors, suggesting that patients with MCC could benefit from anti-PD-L1 therapy. Avelumab is a fully human anti-PD-L1 IgG1 monoclonal antibody that has demonstrated clinical efficacy in patients (pts) with metastatic MCC (mMCC) in a Phase 2 trial with an objective response rate (ORR) of 31.8% in the primary analysis. Assessment of candidate predictive biomarkers may help to identify patients with a greater probability of response to avelumab and to improve understanding of MCC biology. **Methods:** Patients in a Phase 2 trial (NCT02155647) with mMCC and tumor progression on prior chemotherapy received avelumab at 10 mg/kg Q2W. PD-L1 expression, MCPyV status and CD8+ T-cell infiltration in pretreatment tumor samples were evaluated by immunohistochemistry (IHC). MCPyV status was also evaluated by real-time PCR. **Results:** Tumor PD-L1 expression was evaluable in 74 of 88 (84.1%) pts with mMCC treated with avelumab, of which 58 (65.9%) and 19 (21.6%) pts were positive at 1% and 5% cut-offs. ORR was 34.5% and 18.8% for PD-L1 positive and negative pts at 1% cutoff, and 52.6% and 23.6% for PD-L1 positive and negative pts at 5% cutoff. MCPyV status was positive in 60% (46/77) pts evaluable by IHC and 63% (45/71) pts evaluable by PCR; of 66 pts tested by both IHC and PCR, concordance was 90.9%. MCPyV+ and MCPyV– pts had similar frequencies of PD-L1+ tumors (80% and 73%) with an ORR of 26.1% and 35.5% respectively. Baseline CD8+ T-cell infiltration was assessed at tumor invasive margin and tumor center in 53 pts, ORR was 44.4% vs 19.2% and 32.1% vs 28% for pts with high or low CD8+ T-cell density at respective locations. **Conclusions:** In an international cohort of pts with mMCC, avelumab had clinical activity among biomarker subgroups analyzed, including PD-L1 expression, MCPyV status and density of CD8+ tumor-infiltrating T-cells. The current biomarkers were not predictive of response but further research into understanding how avelumab mediates anti-tumor activity in MCC may identify novel biomarkers. Clinical trial information: NCT02155647.

9558 Poster Session (Board #166), Sat, 1:15 PM-4:45 PM

Analysis of mutational burden and adaptive immune response in desmoplastic melanomas treated with PD-1/L1 inhibitors. *First Author: Siwen Hu-Lieskovan, UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: Desmoplastic melanoma (DM) is a rare subtype of melanoma characterized by a dense fibrous stroma, resistance to chemotherapy and no actionable driver mutation for targeted therapy. We investigated the efficacy of PD-1/L1 inhibitors and correlation with genetic landscape and tumor immune microenvironment in DM. **Methods:** Retrospective analysis of 1054 pts with melanoma treated with anti-PD-1/L1, resulting in 57 pts with unresectable or metastatic DM. Available baseline biopsies were analysed by digital quantitative immunohistochemistry (IHC) for CD8 and PD-L1 and by whole exome sequencing (WES), compared to available tissue from non-DM pts treated with anti-PD1/L1 at UCLA. **Results:** At a median follow up of 20 mo, 40 pts (70%, 95% CI 57-82) had an objective response by RECIST 1.1 criteria, including 18 (45%) CRs with no relapse observed to date. Responses were similar in DM subsets (23 pure, 29 mixed and 5 indeterminate). Kaplan-Meier estimated 1-year and 2-year overall survival were 85% (95% CI 78-98) and 74% (95% CI 64-89). WES revealed a median of 1282 (interquartile range 517-1692) non-synonymous somatic mutations per tumor in DM tumors (n = 17), significantly higher (p = 0.02) than the median of 462 (interquartile range 230-1150) in non-DM (n = 23). Mutations in NF-1 were the most common (13/17) followed by loss-of-function TP53 and ARID2, and > 82% of single nucleotide mutations were UV damage signatures. IHC analysis from 19 DM and 13 non-DM revealed a strikingly higher percentage of PD-L1 positive cells in the tumor parenchyma in DM (p = 0.04), highly associated with CD8 density and PD-L1 expression in the tumor invasive margins, indicating an active adaptive immune response. No genetic mechanisms known to cause constitutive PD-L1 expression were detected in these samples. **Conclusions:** Patients with advanced DM derive significant clinical benefit from PD-1/L1 inhibitors, likely related to the high mutational burden and a highly active adaptive immune response as the main mechanism of immune escape prior to therapy. Our results challenge the general conception that dense fibrous stroma around the malignant cells interferes with immune cell infiltration and efficacy of immunotherapy.

9559 Poster Session (Board #167), Sat, 1:15 PM-4:45 PM

Predictive biomarkers of ipilimumab toxicity in metastatic melanoma. *First Author: Michael Gowen, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY*

Background: There are no predictive biomarkers of ipilimumab (IPI) toxicity. Of metastatic melanoma (MM) patients (pts) receiving IPI (3mg/kg), 35% require systemic therapies to treat immune-related adverse events (irAEs) and 20% must terminate treatment (Horvat et al., JCO 2015). Here we tested the hypothesis that a pre-existing autoantibody (autoAb) profile is predictive of IPI irAEs. **Methods:** We measured autoAb levels in pre- and post-treatment sera from mm pts who received IPI (3mg/kg) monotherapy on a proteome microarray containing ~20,000 unique full-length human proteins (HuProt array, CDI Laboratories). Clinical data were prospectively collected with protocol-driven follow-up. IrAEs were categorized by CTCAE guidelines as none (grade 0), mild (grade 1-2), or severe (grade 3-4). AutoAb levels were standardized using median quantile normalization and considered positive hits if > 2-SD above the peak array signal and differed by ≥2 fold with $p < 0.05$ between toxicity groups (Non-parametric Analysis/Wilcox test). **Results:** Seventy-eight sera from 37 mm pts were analyzed. Antibodies against CTLA-4 were significantly elevated post IPI treatment ($p < 0.0001$), validating the assay. The pre-treatment levels of 190 IgG autoAbs were significantly different in pts who experienced irAEs (n = 28) compared to those with no irAEs (n = 9). Comparison of severe irAE (n = 9) and no irAE (n = 9) groups revealed 129 IgG autoAbs that significantly differed in pre-treatment sera. Localization and pathway analysis (UniProt, KEGG, Reactome) showed 81/190 (43%) of the autoAbs targeted nuclear and mitochondrial antigens and were enriched in metabolic pathways (p = 0.015). AutoAbs associated with irAEs did not correlate with treatment response. **Conclusions:** AutoAbs to antigens enriched in metabolic pathways prior to treatment may predict IPI-induced toxicity in MM. The subcellular localization of targeted antigens could explain the autoimmune toxicities associated with IPI. Studies in larger cohorts and in pts receiving other checkpoint inhibitors and/or combination therapies are essential to determine the validity of the data. If validated, our results would support the discovery of the first toxicity predictor in cancer immunotherapy.

9560 Poster Session (Board #168), Sat, 1:15 PM-4:45 PM

Validation, in silico and in vitro, of a gene-signature based risk score in cutaneous melanoma. *First Author: Georg Brunner, NeraCare GmbH, Bönen, Germany*

Background: Melanoma staging, as defined by the American Joint Committee on Cancer (AJCC), is limited in its ability to predict outcome. We have previously identified and validated a prognostic gene signature expressed in primary cutaneous melanoma and adjacent stroma. The signature comprises seven protective genes (down-regulated with tumor progression) and one risk-associated gene (up-regulated). A signature-based risk score independently predicts patient survival, across AJCC stages IA-IIIC, in formalin-fixed, paraffin-embedded (FFPE) melanomas (training cohort, n = 125; p = 0.0003, hazard ratio 1.85). The score has been validated in 206 melanomas, selected to be significantly mis-prognosticated by AJCC staging regarding patient survival (40.8% mis-prognostication). In this cohort, the score outperforms AJCC staging (p = 0.0005, hazard ratio 1.41 vs. p = n.s.), correcting 34.9% of AJCC-based mis-prognostications. **Methods:** Here, we report twofold external validation of the risk score, (i) prognostic performance *in silico* using the SurvExpress web tool (Aguirre-Gamboa et al., 2013), and (ii) technical performance *in vitro*(Dermatologikum Hamburg; IMGM Munich). **Results:** (i) Kaplan Meier analysis and log-rank testing demonstrated that all signature genes combined predicted survival in four different cohorts of metastatic melanoma (from GEO Expression Omnibus or Cancer Genome Atlas; cohorts dichotomized at the median): see table. (ii) The risk score was re-analyzed in melanomas of the training cohort (n=69). The overall concordance of duplicate determinations was 90% (average scores of 1.12 ± 0.14 and 0.97 ± 0.14). **Conclusions:** In conclusion, we have validated a signature-based FFPE melanoma risk score, complementary to AJCC staging in predicting outcome: (i) Signature genes predicted patient survival *in silico*(n=449) (ii) The risk score proved to be reproducible and technically robust *in vitro.* The score improves risk stratification and decision making in melanoma, particularly regarding new adjuvant therapies.

	TCGA (n=16)	GSE19234 (n=44)	GSE22153 (n=54)	TCGA (n=335)
p (log-rank test)	0.0016	0.0002	0.020	0.0002
HR	15.92	5.36	1.96	1.78
(95% CI)	(1.84-137.8)	(2.04-14.08)	(1.1-3.51)	(1.31-2.4)

9561 Poster Session (Board #169), Sat, 1:15 PM-4:45 PM

Humanistic burden of disease in earlier stage metastatic (stage IIIb/c-IVM1a) versus late stage metastatic (IVM1b/c) melanoma patients in a real-world setting in the U.S. *First Author: Jacqueline Buchanan, Amgen, San Francisco, CA*

Background: To assess melanoma specific health-related quality of life (HRQoL) and health states in patients with earlier stage metastatic (IIIb/c-IVM1a) versus late stage metastatic (IVM1b/c) melanoma. **Methods:** Data were collected from the Adelphi Real World Advanced Melanoma Disease-Specific Programme, a cross-sectional survey of 112 physicians and their patients (N = 666). Data were collected between March and July 2016 in the US. A subset of 183 patients completed the Functional Assessment of Cancer Therapy Melanoma (FACT-M) and EuroQol-5D (EQ-5D) one time. Patients were classified by stage of melanoma at time of consultation. Descriptive analyses of HRQoL scores between earlier and late stage metastatic melanoma were assessed using Mann-Whitney U tests. **Results:** The mean age of the earlier stage and late stage metastatic patients was 62 and 64 respectively. More earlier stage metastatic patients had an ECOG status of 0 or 1 versus late stage metastatic patients (85%, 75% respectively). A total of 31% of late stage metastatic patients required caregiver support and had a median time since primary diagnosis of 5.0 months whereas earlier stage metastatic patients reported 14% and 5.2 months respectively. Patients with earlier stage metastatic melanoma had better mean EQ-5D index scores versus late stage metastatic melanoma patients (0.81 (n = 84), 0.76 (n = 93); p = 0.0103). Higher scores indicating better HRQoL were observed between earlier stage metastatic versus late stage metastatic melanoma patients for the FACT-M (120.7 (n = 81), 107.4 (n = 91); p = 0.0017) and subscales (except Social Well Being). Clinically meaningful differences between groups using published minimal important differences (MIDs) were observed in in 6/7 FACT-M subscales and EQ-5D VAS. **Conclusions:** Differences in HRQoL and health states were observed between earlier stage metastatic and late stage metastatic melanoma populations, highlighting the detrimental effect of developing metastatic disease. These results suggest that treatments that delay progression of the disease are important to conserve patients HRQoL

9563 Poster Session (Board #171), Sat, 1:15 PM-4:45 PM

Surveillance imaging with FDG-PET/CT in the post-operative follow-up of stage 3 melanoma. *First Author: Louise Sayers, Department of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: With the evolving treatment landscape in metastatic melanoma, approaches to disease surveillance post resection in stage 3 disease requires reconsideration. We previously reported the outcomes of sub-stage-specific schedules of combined fluorodeoxyglucose-positron emission and computerized tomography (PET/CT) surveillance at high risk of relapse following surgery. The aim of this study was to provide an update on our surveillance protocol with an extended sample size and longer duration of follow-up. **Methods:** From 2009, patients with AJCC stage 3 melanoma underwent PET/CT scans according to pre-specified schedules based on Bayesian probabilities of sub-stage-specific relapse. Schedules were stage 3A: 6, 18 mo; stage 3B: 6, 12, 18, 24, 36, 48, 60 months; stage 3C: 6, 12, 18, 24, 36 months. Contingency tables were used to evaluate the sensitivity, specificity and predictive values of these schedules. **Results:** In total, 171 patients (3A: 34; 3B: 93; 3C:44) underwent 553 PET/CT scans with a median follow up of 47 months. Relapses were identified in 65 (38%) patients of which (72%) were asymptomatic at the time of radiologically documented relapse. False positive results occurred in 8%. The positive predictive value (PPV) of an individual scan for diagnosing true recurrence was 77% (64-87%). Negative scans at 6 months had negative predictive values (NPV) between 57% in Stage 3A to 69% in Stage 3B for relapse. Sensitivity and specificity of the overall approach of sub-stage-specific PET/CT surveillance for detecting disease relapse were 70% and 89%, respectively. Evaluable predictive values for detecting disease relapse were: stage 3A: PPV:56%, NPV:76%; 3B: PPV 83%, NPV 86%; stage 3C: PPV 84%, NPV 84%. 32 of 65 patients (49%; 3A: 1; 3B: 7; 3C: 2) underwent resection of relapsed disease and 10 of these patients remained free of disease with a median follow-up of 24 months. **Conclusions:** Sub-stage-specific PET/CT is effective in detecting asymptomatic recurrence in stage 3 melanoma, and is associated with a high rate of disease resection at relapse.

9564 Poster Session (Board #172), Sat, 1:15 PM-4:45 PM

Circulating tumor DNA as a predictor for response to treatment in BRAF V600E mutant malignant melanoma. *First Author: Jan Braune, Department of Hematology and Oncology, University Medical Center, Freiburg, Germany*

Background: Available biomarkers LDH and S100B possess limited sensitivity and specificity to predict outcome in melanoma. In this pilot study we evaluated the use of circulating tumor (ct)DNA harboring BRAF and NRAS mutations as a predictive biomarker for treatment response and progression-free survival (PFS) in patients with locally advanced or metastatic melanoma. **Methods:** We analyzed 89 retrospective plasma samples from 32 unselected pts, and 158 samples from 12 pts included in a prospective trial (DRKS00009507). We included stage III disease with planned resection or stage IV disease before initiation or change of medical treatment. Blood samples were taken at baseline at d +8, d +28, and thereafter at 3 months intervals for up to two years. We developed a hydrolysis probe based, Locked Nucleic Acid assay to detect BRAF V600E and wild type ctDNA by droplet digital PCR. Results were correlated with LDH, S100B and PFS. **Results:** Sensitivity of BRAF V600E specific assay was 0.01% with a limit of Blank of 0.28 copies/well. Of 31 stage IV pts with retrospective samples, 23 were positive for BRAF V600E ctDNA at least once (74%). Positive pts had a mean of 9 (range: 1-17) and 483 (range: 0.1-16,388) BRAF V600E copies/mL for stage III and stage IV respectively. The presence of ctDNA at baseline predicted poor PFS (hazard ratio [HR] 1.487, 95% CI 0.34-6.45). A negative slope in BRAF V600E ctDNA was a favorable prognostic factor for PFS (hazard ratio [HR] 0.230, 95% CI 0.04-1.20) with a median PFS of 3.42 vs. 2.56 months (Range 1.87-8.9 vs. 0.89-5.02). Residual ctDNA at the first time point after initiation or change of treatment was related to a shorter PFS (hazard ratio [HR] 2.02, 95% CI 0.39-10.53). Based on 144 measurement pairs, BRAF ctDNA strongly correlated with S100 (r = 0.73) and LDH (r = 0.52). **Conclusions:** Residual ctDNA early after change or institution of treatment predicted tumor progression at first clinical response assessment. A positive to negative conversion or a decrease indicated a more favorable course. These data support the use of ctDNA as an early predictive marker for treatment response. We will examine whether two or more detected mutations indicate clonal heterogeneity and confer adverse prognosis. Clinical trial information: DRKS00009507.

9565 Poster Session (Board #173), Sat, 1:15 PM-4:45 PM

Evaluation of the Melanoma Tumor Burden Score (MTBS) in a real-world setting. *First Author: Michael Weichenthal, University Department of Dermatology, Kiel, Germany*

Background: Clinical cancer registration is increasingly important for healthcare delivery and outcome research in oncology. As compared to clinical trial data, information from clinical routine is often limited regarding the granularity and quality of measures for individual tumor load and distribution. **Methods:** In an effort to implement a robust and useful measure of tumor burden for patients with metastatic melanoma in a German national skin cancer registry (ADOReg) we evaluated the melanoma tumor burden score (MTBS), originally developed for analyzing chemotherapy data in melanoma patients. The MTBS contains a simple categorization of size, number an distribution of metastatic lesions in individual patients. It is aimed at being used on routine radiologic report allowing for a certain level of uncertainty and imprecise quantification of metastatic lesions. Basically, the lesions are categorized per affected organ with respect to number (solitary, few, multiple) and size (≤1cm, >1- 5cm, >5cm). For evaluation of prognostic significance the summary score was calculated and included in univariate and multivariate survival analysis. We performed extensive sensitivity analyses for a variety of different model settings. **Results:** In the primary analysis set we re-evaluated 898 radiologic reports in a total of 235 various chemotherapies in n=128 stage IV melanoma patients. The confirmatory data sets consisted of n=384 stage IV melanoma patients with various treatments including chemotherapy, BRAF inhibitor treatment, and immune checkpoint blockade. MTBS categorization could be applied on routine radiologic reports in the majority of cases (95.7 %). In a multivariate model MTBS remained significantly correlated with outcome when adjusted for age, sex, LDH, and number of metastatic sites. Moreover, change in MTBS correlated to a formal response evaluation according to RECIST. **Conclusions:** The MTBS appears to be a promising tool for meaninful quantification of metastatic tumor load in metastatic melanoma for real life data collection like in clinical cancer registries.

MTBS	n	PFS [months]	95%-CI	OS [months]	95%-CI
1-9	81	3.6	3.1 - 4.9	20.2	15.5 - 25.7
10-19	96	2.5	2.3 - 2.7	9.5	7.7 - 11.3
>19	59	2.2	1.9 - 2.5	4.7	3.7 - 6.2

9566 Poster Session (Board #174), Sat, 1:15 PM-4:45 PM

Clinical presentation of immune-related colitis associated with PD-1 inhibitor monotherapy (MONO) and combination PD-1/CTLA-4 inhibitors (COMBO) in melanoma. *First Author: Daniel Ying Wang, Vanderbilt University Ingram Cancer Center, Nashville, TN*

Background: Ipilimumab-related colitis has been well described, but the clinical presentation of colitis related to MONO or COMBO therapy has not. We aimed to characterize clinical features that define this serious adverse event. **Methods:** This retrospective study included melanoma pts with colitis screened from 6 academic centers treated with either MONO or COMBO therapy. Clinically relevant colitis was defined as diarrhea/colitis symptoms requiring systemic steroids. The onset, management, and outcomes related to colitis were summarized. **Results:** We screened 866 pts and identified 72 with clinically relevant colitis. For the MONO cohort, the incidence was 3.5% (23/657) and 23.4% (49/209) in the COMBO cohort. MONO-colitis occurred at a median 33 weeks (wks) into therapy, while median onset was 8 wks with COMBO therapy. One pt had grade 5 colitis from COMBO therapy. Despite the use of systemic steroids, COMBO-colitis needed more infliximab therapy (38.8% vs 26.1%). The median prednisone equivalent dose was higher for COMBO therapy (1.5 vs 1 mg/kg), and the median taper was shorter for MONO-colitis (4 vs 6 wks). Steroid dose-escalation for worsening symptoms during taper was more common with COMBO-colitis (42.9% vs 17.3%). Relapse was similar between cohorts (MONO: 26.1%, COMBO: 20.4%). Relapses occurred more frequently in COMBO therapy with tapers shorter than the median (38.1% vs 25.0%), and more frequently in MONO therapy with steroid doses lower than the median (60% vs 21.7%). MONO-colitis pts (17.4%) were less likely than COMBO-colitis pts (46.9%) to be restarted on PD-1 therapy. When restarted, only 13% with COMBO therapy relapsed as compared to 50% with MONO therapy. Objective response rates for MONO and COMBO cohorts were 72.7% and 56.1%, respectively. **Conclusions:** Colitis occurred with a much higher incidence in COMBO therapy. MONO-colitis was associated with a milder course with later onset, shorter duration and lower dose of steroids, fewer dose-escalations, and need for infliximab as compared to COMBO therapy. Relapse of colitis was generally associated with shorter steroid tapers for COMBO therapy and lower steroid doses for MONO therapy.

9567 Poster Session (Board #175), Sat, 1:15 PM-4:45 PM

Mutation burden as a potential prognostic marker of melanoma progression and survival. *First Author: Danny Simpson, New York University Medical Center, New York, NY*

Background: Recently, tumor mutation burden (TMB) has been shown to increase the presentation of neoantigens that stimulate immune tumor recognition, resulting in improved immunotherapy (IT) outcomes in melanoma and other cancers. As melanoma is highly immunogenic, here we tested whether TMB associates with immune recognition during tumor progression, hence impacting melanoma overall survival (OS), independently of IT treatment. **Methods:** We have generated somatic mutation data from 314 IT-naive metastatic melanomas from The Cancer Genome Atlas (TCGA). In the TCGA cohort, TMB has been calculated for 210 genes (200GS) previously established from TMB studies of anti-CTLA4 and anti-PD1/PD-L1 IT. For validation, we have sequenced exonic regions of 20 genes (20GS) with the highest TMB among 200GS in 89 IT-naive metastatic melanomas ascertained at New York University Langone Medical Center. The TMB was defined using total number of somatic, non-synonymous mutations in either 200GS (TCGA discovery) or 20GS (validation), respectively. For discovery and validation cohorts, OS from primary diagnosis of samples with high TMB was compared against low TMB, using thresholds established in previous studies. **Results:** We found that total TMB predicts better OS ($p = 0.03$, HR = 2.64) in TCGA melanomas. Restricting the analysis only to the established 200GS, this association became more significant in all patients ($p = 0.01$, HR = 2.67) as well as in patients without IT ($p = 0.01$, HR = 2.67). In the validation stage of 89 melanomas without prior IT treatment, a high TMB in a subset of 20GS accurately determined favorable OS ($p = 0.02$, HR = 2.69) and confirmed TCGA observations from the 200GS. **Conclusions:** Here we show, for the first time, that in addition to IT, high TMB predicts more favorable OS in patients that never received IT, potentially serving as a novel marker of prognosis of melanoma and likely other immunogenic tumors at early stages. In addition, our study suggests that TMB test can be robust when applied to only a small subset of genes that trigger significantly higher immunogenicity. This may also eventually assist with accurate sub-selection of early stage patients likely to respond to IT regimens.

9568 Poster Session (Board #176), Sat, 1:15 PM-4:45 PM

Clinicopathologic features and survival in immunocompromised vs. immunocompetent patients with Merkel cell carcinoma: An exploratory analysis of a series of consecutive patients. *First Author: Michael Del Rosario, Eisenhower Medical Center, Rancho Mirage, CA*

Background: Clinicopathologic characteristics and outcomes between immunocompromised and immunocompetent Merkel cell carcinoma (MCC) patients may differ. **Methods:** With approval of IRB, we conducted retrospective analysis in 40 consecutive patients with MCC treated at our institution in 2006-2016. 10 patients were immunocompromised and 30 immunocompetent. Immunosuppressed patients included patients with organ transplantation (n = 3), chronic lympocytic leukemia (n = 2), metastatic skin cancer post chemotherapy (n = 1), rheumatoid arthritis on azathioprine (n = 1), myasthenia gravis on mycophenolate mofetil (n = 1), follicular lymphoma post chemotherapy (n = 1) and human immunodeficiency virus infection (n = 1). Clinicopathologic features, therapy and survival were compared between two cohorts. Significance of associations was assessed via Fishers' exact test. Survival analysis was performed via Cox proportional model and 95% confidence intervals (CI). **Results:** Compared to immunocompetent MCC patients, the immunocompromised had an absolute male predominance (100% vs. 67%; $p < 0.01$), more TNM stage III disease (40% vs. 33%; $p = 0.021$) but less lymphovascular invasion (30% vs. 7%; $p < 0.01$). They received more chemotherapy (50% vs. 30%; $p < 0.01$) and radiation therapy (80% vs 57%; $p < 0.01$). Survival was worse in immunocompromised subjects (average time to death 290.13 days vs. 618.2 days ($p < 0.001$), and they were 5 times more likely to die (RR = 5.01, 95% CI = 1.49-16.86). **Conclusions:** Immunocompromised MCC patients displayed significantly shorter survival than their immunocompetent counterparts. They were all male, with more advanced disease but less lymphovascular invasion. They received more chemo- and radiotherapy presumably due to a more advanced stage. As our study is limited by sample size, larger studies are needed to confirm the significance of our findings.

9569 Poster Session (Board #177), Sat, 1:15 PM-4:45 PM

Multivariate analysis of prognostic factors among 706 mucosal melanoma patients. *First Author: Bin Lian, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Mucosal melanoma is rare and associated with extremely poor prognosis. Little is known about its outcome and prognostic analysis. In this study, we evaluated prognostic factors among mucosal melanomas. **Methods:** The survival rates, Relapse Free Survival (RFS), Overall Survival (OS) and prognostic factors were compared for 706 mucosal melanomas at different anatomical sites. **Results:** Mucosal melanoma from nasal pharyngeal and oral (268 pts), upper and lower gastrointestinal (GI) (221 pts), gynecological and urological (196 pts) had a similar survival with a 1-y survival rate (88%, 83%, 86%), 2-y survival rate (66%, 57%, 61%), 5-y survival rate (27%, 16%, 20%), respectively. Multivariate analysis revealed that Depth of Invasion ($p < 0.001$), Lymph node metastases ($p < 0.001$), Distant metastases ($p < 0.001$) were three independent prognostic factors for OS among 706 pts. Anatomical site ($p = 0.031$), Depth of Invasion ($p < 0.001$), Lymph node metastases ($p < 0.001$) were three independent prognostic factors for RFS among 543 pts. KPS status, Depth of Invasion, Lymph node metastases, Distant metastases were independent factors for OS among nasal pharyngeal and oral pts. Depth of Invasion, Lymph node metastases, CKIT Mutation were independent factors for RFS among nasal pharyngeal and oral pts. Gender, Lymph node metastases, Distant metastases were independent factors for OS among GI pts. Gender, Depth of Invasion, Lymph node metastases were independent factors for RFS among GI pts. Lymph node metastases, Distant metastases were independent factors for OS among Gynecological and Urological pts. Depth of Invasion, Lymph node metastases were independent factors for RFS among Gynecological and Urological pts. **Conclusions:** This is the first prognostic analysis for mucosal melanoma with the largest sample size for the first time. with few exceptions, It revealed that Depth of Invasion, Lymph node metastases, Distant metastases were independent prognostic factors for OS, Depth of Invasion and Lymph node metastases were independent prognostic factors for RFS. These results should be incorporated into the establishment of stage system and design of future clinical trials involving patients with mucosal melanoma.

9570 Poster Session (Board #178), Sat, 1:15 PM-4:45 PM

Investigation of the immune infiltrate of melanoma metastases under immune checkpoint inhibition. *First Author: Jessica Cecile Hassel, University Hospital Heidelberg, Heidelberg, Germany*

Background: Tumor infiltrating lymphocytes (TIL) play a crucial role in the therapeutic impact of immune checkpoint blockers. **Methods:** We investigated metastases from 56 melanoma patients before and during treatment with immune checkpoint blockers (i) immunohistochemically, (ii) with TCR repertoire profiling and (iii) analysis of the transcriptome. The patients were treated with ipilimumab (n = 25) or pembrolizumab (n = 23) or ipilimumab/nivolumab (n = 7); half of them had a disease control, the other half progressed as best response to treatment. **Results:** In contrast to previous reports immunohistochemical analysis of the immune infiltrate revealed no significant difference in the number of CD8+ TILs in pretreatment samples of responders and non-responders. Instead, the number of CD4 + TILs including regulatory T cells (Treg) and the number of PD-1 + cells was higher in responders especially when receiving pembrolizumab. Samples taken at least 6 weeks after start of the immune checkpoint blocker showed a significant higher number of immune cells in responders through all T cell subsets (CD3,4,8,FoxP3, PD-1), B cells (CD20) as well as macrophages (CD68, CD163). TCR repertoire profiling by deep TCR sequencing demonstrated that responders develop a more diverse repertoire under treatment ($p = 0.05$). Pretreatment samples as well as the size of the top 10 TCR clones posttreatment did not differ significantly in responders and non-responders. By RNA sequencing no differential expression profiles between responders and non-responders was found pretreatment. Posttreatment samples expressed different genes compared to pretreatment samples in responders including MHC molecules, CDK2/4, Myc, TNF family members and different apoptosis-inducing genes. There was no differential gene expression in non-responders pre- and posttreatment. **Conclusions:** Pretreatment metastases from responders and non-responders do not differ much. With treatment responding patients have significant higher numbers of immune cells including T- and B- cells as well as macrophages and develop a more diverse TCR repertoire. RNA sequencing revealed a differential expression pre- versus posttreatment only in responding patients.

9571 Poster Session (Board #179), Sat, 1:15 PM-4:45 PM

Exploratory analysis of multiprotein serum predictors at baseline of progression-free survival of ipilimumab or ipilimumab and nivolumab in the Checkmate-069 study. *First Author: Krisztian Homicsko, University Hospital Lausanne, CHUV, Lausanne, Switzerland*

Background: Checkpoint inhibitors have revolutionized the treatment of stage IV melanoma patients. Selection of patients for PD-1 monotherapy or CTLA4/PD1 combination remains an important challenge. We set out to perform a discovery study of pretreatment serum protein biomarkers to identify predictors of progression free survival (PFS) for ipilimumab (IPI) or ipilimumab/nivolumab (IPI/NIVO)**. Methods:** We performed an exploratory analysis of baseline serum samples from 135 treatment-naive patients with metastatic melanoma included in the randomized phase II clinical trial, CheckMate 069 (NCT01927419). We used the RayBiotech 440 human cytokine array and evaluated the relationship of serum protein levels with 44 clinical parameters. R, Prism 7.0 and TensorFlow were used for analyses. **Results:** We focused on correlation of serum protein markers with PFS as a predictor of long-term benefit. In the IPI arm ($n = 46$), high FGF4 correlated with worse PFS outcome ($p = 0.0012$). However, FGF4 levels alone were unable to select responsive vs. non-responsive patients. In contrast, a set of three markers consisting of FGF4 ($<$ 760pg/ml), CCL15 ($>$ 2.7 ng/ml), and TACE ($>$ 600pg/ml) separated non-progressing versus progressing patients. Moreover a small group of FGF4-high patients who were concomitantly TIM-3-low also had longer PFS (combined of both: $p = 0.0004$, $HR_{logrank}$: 0.07, 95% CI: 0.03279 to 0.1533). The same markers did not discriminate between IPI/NIVO patients ($p = 0.467$, HR: 15). In the IPI/NIVO arm, three different markers could select patients. Patients either with low CCL2 ($<$ 72 pg/ml) or alternatively with high CCL2 combined with high PDGF-AA ($>$ 8.2 ng/ml) and low GASP-1 ($<$ 1.3 ng/ml) had longer PFS ($p < 0.0001$, HR: 0.115, 95% CI: 0.03848 to 0.3408). Conversely, these markers did not predict benefit for IPI-monotherapy. **Conclusions:** In this study we identified protein signatures in baseline serum that correlate with PFS for therapies with IPI or IPI/NIVO. The markers were exclusive for IPI or IPI/NIVO but not for both. Additional research is warranted to substantiate these results and evaluate the possibility of incorporating into clinical practice.

9572 Poster Session (Board #180), Sat, 1:15 PM-4:45 PM

Correlation between baseline parameters and overall survival in patients with advanced melanoma treated with ipilimumab. *First Author: Marnix Heimen Geukes Foppen, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Checkpoint inhibitors (IT) have revolutionized treatment options for patients (pts) with advanced melanoma. Recently, we proposed a framework of 7 parameters (PM) describing requirements for a sufficient anti-tumor immune response (the "cancer immunogram"). In a first analysis we tested pts from our ipi cohort for outcome. Using this framework pts benefitting the most from treatment with ipi might be selected upfront, and in the future also from other checkpoint inhibitors. **Methods:** Using Kaplan-Meier- and Cox-regression-analysis correlations between 6 of these PM at baseline and overall survival (OS) were investigated in a single center cohort of pts treated with 3 mg/kg ipi for metastatic melanoma. Results of the 7thPM are currently being finalized. **Results:** PM assessed were: LDH ($\leq$ULN vs $>$ ULN), erythrocyte sedimentation rate (ESR,$\leq$ULN vs $>$ ULN), absolute lymphocyte count (ALC, $<$ 1000/mm^3 vs $\geq$1000/mm^3) and IHC on tumor material for CD8+ T-cell infiltration ($<$ median vs $\geq$median), PD-L1 expression ($<$ 1% vs $\geq$1% positive cells) and MHC-class I expression (loss vs weak/positive). We analyzed 179 pts treated with ipi between 2010 and 2013. Median age was 55 years (19–88) and 61% of pts were male. Minimum follow-up of pts alive was 42 months(mo). Data were available as follows:177 cases LDH, 159 ALC/ESR, 118 PD-L1, 99 CD8 and 68 MHC-class I. Median OS was 7.1 mo. In univariable analysis LDH (HR 2.5, 95%CI 1.8-3.5), ALC (HR 1.6, 95%CI 1.1-2.4), ESR (HR 2.4, 95%CI 1.5-3.8) and CD8 (HR 1.8 95%CI 1.2-2.8) were significant for OS ($p < 0.01$). Pts with all 4 favorable PM had a median OS of 25.1mo(95%NR), pts with 3 PM 15.8 mo(95%CI 7.0-24.7), 2 PM 8.1 mo (95%CI 1.0-15.3), 1 PM 4.8 mo(95%CI 3.3-6.3) and no favorable PM 1.7 mo (95%CI 0–4.9). In multivariable analysis LDH(HR 2.4,95%CI 1.5-4.0) and CD8(HR 1.7,95%CI 1.1-2.8) were the only independent PM. Pts with a normal LDH and high CD8 had a median OS of 15.8 mo(95%CI 9.5-22.2) vs 3.8 mo (95%CI 1.8-5.7) for pts that did not ($p < 0.01$). **Conclusions:** In conclusion, low values of baseline LDH and high values of CD8 are the strongest PM associated with a favorable outcome in pts with advanced melanoma, treated with ipi. The other PM added low effect on the pts outcome upon ipi.

9573 Poster Session (Board #181), Sat, 1:15 PM-4:45 PM

Interim analysis of survival outcomes in a prospective cohort evaluating a prognostic 31-gene expression profile (GEP) test for melanoma. *First Author: Eddy C. Hsueh, Saint Louis University, St. Louis, MO*

Background: DecisionDx-Melanoma has been validated as an accurate prognosticator of cutaneous melanoma (CM) metastasis risk. The GEP test classifies CM pts as Class 1 (low risk) or Class 2 (high risk). Interim survival analysis from two clinical registry studies (NCT02355574/NCT02355587) designed to prospectively evaluate outcomes in pts for whom the GEP test was performed is described. **Methods:** Eleven US dermatologic and surgical centers participated in the IRB-approved protocols. Physicians enrolled CM pts who were ≥16 years old and had successful GEP test results. Endpoints of recurrence-free (RFS), distant metastasis-free (DMFS) and melanoma-specific survival (MSS) were assessed using Kaplan-Meier and Cox regression analysis. As an interim analysis at year 3 of an expected 5-year study, the critical alpha level (p-value) was 0.01. **Results:** At the time of data extraction, 322 pts were accrued and completed at least one follow-up visit. Median age was 58 years (range 18-87), median Breslow thickness (BT) was 1.2mm, 55% were male, 20% (58/296) were ulcerated, and 15% (36/237 biopsied) had a positive sentinel lymph node (SLN). Median follow-up time was 1.5 years for pts without a recurrence. Of 25 recurrent cases, 80% (20/25) were Class 2 and 40% (10/25) were SLN-positive. Two percent of Class 1 pts had a recurrence compared to 6% (12/201 biopsied) of SLN-negative pts. Of the SLN-negative pts who recurred, 75% (9/12) were called Class 2. Combined GEP and SLN risk prediction identified 88% (21/24) of recurrences. Kaplan-Meier event rates for each class are shown in the table. In Cox multivariate analysis, BT and GEP Class 2 were significant predictors of recurrence ($p<0.01$ for each). **Conclusions:** Results of this analysis show that the GEP test provides prognostic information that complements conventional staging and significantly enhances identification of high risk CM pts, consistent with reported validation studies.The results support use of the test for guiding surveillance decisions and enrollment of CM pts in clinical trials. Clinical trial information: NCT02355574, NCT02355587.

Clinical outcome rates at 1.5 years in prospective cohort.

	RFS	DMFS	MSS
Class 1 (n=259)	97%	99%	99%
Class 2 (n=76)	77%	89%	92%

$p<0.001$ for each endpoint

9574 Poster Session (Board #182), Sat, 1:15 PM-4:45 PM

Prognostic factors for overall survival (OS) in metastatic melanoma (MM) patients (pts) treated with immune checkpoint inhibitors: A single institution study of 696 pts. *First Author: Meredith Ann McKean, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Limited OS data, including prognostic and predictive factors of response, is available in mm pts treated with immune checkpoint inhibitors. **Methods:** A single-institution retrospective review was conducted on 696 mm pts treated with single-agent anti CTLA-4 or anti PD-1 on and off clinical trial between 2011-2015. Median OS was calculated from mm diagnosis. **Results:** Median age at mm diagnosis was 60 years old (range 15-86) and 65.2% were male. Subtypes were 63.2% non-acral cutaneous, 17.2% unknown primary, 7.8% mucosal, 6.5% acral, and 5.3% uveal. AJCC v7 staging at diagnosis was 7.9% M1a, 16.5% M1b, 33.0% M1c, and 42.5% not staged due to unknown LDH. LDH was elevated in 18.0% (400 pts). Mutation rates were 30.0% BRAF V600E/K (636 pts tested) and 24.5% NRAS (429 pts tested). First-line therapy for BRAF V600E/K mm pts included anti CTLA-4 (24.1%), BRAF/MEK targeted therapy (21.5%) and anti PD-1 (8.9%). First-line therapy for BRAF WT mm pts included anti CTLA-4 (28.1%) and anti PD-1 (12.8%). Median OS from mm for the cohort was 36.5 months (95% CI 33.3-44.9). Elevated LDH and staging correlated with OS ($p < 0.001$, $p < 0.001$, respectively) on univariate analysis. Age, gender, subtype and mutation status were not significantly associated with OS. Compared to BRAF WT, pts with BRAF V600E/K mutation were younger (median = 53 vs 62 yrs, $p < 0.001$), more likely to have non-acral cutaneous mm (83.2% vs 58.0%, $p < 0.001$) and have a diagnosis of brain metastasis during the disease course (57.0% vs 28.8%, $p < 0.001$). While adjusting for stage, there was no significant difference in OS based on first or second line therapy in pts with BRAF V600E/K mm or first line therapy in BRAF WT MM; however, BRAF WT pts treated second line with anti-PD1 were observed to have improved OS compared with pts receiving anti-CTLA 4 (HR 0.43 95% CI:0.23-0.84 p = 0.012). **Conclusions:** This study demonstrates that LDH and stage are prognostic of OS in all mm pts treated with single agent immune therapy. Second line therapy in BRAF WT pts treated with single agent immune therapy is also prognostic of OS thus prompting further investigation to determine advantageous therapy sequencing in MM.

9575 Poster Session (Board #183), Sat, 1:15 PM-4:45 PM

Multidimensional spatial characterization of the tumor microenvironment (TME) in synchronous melanoma metastases (SMM) to yield insights into mixed responses to therapy in metastatic melanoma (MM) patients (pts). *First Author: Alexandre Reuben, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Although both targeted and immune therapies have significantly improved outcomes for mm pts, only a minority of pts experience durable responses with many pts with multiple SMM demonstrating differential responses to therapy. We performed multidimensional spatial characterization of immune markers in SMM from mm patients treated with targeted and immune therapies to improve our understanding of correlations and determinants of response. **Methods:** NanoString's Digital Spatial Profiling research platform was used on 6 SMM from 3 pts (treatment-naïve; BRAF + MEK targeted therapy treated; anti-PD-1 immunotherapy treated) for 30 immune and signaling proteins. For analysis, we selected and compared immune-rich (CD45+) and tumor-rich (S100B+) regions across SMM. Results were compared to lesion-specific clinical responses. **Results:** Striking differences in patterns of expression across SMM from individual pts were detected, including in Ki67, CD68 myeloid cells, and the potent immunosuppressor B7-H3. SMM progressing after targeted therapy demonstrated higher pAKT and PD-L1 expression, consistent with described resistance mechanisms. Large differences in expression of PD-L1 were noted following anti-PD-1 therapy, which could contribute to heterogeneous responses. Differential expression patterns in the TME associated with response were also detected, including in increases in CD4 and CD14 cells in progressing lesions. **Conclusions:** Striking differences in responding and non-responding SMM were observed, providing potential explanations for the heterogeneous clinical responses frequently observed in mm pts. Studies are ongoing to further characterize interactions and spatial distribution of cell types, as well as integrate these findings with previous molecular and immune profiling data (whole exome sequencing, gene expression profiling, flow cytometry, IHC, TCR sequencing) in these and additional SMM to identify actionable strategies to homogenize responses across metastases in mm pts.

9576 Poster Session (Board #184), Sat, 1:15 PM-4:45 PM

Performance of a 31-gene expression profile (GEP) test for metastatic risk prediction in cutaneous melanomas (CM) of the head and neck. *First Author: John T. Vetto, Knight Cancer Institute, Oregon Health & Science University, Portland, OR*

Background: Accurate prognostication of distant metastatic risk using sentinel lymph node (SLN) biopsy for CM can be challenging in melanomas of the head and neck due to a higher false negative rate compared to other anatomical areas. A GEP signature that predicts metastatic risk based on primary tumor biology, providing a binary outcome of Class 1 (low risk of metastasis) or Class 2 (high risk), was previously described. The prognostic capabilities of the GEP independently and in combination with SLN status in a cohort of patients with primary head and neck CM are assessed here. **Methods:** All samples and clinical data were collected under an IRB-approved multicenter protocol. qPCR analysis was used to assess expression of the gene signature (Class 1 vs. Class 2). Distant metastasis-free survival (DMFS) and melanoma-specific survival (MSS) were assessed. **Results:** 157 subjects with primary CMs in the head and neck region were identified. 110 of 157 subjects had a SLN biopsy performed. Median age was 65 years (range 25-89) and median Breslow depth was 1.6 mm (range 0.2-15.0 mm). In 71 SLN-negative patients, 18 of 27 (67%) distant metastatic events were GEP Class 2. Overall, 73% (47 of 64) distant metastases, and 88% (22 of 25) deaths due to CM were called Class 2. By comparison, sensitivities for DMFS and MSS were 41% (26 of 64) and 52% (13 of 25), respectively, using SLN biopsy alone, and increased to 80% (51 of 64) and 88% (22 of 25), respectively, when combining the SLN status and GEP class. Kaplan-Meier 5-year DMFS and MSS rates based on SLN status alone or in combination with GEP are shown in the table. **Conclusions:** These data support the ability of the GEP test to accurately identify low- and high-risk cases of head and neck melanoma. The results strongly support the role of GEP testing to enhance current staging by better predicting the risk of distant metastasis and death for patients with melanoma in an anatomic region that is associated with a higher SLN biopsy false negative rate.

	5-year DMFS	5-year MSS
SLN– (n = 71)	64%	88%
SLN+ (n = 39)	28%	61%
Class 1 (n = 79)	81%	96%
Class 2 (n = 78)	37%	68%
Class 1/SLN- (n = 41)	80%	92%
Class 1/SLN+ (n = 7)	43%	100%
Class 2/SLN- (n = 30)	42%	82%
Class 2/SLN+ (n = 32)	24%	50%

9577 Poster Session (Board #185), Sat, 1:15 PM-4:45 PM

Primary melanoma histologic subtype (HS) impacts melanoma specific survival (MSS) and response to systemic therapy. *First Author: Michael Lattanzi, Department of Medicine, New York University School of Medicine, New York, NY*

Background: Unlike other solid tumors, the impact of primary HS on melanoma survival and response to systemic therapy is not well studied. Nodular melanoma (NM) has a worse prognosis than superficial spreading melanoma (SSM), which is usually attributed to thicker primary tumors. Herein, we examine the hypothesis that HS might have an impact on MSS independent of thickness and that NM and SSM exhibit different mutational landscapes that associate with response to checkpoint inhibitor immunotherapy (IT) and BRAF targeted therapy (TT) in the metastatic setting. **Methods:** Primary NM and SSM patients prospectively enrolled at NYU (2002 - 2016) were compared to the most recent SEER cohort (1973 - 2012) and analyzed with respect to MSS. Next-Generation Sequencing (NGS) was performed on a subset of matched tumor-germline pairs, allowing a comparison of the mutational landscape between NM and SSM. In the metastatic setting, survival analyses were used to compare outcomes and responses to treatment across HS. **Results:** The NYU cohort of 1,621 patients with either NM (n = 510) or SSM (n = 1,111) was representative of the analogous SEER cohort (21,339 NM, 97,169 SSM), with NM presenting as thicker, more ulcerated, and later stage (all $p < 0.001$). Among the NYU cohort, NM was found to have lower rates of TIL ($p = 0.047$), higher mitotic index ($p < 0.001$), and higher rates of NRAS mutation ($p < 0.001$). In multivariate Cox models, NM was a significant predictor of worse MSS, independent of thickness and stage ($p = 0.01$). NM had a significantly lower mutational burden across the exome ($p < 0.001$). Some of the most under-mutated genes noted in NM were NOTCH4, BCL2L12 and RPS6KA6 (all $p < 0.01$). Among patients treated with TT (n = 56), NM remained a significant predictor of worse MSS ($p = 0.004$). However, there was no difference in response to IT. **Conclusions:** NM and SSM show divergent mutational patterns which may contribute to their different clinical behaviors and responses to BRAF targeted therapy. More studies are needed to better understand the key molecular and cellular processes driving such differences. Integration of HS data into prospective clinical trial reporting is needed to better assess its impact on response to treatment.

9578 Poster Session (Board #186), Sat, 1:15 PM-4:45 PM

Performance of a prognostic 31-gene expression profile test in stage III cutaneous melanoma subjects. *First Author: Martin D. Fleming, University of Tennessee Health Sciences Center, Memphis, TN*

Background: The management of stage III cutaneous melanoma (CM) patients has changed significantly with the introduction of contemporary therapies. A 31-gene expression profile (GEP) test that provides a prediction of low or high risk of melanoma metastasis has been validated as an independent prognosticator of distant metastasis-free (DMFS) and melanoma-specific survival (MSS). We examine the prognostic accuracy of the test in a cohort of stage III, and particularly stage IIIA, subjects from a multicenter validation study. **Methods:** 207 primary CM tumors from 16 centers were analyzed as part of an IRB-approved study. Quantitative RT-PCR and predictive modeling were performed to classify metastasis and survival risk as Class 1 (low risk) or Class 2 (high risk). Results for Kaplan-Meier and Cox regression survival analysis are reported. **Results:** Of the 207 subjects with stage III melanoma, 76 were stage IIIA. The table shows 5-year DMFS and MSS rates for all stage III and stage IIIA groups. Patients with Class 2 GEP had significantly worse outcomes compared to Class 1. In univariate analyses, GEP was a significant predictor of DMFS and MSS with a hazard ratio for DMFS of 2.8 (95%-CI; 1.7-4.6) and for MSS of 4.0 (95%-CI; 1.7-9.4) for all stage III, while HR of 2.2 for DMFS (95%-CI; 1.0-4.7) and 4.3 for MSS (95%-CI; 1.2-15.2) were observed for the stage IIIA group. For all stage III cases, Breslow thickness and GEP were significant predictors of DMFS and MSS in multivariate models including ulceration and mitotic rate ($p < 0.05$). **Conclusions:** The results support the capability of the GEP to accurately predict stage III distant metastasis and survival, and that the test complements existing prognostic factors. GEP testing may be useful in identifying stage IIIA patients who are appropriate for adjuvant therapies and/or enrollment in clinical trials.

DMFS	Class	Event-free (95%CI)	p-value
Stage III (n = 207)	Class 1 (n = 63)	72% (61-85%)	< 0.0001
	Class 2 (n = 144)	42% (33-52%)	
Stage IIIA (n = 76)	Class 1 (n = 34)	75% (61-92%)	< 0.05
	Class 2 (n = 42)	53% (39-74%)	
MSS			
Stage III (n = 207)	Class 1 (n = 63)	92% (85-100%)	< 0.0001
	Class 2 (n = 144)	66% (56-76%)	
Stage IIIA (n = 76)	Class 1 (n = 34)	97% (91-100%)	< 0.02
	Class 2 (n = 42)	68% (53-86%)	

9579 Poster Session (Board #187), Sat, 1:15 PM-4:45 PM

Molecular and immune predictors of response and toxicity to combined CTLA-4 and PD-1 blockade in metastatic melanoma (MM) patients (pts). *First Author: Wei-Shen Chen, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Combined treatment with ipilimumab and nivolumab (Ipi/Nivo) achieves clinical responses in > 50% of mm pts. However, responses are not universal and toxicity may be limiting, thus biomarkers of response and toxicity are needed to optimize and personalize this therapy. **Methods:** Tumor biopsies were collected before (n = 29) and on treatment (n = 7) from mm pts (n = 40) treated with Ipi/Nivo. Whole exome sequencing (WES), gene expression profiling, TCR sequencing, and immunohistochemistry (IHC) were performed to define molecular and immune features of the tumors. Radiographic responses in patients were assessed via RECIST 1.1criteria, and patients were classified as responders (R) deriving clinical benefit (with SD, PR, CR) and non-responders (NR) not deriving clinical benefit (PD). Toxicity was also scored, with patients dichotomized into low toxicity (< grade 2) versus high toxicity (> grade 3) re: immune-related (IR) toxicities. **Results:** In this cohort, the response rate was 80%, with 53% of patients experiencing > grade 3 toxicity. There was no significant difference in baseline mutational load in responders (R) vs non-responders (NR) to Ipi/Nivo, but NR had a higher burden of copy number alterations (CNA; $p = 0.013$), with frequent alterations detected in *PTEN*, *JAK2*, and *B2M*. There were no significant differences in baseline CD8+ T cell density, expression of immune-related genes, or T cell clonality for R vs NR pts. Ipi/Nivo treatment increased intratumoral T cell clonality, but this did not correlate with response. A more diverse peripheral T cell repertoire at baseline was detected in pts who developed IR toxicity ($p < 0.05$). **Conclusions:** This data suggests that responses to Ipi/Nivo in mm may occur in the absence of high mutational load or brisk immune infiltrate at baseline. Putative mechanisms of resistance to Ipi/Nivo include high burden of CNA and alterations in *PTEN, JAK2, and B2M*. Together these studies identify candidate biomarkers of resistance and toxicity for Ipi/Nivo, though they need to be tested in larger cohorts and across cancer types.

9580 Poster Session (Board #188), Sat, 1:15 PM-4:45 PM

Characterizing the tumor microenvironment (TME) in primary melanomas using multiplex immunohistochemistry (mIHC). *First Author: Robyn Denise Gartrell, Columbia University Medical Center, New York, NY*

Background: Biomarkers are needed in primary melanoma to risk stratify for adjuvant trials. High levels of infiltrating cytotoxic (CD8+) T lymphocytes (CTLs) and low levels of CD68+ macrophages (MΦ) may correlate with prolonged survival but quantification methods are not standardized for clinical practice. HLA-DR is a marker of MΦ activation not expressed by suppressor myeloid cells. A novel pathology technique using mIHC allows for quantitative and spatial analysis of immune cell subsets. **Methods:** In a pilot set of stage II/III primary melanomas from Columbia University Medical Center (n = 94), clinical follow up is available for 51 cases. 32 had no evidence of recurrence at last follow up (minimum 2 years) while 19 died of melanoma. 5μm slides were stained using Opal multiplexed IHC (mIHC) for DAPI, CD3, CD8, CD68, SOX10, HLA-DR and Ki67. Tumor areas were pre-selected by a dermatopathologist, visualized using Mantra (Perkin Elmer) and analyzed using inForm (Perkin Elmer) and Spotfire (TIBCO). **Results:** In all patients (n = 94), CTLs are farther from tumor (SOX10+) cells when they are proliferating (Ki67+) ($p < 0.0001$***), while they are closer to MΦ when they are activated (HLA-DR+) ($p = 0.0002$***). Next, we evaluated impact on prognosis using disease specific survival (DSS) as an outcome based on median value (n = 51). In this exploratory study no correction for multiple comparisons was made. We find that CTL density correlates with prolonged DSS in tumor ($p = 0.0185$*) but not in stroma ($p = 0.1630$ ns). Ratio of density of CD8/CD68+HLA-DR- correlates with DSS in both tumor ($p = 0.027$*) and stroma ($p = 0.017$*). Finally, distance from CTLs to HLA-DR- MΦ was significantly greater in non-recurrent melanomas as compared to recurrent ones ($p = 0.0167$*). **Conclusions:** HLA-DR expression on MΦ and Ki67 expression on tumor cells correlate with position of CTLs in TME in primary melanoma. CTL density is a favorable prognostic marker while HLA-DR non-expressing MΦ may favor tumor progression. Quantitative mIHC allows for accurate spatial analysis of immune subsets within the TME and the development of novel, more accurate and potentially clinically relevant biomarkers.

9581 Poster Session (Board #189), Sat, 1:15 PM-4:45 PM

Preliminary results from the international neoadjuvant melanoma consortium (INMC). *First Author: Alexander M. Menzies, Melanoma Institute Australia, Royal North Shore Hospital, The University of Sydney, Sydney, Australia*

Background: For several cancers, response to neoadjuvant therapy (NAT) correlates with survival. Targeted and immune therapies achieve high response rates and durable survival in many patients with metastatic melanoma. Their role as NAT for stage III disease is not clear, and whether pathological response following NAT correlates with relapse-free (RFS) or overall survival (OS) in melanoma is unknown. **Methods:** Pooled clinical data from four ongoing NAT clinical trials (NCT02437279, NCT02231775, NCT02519322, NCT01972347) at three large melanoma centers participating in the INMC were examined. All trials included only patients with surgically resectable clinical stage III melanoma. NAT regimens included dabrafenib/trametinib (DT) and nivolumab (nivo) [single agent or in combination with ipilimumab (ipi/nivo)]. Patients who had undergone surgery prior to 27th January 2017 are included in this preliminary analysis. A pathological complete response (pCR) was defined as no viable melanoma cells in the resected specimen by hematoxylin and eosin evaluations by dedicated dermatopathologists. **Results:** 58 patients with clinical stage III melanoma (AJCCv7: 18 IIIB, 40 IIIC) have completed NAT and undergone surgery. 18 received neoadjuvant immunotherapy (IT): ipi/nivo x2 doses (N = 10), ipi/nivo x3 doses (N = 4) or nivo x4 doses (N = 4). 40 received neoadjuvant DT, either for two (N = 10) or three months (N = 30). Median age is 55 years (range 22-84). A pCR was observed in 50% of patients, 7 (39%) with IT and 22 (55%) with DT. Median follow-up is 10.2 months (95% CI 8.7-12.5). 14 (24%) patients have recurred (5 local, 8 distant, 1 both), 2 (11%) after IT, 12 (30%) after DT. For those with pCR, 14% have recurred, 0/7 (0%) after IT, 4/22 (18%) after DT. In contrast, for those without pCR, 34% have recurred, 2/11 (18%) after IT and 8/18 (44%) after DT. Two deaths have occurred, both after neoadjuvant TT. Early data suggests improved RFS in those with pCR. **Conclusions:** Neoadjuvant targeted and immunotherapy are active regimens in clinical stage III melanoma patients and are associated with high pCR rate. Preliminary data suggest pCR correlates with improved RFS. Updated data will be presented. Clinical trial information: NCT02437279, NCT02231775, NCT02519322, NCT01972347.

9582 Poster Session (Board #190), Sat, 1:15 PM-4:45 PM

A toll-like receptor agonist to drive melanoma regression as a vaccination adjuvant or by direct tumor application. *First Author: Richard Eldon Royal, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Toll like receptor (TLR) agonists may enhance vaccination or direct immune activation at the tumor microenvironment. This trial evaluates the biologic and clinical effects of Resiquimod, a TLR 7/8 agonist that can activate both myeloid (mDC, TLR 8) and plasmacytoid (pDC, TLR 7) dendritic cells, in patients with advanced stage melanoma. **Methods:** Class I HLA-A0201+ subjects with in-transit melanoma metastases or high risk for recurrence were vaccinated weekly with peptide vaccination (class I restricted peptide $GP100_{209\text{-}2m}$ and, if HLA-DP4+, also with class II restricted peptide MAGE-$3_{243\text{-}258}$). Subjects were randomized 1:1 to receive Resiquimod as an adjuvant applied to the GP100 vaccination site. Subjects with in-transit disease were thereafter treated with resiquimod topically on half of the target lesions. **Results:** All patients (n = 47) underwent $GP100_{209\text{-}2m}$ vaccination, a majority (39) also received the MAGE-$3_{243\text{-}258}$ peptide. The type I interferon-inducible genes (Mx A and IRF7), IFNg, and IP-10 RNA expression were up-regulated only in vaccination sites treated with Resiquimod (each $p < 0.01$) , demonstrating pDC activation (Type I interferon) and possibly T and NK cell activation (IFNg and IP-10). Nineteen subjects had in-transit disease at entry into the trial. In response to peptide vaccination alone, tumor regression was more likely in patients who received Resiquimod at the vaccination site (group A) compared to those who did not (group B). (4/9 vs 0/10, p = 0.033). In group A, 5 patients continued treatment with Resiquimod topically on the tumors, and all had tumor response (4PR, 1CR). In group B, 5 continued to tumoral resiquimod and 3 had regression (3 PR). **Conclusions:** Resiquimod increases Type I interferon and IFNg at the peptide vaccination site by activation of pDC/mDC and increases the antitumor response sufficiently to mediate regression of in-transit melanoma metastasis. Resiquimod on in-transit melanoma, in vaccinated hosts, drives regression of metastases, regardless of previous exposure at vaccination. Clinical trial information: NCT00960752.

9583 Poster Session (Board #191), Sat, 1:15 PM-4:45 PM

Use of circulating tumor DNA to predict survival in patients with resected high-risk stage II/III melanoma. *First Author: Rebecca Lee, Molecular Oncology Group, Cancer Research UK Manchester Institute, Manchester, United Kingdom*

Background: Patients with high-risk stage II/III resected melanoma commonly develop metastatic disease. Adjuvant high dose interferon and ipilimumab 10mg/kg are associated with survival benefit, but at the expense of toxicity. At present, we cannot differentiate between patients who will progress to stage IV disease or those cured by surgery. Circulating tumor DNA (ctDNA) is a biomarker of disease progression in many cancers including stage IV melanoma, however its utility in the adjuvant setting has not been investigated. **Methods:** We performed droplet digital polymerase chain reaction to detect *BRAF* and *NRAS* mutations in plasma of 161 stage IIB, IIC/III high-risk melanoma patients enrolled in AVAST-M; a randomized study of bevacizumab vs. observation. Baseline plasma samples were collected within 12 weeks of surgery for both arms. **Results:** Mutant *BRAF* or *NRAS*ctDNA was detectable (> 1 copy of mutant ctDNA) in 12% (19/161) of patients. Patients with detectable ctDNA had a decreased disease free interval (DFI; hazard ratio [HR] 3.12; 95% confidence interval [CI] 1.79-5.47; $p < 0.0001$) and distant metastasis-free interval (DMFI; HR 3.22; 95% CI 1.80-5.79; $p < 0.0001$) vs. those with undetectable ctDNA. One year DFI rate for patients with detectable ctDNA was 26% (95% CI 10-47%) vs. 74% (95% CI 66-81%) for those with undetectable ctDNA. One year DMFI rate for patients with detectable ctDNA was 37% (95% CI 17-57%) vs. 84% (95% CI 77-89%) with undetectable ctDNA. Detectable ctDNA remained a significant predictor after adjustment for N classification and performance status (PS) (DFI HR 3.48; 95% CI 1.95-6.19, $p < 0.0001$; DMFI HR 3.41, 95% CI 1.88-6.20, $p < 0.0001$). Five year overall survival (OS) rate for patients with detectable ctDNA was 33% (95% CI 14-55%) vs. 65% (95% CI 56-72%) for those with undetectable ctDNA. OS was significantly worse for patients with detectable ctDNA (HR 2.63; 95% CI 1.4-4.96); p = 0.003) and remained significant after adjustment for PS (HR 2.5, 95% CI 1.32-4.74, p = 0.005). **Conclusions:** CtDNA is predictive of relapse and survival in high-risk, resected melanoma and can potentially aid stratification of patients for adjuvant therapy.

9584 Poster Session (Board #192), Sat, 1:15 PM-4:45 PM

Patterns of histologic response to neoadjuvant targeted therapy in patients with BRAF mutant melanoma. *First Author: Zeynep Eroglu, Moffitt Cancer Center, Tampa, FL*

Background: While BRAF and MEK inhibitors are approved for patients with BRAF V600 + unresectable/metastatic melanoma, their role in the neoadjuvant setting is less well defined. Results from small trials have noted robust response rates, but less is known about histological patterns of response in resected tumor specimens and relation to outcome in these patients (pts). **Methods:** In a retrospective study, we analyzed the clinical and pathologic patterns of response to neoadjuvant BRAF ± MEK inhibitor therapy in pts with locally advanced melanoma subsequently rendered disease free with surgery. **Results:** Twenty pts were identified, nine with stage IIIC and 11 with stage IV melanoma. Seven patients received neoadjuvant vemurafenib (VEM), 12 received dabrafenib + trametinib (D+T), and one encorafenib + binimetinib. The median duration of treatment was 7.8 months. Seven patients (35%) had a pathologic complete response (pCR); six of them had received combination therapy, 5 with D+T, 1 VEM with an HSP90 inhibitor. Four distinct histologic patterns were observed in the resected tumor specimens: necrotic, fibrotic/melanotic (tumoral melanosis), hyalinized, or mixed. With median follow-up of 25 months (range 1-60), six pts (30%) had experienced recurrence; three developed CNS metastases. Four of the six patients had received neoadjuvant D+T; three were restarted on their prior targeted therapy at recurrence and all responded. All 6 pts with recurrence had residual disease in the surgical specimen; three had no necrosis identified. In contrast to the 13 pts with persistent tumor, none of the 7 pCR pts has relapsed (p = 0.05). There was a trend towards improved relapse-free-survival (RFS) with a pCR, with a 1 yr of RFS-rate of 50.4% vs 100% in pCR.(p = 0.08) Of the 14 patients without subsequent recurrence, 9 had either a pure necrotic histology, or a mixed histological pattern that included necrosis. **Conclusions:** In locally advanced or M1a BRAF mutant melanoma, attaining a pCR to neoadjuvant targeted therapy may correlate with improved patient outcomes and be more likely achieved with combination therapy. Presence of necrosis in the surgical specimen appears be a favorable prognostic factor.

9585 Poster Session (Board #193), Sat, 1:15 PM-4:45 PM

Clonality of T cell repertoire in the tumor (TME) and peripheral blood of regionally advanced melanoma patients (pts) treated with neoadjuvant ipilimumab (ipi) and high dose interferon-α (HDI). *First Author: Priyanka Vallabhaneni, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: Pts with regionally advanced melanoma were treated with neoadjuvant ipi and HDI in a reported study (*Tarhini.J Clin Oncol suppl, 2016; abstr 9585*). Pathologic complete response (pCR) was found in 32% of pts. Clonality of T cell repertoire was investigated in TME and peripheral blood mononuclear cells (PBMC). **Methods:** Pts were randomized to neoadjuvant ipi 3 or 10 mg/kg combined with HDI. Tumor biopsies were evaluable for testing at pretreatment (N = 20 pts) and definitive surgery (week 6-8; N = 25). When available, primary (N = 24) and relapse tumors (N = 6) were tested. PBMC: pretreatment (N = 29), 6 weeks (wk) (N = 24), then 3 (N = 23), 6 (N = 21), 12 (N = 14) months. T cell receptor beta chain (TCRB) repertoire was immunosequenced in PBMC and TME to determine repertoire clonality and T cell fraction in blood and TME (TIL; fraction of all nucleated cells identified as T cells). **Results:** PBMC T cell fraction when measured early on-treatment (6 wks) was significantly higher in pts who had pCR or microscopic residual disease vs. gross disease at the 6-8 wks surgery (p = 0.047). PBMC clonality was significantly lower at 12 wks (p = 0.025) for pts who continued to be relapse free (NED) long term vs. those who eventually relapsed. In TME, except for trends no significant difference in clonality was seen, but in pts with pCR TIL fraction was significantly higher when measured in primary tumors (p = 0.033). The number of tumor-associated clones that were expanded in blood post-treatment was strongly correlated with both TIL fraction (Rho 0.7299, p = 0.0003) and TIL clone diversity (Rho 0.882, p = 2.7^{-7}). **Conclusions:** Higher T cell fraction and lower clonality in PBMC when measured early on-treatment, and higher TIL fraction in primary tumor constituted promising biomarkers of response. Pts with higher TIL fractions were more likely to have tumor-associated clones detectable in blood, suggesting these may be useful for tracking the immune response. These findings warrant validation in an independent cohort and exploration with other immunotherapeutics. Clinical trial information: NCT01608594.

9586 Poster Session (Board #194), Sat, 1:15 PM-4:45 PM

Neoadjuvant ipilimumab + nivolumab (IPI+NIVO) in palpable stage III melanoma: Updated data from the OpACIN trial and first immunological analyses. *First Author: Elisa A. Rozeman, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: The combination of IPI+NIVO induces high response rates and improved overall survival in late stage melanoma. T cell checkpoint inhibition is of greatest value at the moment of TCR triggering and therefore dependent on the amount of antigen present, indicating that adjuvant immunotherapy may work most efficiently, when initiated prior to surgery. **Methods:** Two-arm Phase 1b feasibility trial of 20 high risk AJCC stage IIIB and IIIC melanoma patients with palpable nodal disease receiving the combination of IPI 3mg/kg and NIVO 1mg/kg, either adjuvant four courses after surgery, or split two courses neo-adjuvant and two courses adjuvant. **Results:** In this update all 20 patients are evaluable. Neo-adjuvant application of IPI+NIVO was feasible and no surgery-associated adverse events were attributed to (neo-)adjuvant therapy. 18/20 patients had to stop early due to grade 3/4 toxicities. Neo-adjuvant IPI+NIVO reduced tumor load in 8/10 patients (3 pCR, 4 near-pCRs [minimal remaining micrometastases], 1 pPR [75% reduction], 1 SD and 1 PD). To date, after a median follow-up of 45 weeks (range 13-74), none of the responders in the neoadjuvant arm has relapsed. Relapse was observed for both non-responders within the neoadjuvant arm and for 3 patients within the adjuvant arm. TCR sequencing and MHC tetramer-based analysis to compare the induction and expansion of tumor (neo-)antigen-specific T cell responses between both treatment arms are underway and will be presented. **Conclusions:** The combination of IPI +NIVO in the (neo-)adjuvant treatment setting for high risk stage III melanoma patients is feasible and induces very frequent responses. At the same time, severe grade 3/4 toxicity is more frequent than expected from stage IV melanoma patient study data. These results indicate that IPI+NIVO is a promising combination for neo-adjuvant treatment in stage III melanoma. Adjusted combination schemes are currently tested in the phase 2 OpACIN-neo trial, with the aim of reducing toxicity while preserving efficacy. Clinical trial information: NCT02437279.

9587 Poster Session (Board #195), Sat, 1:15 PM-4:45 PM

Relapse-free survial and target identification to enhance response with neoadjuvant and adjuvant dabrafenib + trametinib (D+T) treatment compared to standard-of-care (SOC) surgery in patients (pts) with high-risk resectable BRAF-mutant metastatic melanoma. *First Author: Jennifer Ann Wargo, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Targeted and immune therapies have dramatically improved outcomes in stage IV metastatic melanoma pts. These agents are now being tested in earlier-stage disease. SOC surgery for high-risk resectable melanoma (AJCC stage IIIB/IIIC), with or without adjuvant therapy, is associated with a high risk of relapse (~70%). We hypothesized that neoadjuvant (neo) + adjuvant treatment with D+T improves RFS in these pts. Longitudinally collected biospecimens from pts receiving this treatment were analyzed to identify candidate strategies to further improve outcomes. **Methods:** A prospective single-institution randomized clinical trial (NCT02231775) was conducted in BRAF-mutant pts with resectable Stage IIIB/C or oligometastatic stage IV melanoma. Pts were randomized 1:2 to SOC (Arm A) versus neo + adjuvant D+T (Arm B; 8 wks neo + 44 wks adjuvant). The primary endpoint was RFS. Tumor biopsies were collected at baseline, week 3, and at surgery for molecular and immune profiling (whole exome sequencing, gene expression profiling, IHC, flow cytometry). **Results:** 21 of a planned 84 patients were enrolled (Arm A = 7, Arm B = 14). Arms were well balanced for standard prognostic factors, and toxicity was manageable. RECIST response rate with neo D+T was 77%, and the pathologic complete response rate (pCR) was 58%. First interim analysis revealed significantly improved RFS in the D+T arm over SOC (HR 62.5, p < 0.0001), leading to early closure to enrollment. Pts with a pCR at surgery had significantly improved RFS versus pts without pCR (p = 0.04) on neo D+T. Tumor profiling revealed incomplete MAPK pathway blockade and higher levels of CD8+ T cells expressing immunomodulators Tim-3 and Lag-3 in pts who did not achieve a pCR. **Conclusions:** Neo + adjuvant D+T is associated with a high pCR rate and markedly improved RFS over SOC in pts with high-risk resectable BRAF-mutant metastatic melanoma. pCR at surgery is associated with improved RFS. Tumor analyses reveal candidate targets for testing in future trials to enhance responses to neo D+T. Clinical trial information: NCT02231775.

9588 Poster Session (Board #196), Sat, 1:15 PM-4:45 PM

Financial toxicity and cancer-related distress among melanoma survivors. *First Author: Joanne S Buzaglo, Cancer Support Community, Research and Training Institute, Philadelphia, PA*

Background: Melanoma survivors are at risk for significant financial burden due to cancer care and out of pocket costs. We explored 1) the financial impact of melanoma and its relationship to cancer-related distress, and 2) survivors' experiences discussing financial burden with their health care team. **Methods:** Of 110 melanoma survivors enrolled in the Cancer Support Community's online Cancer Experience Registry, 56 completed questions about financial impact of cancer and cost of care communication. Participants rated concern (0 = not at all; 4 = very seriously) about 27 items encompassing psychological, emotional, physical and practical concerns; items were summed into a total distress score (mean = 33, SD = 21, range 0-88). Financial impact and overall distress were examined via regression analysis. **Results:** Participants were 71% female, 89% Caucasian, median age 54, and median time since diagnosis 2.5 years. Total annual income: 34% < $60K; 46% $60K+; 20% not reported. 24% spent $101-250/month on melanoma out of pocket costs; 20% spent $251-500; and 24% spent ≥$500. The top concern was health insurance/money worries (69% moderately to very seriously concerned). Due to medical costs, 57% depleted their savings, 20% borrowed against or used retirement money, 20% used pharmaceutical assistance programs, 13% skipped medicine dosages at least sometimes, and 17% postponed filling prescriptions. Only 28% reported that their health care team spoke to them about cost of care, and 28% were asked about financial distress; 42% desired financial assistance. Financial impact was associated with an increase in overall distress for those with income < $60K (p < .05; interaction p < 0.05). **Conclusions:** Substantial proportions of melanoma survivors experience financial burden that can impact quality of life, particularly lower income individuals. Although oncologists are encouraged to discuss treatment costs, most patients report they have not had these discussions with providers. These results support the development/evaluation of interventions to enhance doctor-patient communication, and financial counseling to minimize financial burden of melanoma and the risks it can confer for quality of life, course of cancer care, and health outcomes.

9589 Poster Session (Board #197), Sat, 1:15 PM-4:45 PM

Whole genome and RNA sequencing reveal the distinct genomic landscape of acral melanoma. *First Author: Yan Kong, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Acral melanoma is a common subtype of melanoma in Asians with extremely poor prognosis, and therapy strategy has not been clearly established for acral melanoma. The aim of this study is to perform genomic and RNA profiling of acral melanoma to obtain the comprehensive genomic view of this subtype of melanoma. **Methods:** Genomic DNA was extracted with Qiagen DNeasy Blood or Tissue Kit . DNA libraries were prepared using a CancerPROTM-P88 BOX library Prep kit and sequencing was performed using the Illumina HiSeq X10. RNA was isolated with Qiagen RNeasy mini-spin column. cDNA was synthesized from total RNA using the SuperScript III first-strand synthesis system . RNA libraries were prepared using the NEBNext Ultra II Directional RNA Library Prep Kit and sequencing was performed using the Illumina HiSeq X10. **Results:** To obtain a comprehensive genomic and functional genomic view of acral melanoma, we sequenced the genomes of 14 acral melanoma and transcriptomes of 11 of these melanoma samples. We found a new mutation in the V28 codon of BRAF in three patients. Furthermore, we identified recurrent non-synonymous single nucleotide variants in previously described oncogene NRAS, as well as in genes encoding keratin associated proteins (KRTAP4-7, KRTAP4-5) and mucin (MUC2, MUC21). Notably, a recurrent noncoding hotspot mutation was discovered in 4 of 11 cases. By analyzing the RNA sequencing data, we found significant divergence on transcriptome between patients with or without ulcer. In total, we identified 201 genes were significantly up-regulated and 386 genes significantly down-regulated in acral melanoma patients with ulcer. Differentially expressed genes were enriched in pathways associated with cancers, melanogenesis, cell death signaling, skin diseases, etc. **Conclusions:** Our study reveals potentially different driver mutations and distinct transcriptome in acral melanoma patients compared with cutaneous melanoma patients and sheds lights to the further personalized medicine for acral melanoma patients.

9590 Poster Session (Board #198), Sat, 1:15 PM-4:45 PM

Hyperproliferative keratinocytic cutaneous adverse events and inflammatory palmoplantar erythrodysesthesia in melanoma patients treated with encorafenib compared to other BRAF inhibitors. *First Author: Simone M. Goldinger, University Hospital Zurich, Zurich, Switzerland*

Background: BRAF inhibitor (BRAFi) an MEK inhibitor (MEKi) monotherapies have shown to cause more cutaneous adverse events (cuAEs) in monotherapy compared to combination therapy. Encorafenib in combination with binimetinib showed improved PFS in patients with BRAF mutant melanoma (14.9 months). Furthermore, encorafenib showed superiority over vemurafenib. Objective:The aim of this study was to investigate cuAEs of melanoma patients treated with encorafenib and/or binimetinib and compare them to other BRAFi and MEKi induced cuAEs reported in the literature and observed in our control population. **Methods:** Patients treated with encorafenib, binimetinib, and other BRAFi/MEKi within approved clinical trials at the University Hospital of Zurich were collected and analyzed. Clinical and histological assessments were performed. **Results:** In 111 patients treated with BRAFi and/or MEKi, 212 related or possibly related cuAEs were identified. The percentage of patients with at least one cuAE is shown in the table below. The most frequent cuAEs observed in patients treated with encorafenib where palmoplantar hyperkeratosis (PPH, 50%), palmoplantar erythrodysesthesia (PPD, 53.8%) and alopecia (42.3%), whereas acanthopapillomas (83%), maculopapular exanthemas (63.3%), PPH and PPD (each 50%) prevailed in patients treated with vemurafenib. The most frequent observed cuAE in patients with dabrafenib/trametinib combination therapy were maculopapular exanthemas (18.2%) and erythema-annulare-like eruptions (18.2%), with encorafenib/binimetinib combination therapy PPH (10.6%) respectivly. **Conclusions:** Encorafenib showed less hyperproliferative cuAEs as previous BRAFi. However, PPH and PPD seem to occur more often compared to the literature of other BRAFi. Both is supporting the argument that encorafenib is a second generation BRAFi with a longer dissociation time.

Substance (n)	% of patients with at least one cuAE
encorafenib (n=26)	73.1
vemurafenib (n=6)	100
encorafenib plus binimetinib (n=48)	31.9
dabrafenib plus trametinib (n=11)	45.4
trametinib (n= 8)	87.5
binimetinib (n=25)	92

TPS9591 Poster Session (Board #199a), Sat, 1:15 PM-4:45 PM

Phase 1 study to evaluate safety and efficacy of ipilimumab + nivolumab + external beam radiotherapy in patients with metastatic melanoma. *First Author: Michael Andrew Postow, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Immunotherapy (IMT) with checkpoint blocking antibodies has led to progress in metastatic melanoma with 3 FDA-approved drugs, including the combination of ipilimumab (IPI), a CTLA-4 antibody, and nivolumab (NIVO), a PD-1 antibody. Although radiotherapy (RT) is primarily used as local palliative therapy in metastatic melanoma, it also possibly affects systemic antitumor immunity. Preclinical data suggest RT alters the tumor microenvironment and renders tumor cells more susceptible to immunologically-mediated disease regression. These preclinical immunologic effects of RT have been shown to vary by RT dose and fractionation. We are now conducting the first clinical trial in patients to evaluate the triple combination of IPI + NIVO + RT using 2 different dose/fractionation schemes of RT. **Methods:** This ongoing Phase 1, open-label, multicenter study (NCT02659540) evaluates safety, efficacy, and immunologic effects of IPI + NIVO + RT in 18 patients with unresectable stage IV melanoma. Patients must have 1 melanoma metastasis that can be safely irradiated for palliative purposes and at least 1 measurable lesion that will not be irradiated. Patients receive concurrent IPI (3 mg/kg) and NIVO (1 mg/kg) every 3 weeks (Q3W) x 4, followed by NIVO monotherapy (240 mg Q2W), with RT initiated between the first and second doses of IPI + NIVO. In Cohort A, the irradiated metastasis receives a conventionally fractionated low dose of 30 Gy in 10 fractions of 3 Gy each over 2 weeks. If $\leq$7 of 9 patients (78%) in Cohort A have Grade 3/4 drug- or radiation-related adverse events, safety is deemed acceptable and Cohort B enrollment opens. In Cohort B, the irradiated metastasis receives a hypofractionated high dose of 27 Gy in 3 fractions of 9 Gy each over 2 weeks. The primary endpoint is safety. Secondary endpoints are objective response rate and disease control rate by RECIST and immune-related RECIST measured at Weeks 12 and 18, duration of response, progression-free survival, and overall survival. Exploratory endpoints include correlative studies of immunological effects. Enrollment opened on 05 Aug 2016. As of 31 Dec 2016, 4 patients are enrolled in Cohort A; enrollment is ongoing. Clinical trial information: NCT02659540.

TPS9592 Poster Session (Board #199b), Sat, 1:15 PM-4:45 PM

NCI 9922: Phase 2 study of ibrutinib in treatment-refractory distant metastatic cutaneous melanoma (DMCM). *First Author: Stergios J. Moschos, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: We have previously shown that the IL-2 inducible kinase (ITK) is highly expressed in primary melanomas compared with nevi due to promoter hypomethylation (Conway PCMR 2011). We have also shown using 2-color immunofluorescence (2CIF) that ITK protein expression is increased even more in metastatic compared to primary melanomas (S100+) and that molecular targeting (shRNA) or pharmacologic inhibition of ITK (BI 10N) in various melanoma cell lines, various melanoma xenografts and an immunocompetent melanoma mouse model suppresses cell proliferation and retards tumor growth without inducing cell death (Carson CCR 2015). We have also shown by intracellular stain of peripheral blood mononuclear cells (PBMC) that ITK is expressed in PBMC obtained from patients (pts) treated with MAPK or CTLA-4 inhibitors. Other groups have shown that ITK and BTK are expressed in Th2 cells, myeloid-derived suppressor cells, and tumor-associated macrophages. We have also shown that ibrutinib suppresses proliferation of various melanoma cell lines in low nM concentrations depending on tumoral expression of ITK. We hypothesize that targeting DMCM with ibrutinib alone will induce antitumor responses and/or prolong survival if DMCM expresses high levels of melanoma-associated ITK by 2CIF (S100/ITK). **Methods:** This is an open-label, single-arm, multicenter, phase II study of DMCM refractory to or ineligible for PD-1 and MAPK inhibitors. Ibrutinib will be dosed at 840 mg p.o. qd. The null hypothesis is that an ineffective drug will confer a 5% response rate (RR) and 18% 6-month PFS (6m PFS), whereas ibrutinib will confer $>=$ 20% RR and $>=$ 35% 6m PFS (KEYNOTE-002). This trial accrues in two stages; if either the RR and/or 6m PFS endpoint are met after 18 patients, then 14 additional pts will be accrued for a total of 32. The Simon's design will reject the null hypothesis if $>=$ 4 responses are observed or $>=$ 9 pts have PFS better than 6 months out of 32 patients. All pts are required to have baseline tumor tissue available for analysis of ITK expression by 2CIF. Immune monitoring will be performed on PBMC collected at baseline and various time points during treatment. Trial is currently recruiting pts (NCT02581930). Clinical trial information: NCT02581930.

TPS9593 Poster Session (Board #200a), Sat, 1:15 PM-4:45 PM

Pembrolizumab with or without vismodegib in treating metastatic or unresectable basal cell skin cancer. *First Author: Anne Lynn S. Chang, Stanford University School of Medicine, Stanford, CA*

Background: Basal cell carcinomas (BCCs) are the most common cancer in humans and have increased > 75% in the past two decades, with > 28,000 cases of advanced or metastatic diseases per year. Targeted therapy in the form of Smoothened inhibitors (SIs) are FDA approved for advanced BCC, however, over half of patients do not respond or become resistant to SI monotherapy after initial response. At this time, there are no other FDA approved drugs for advanced BCCs, however, emerging data indicates that a significant proportion of BCCs express programmed cell death ligand (PD-L)-1, suggesting potential response to PD-1 inhibition. In addition, BCCs are keratinocytic tumors, and our case series of PD-1 inhibitors against cutaneous squamous cell carcinomas, another keratinocytic tumor, have shown activity. Here, we present a proof-of-principle, phase 1b, open-label investigator initiated study of pembrolizumab for unresectable or metastatic BCC (NCT02690948). **Methods:** Following institutional review board approval, patients with locally advanced or metastatic BCCs who met all eligibility criteria were enrolled at a single academic center. Participants were allocated into either Arm 1 (pembrolizumab 200 mg IV every 3 weeks) or Arm 2 (pembrolizumab 200 mg IV every 3 weeks and concurrent vismodegib 150 mg by mouth daily) until disease progression or intolerable toxicity. Major inclusion criteria include individuals aged > or = 18 years with histologically verified unresectable and/or metastatic BCC, and with measurable disease by Response Evaluation Criteria for Solid Tumors version 1.1. Exclusion criteria include immunosuppresion, active infection, history of pneumonitis and autoimmune disease requiring systemic treatment. The primary outcome measures are the overall response rates in Arm 1 and 2. Secondary outcome measures include incidence and severity of adverse events (AEs) as defined by the Common Terminology Criteria for Adverse Events verson 4.0, and progression free survival. This study is currently enrolling, with 10 of 26 patients accrued to date (6 of 13 in Arm 1; 4 of 13 in Arm 2), and the study stopping rule (based on first 10 enrolled patients displaying progressive disease) did not need to be deployed. Clinical trial information: NCT02690948.

TPS9594 Poster Session (Board #200b), Sat, 1:15 PM-4:45 PM

A phase II study of oral azacitidine (CC-486) in combination with pembrolizumab (PEMBRO) in patients with metastatic melanoma (MM). *First Author: Emily Keung, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint inhibitors have impressive response rates and improved survival for many pts with MM, offering durable responses in up to 35% of pts while others have short-lived or no response (> 40%). A potentially targetable mechanism for immune escape is for cancers to subvert the cellular epigenetic machinery, affecting multiple aspects of the immune response from suppression of tumor antigen expression [such as Cancer Testis Antigens (CTA)] to antigen processing and presentation, thus allowing tumor proliferation to continue undetected. In preclinical models, decitabine (DAC), a DNA hypomethylating agent (HMA), has been able to revert heterogeneous CTA expression profiles, increasing cancer cell immunogenicity. HMAs also increased TH1-chemokine expression, T cell tumor infiltration, T cell-mediated tumor killing, and have been shown to be synergistic with checkpoint inhibitors in preclinical models. This suggests that epigenetic therapy with checkpoint inhibition is a rational combination to target MM. Clinical advantages of the HMA CC-486 over DAC include oral bioavailability and potential versatility in dosing and schedule. We hypothesize that CC-486 + PEMBRO will be tolerated at biologically relevant doses; enhance response to PEMBRO in pts with mm who are PD-1 naïve; and reverse resistance to immunotherapy in pts refractory/resistant to PD-1 directed therapy. **Methods:** This study will evaluate the safety and efficacy of CC-486 + PEMBRO defined by Objective Response Rate (ORR) by RECIST 1.1 in pts with MM. Pts who are PD-1 naïve (Arm A, n = 36) and pts who have progressed on prior PD-1 directed therapy (Arm B, n = 35) will be enrolled. Unlimited prior systemic therapies will be allowed. Pts will receive 300mg PO of CC-486 on days 1-14 and 200mg IV of PEMBRO every 3 weeks. Continuous monitoring for toxicity and futility will be performed and assumes an ORR of > 35% and > 15% for Arms A and B, respectively (95% power). Tumor biopsies at baseline and post treatment are required. Effects of CC-486 + PEMBRO on CTAs, MDSCs and Tregs, and correlation between mutation burden and response will be studied. This study is open for enrollment. Clinical trial information: NCT02816021.

TPS9595 Poster Session (Board #201a), Sat, 1:15 PM-4:45 PM

An open-label, uncontrolled, single arm phase II trial of the PI3K inhibitor buparlisib in patients with melanoma brain metastases. *First Author: Friedegund Elke Meier, Universitatsklinikum Carl Gustav Carus, Dresden, Germany*

Background: The approval of effective BRAF +/- MEK inhibitors and immune checkpoint inhibitors has revolutionized the treatment of metastatic melanoma. However, available therapies appear to be less effective on cerebral than extracerebral metastases. Hyperactivation of the PI3K-AKT survival pathway is a prominent feature of melanoma brain metastases (MBM). This trial aims to determine the activity and safety of the PI3K inhibitor buparlisib in patients (pts) with MBM. **Methods:** The study enrolls adults suffering from MBM not eligible for neurosurgery or/and radiosurgery. Patients must have failed prior treatment with BRAF +/- MEK Inhibitors (BRAF-V600E mutated population) and anti-PD-1 or/and anti-CTLA-4 antibodies (BRAF wild-type population), respectively. Patients are treated with buparlisib 100 mg PO daily until disease progression or unacceptable toxicity. The Simon-Two-Step design for phase 2 studies was used to determine sample size. Assuming a response rate of 12.5% in comparison to historical 10% for chemotherapy 22 (8/14) pts would be required. If there are one or fewer responses in the first 8 pts the study would stop. Prespecified activity goal for the first stage of accrual was met; currently 11/22 pts are enrolled. Clinical trial information: NCT02452294.

TPS9596 Poster Session (Board #201b), Sat, 1:15 PM-4:45 PM

CARSKIN: Pembrolizumab as first line therapy in patients with unresectable cutaneous squamous cell carcinoma (cSCC). *First Author: Eve Maubec, AP-HP, Hôpital Avicenne, Bobigny, France*

Background: Treatment options are limited for patients (pts) with locally advanced or metastatic cSCCs. Cisplatin-based combinations have some efficacy but their toxicity often prohibits their use, particularly for the elderly. New therapeutic options are needed. Tumors divert the programmed death receptor 1 (PD-1) pathway suppressing immune control. Pembrolizumab (MK-3475) is a high-affinity humanized monoclonal anti-PD-1 antibody. It leads to dual PD-1 ligand (PD-L1 and PD-L2) blockade that may reactivate the immune surveillance and elicit anti-tumor response. It has antitumor activity in several tumors including head and neck SCCs. Moreover, an efficacy of pembrolizumab in cSCCs has been reported recently in a series of 6 cases. **Methods:** CARSKIN (ClinicalTrials.gov, NCT02883556) is a French multicenter, open-label, nonrandomized phase 2 trial, designed to evaluate the efficacy and safety of pembrolizumab in 39 pts with unresectable and/or metastatic cSCCs, naive of chemotherapy and of EGFR inhibitors. Pembrolizumab is administered (200 mg IV Q3W) for up to 24 months or until disease progression or unacceptable toxicity. Eligible pts must undergo a baseline biopsy of the tumor prior to treatment for PD-L1 evaluation. Response is to be assessed at baseline, wk 9, 15 and 24, and thereafter Q12W by central radiology review per RECIST 1.1 and per modified RECIST v1.1. The primary objective is response rate (RR) at wk 15 per RECIST 1.1. Secondary efficacy objectives are to assess whether patients with PD-L1+ tumors have a better RR than the whole sample at wk 15 and to assess in the whole sample and in PD-L1+ pts, disease control rate (DCR) at wk15, RR at wk 24, best RR, overall survival (OS), progression free survival (PFS), duration of response / control and time to disease progression. A Simon optimal two-stage design will be used. Four responders among 19 pts will be needed in the 1st step to continue the trial. Overall 9 responses will be needed to conclude the effectiveness. Kaplan-Meier statistics will assess PFS and OS. Adverse events (AEs) will be assessed throughout the study and for 30 d thereafter (6 m for serious AEs) and graded per NCI CTCAE v4.0. Clinical trial information: NCT02883556.

TPS9597 **Poster Session (Board #202a), Sat, 1:15 PM-4:45 PM**

Multi-center phase Ib study of intermittent dosing of the MEK inhibitor, selumetinib, in patients with advanced uveal melanoma not previously treated with a MEK inhibitor. *First Author: Kimberly Mayumi Komatsubara, Columbia University Medical Center, New York, NY*

Background: Uveal melanoma (UM) is a rare subtype of melanoma with no effective therapy for advanced disease. UM is characterized by mutations in GNAQ and GNA11 leading to constitutive activation of the mitogen activated protein kinase (MAPK) pathway. We have previously shown that targeting the MAPK pathway though MEK inhibition with Selumetinib (AZD6244, ARRY-142886) using a continuous dosing schedule improved progression free survival (PFS) in a randomized Phase II study of Selumetininb versus chemotherapy in patients with metastatic UM; however, no PFS or overall survival (OS) benefit was observed in a subsequent randomized Phase III study of Selumetinib and chemotherapy versus chemotherapy alone. We hypothesize that an intermittent dosing schedule of Selumetinib may be more effective than continuous dosing by achieving higher dose levels, better drug tolerability, and more complete target inhibition. We propose a Phase Ib study of Selumetinib in UM using an intermittent dosing schedule. **Methods:** A total of 28 subjects will be enrolled using the time to event continual reassessment method (TITE-CRM). Key inclusion criteria include a diagnosis of advanced UM, measurable disease by RECIST v1.1, and no prior MEK inhibitor therapy. Eligible subjects will be treated with Selumetinib starting at a dose level of 125 mg orally twice a day, using a 3-days-on and 4-days-off per week schedule. The primary goal of this study is to estimate the maximum tolerated dose (MTD) of intermittently dosed Selumetinib. Secondary endpoints are response rate, PFS and OS. Responses will be evaluated every 8 weeks by a CT scan of the chest and CT or MRI of the abdomen/ pelvis using RECIST v1.1 criteria. Mandatory tumor biopsies will be obtained at baseline, cycle 1 day 3 (Selumetinib-on day), and between cycle 1 day 11-14 (Selumetinib-off day) in 20 subjects, and optionally at progression. Tumor tissue will be assessed for MAPK pathway inhibition and reactivation at each time point, as well as mechanisms of resistance. Recruitment is currently ongoing. Clinical trial information: NCT02768766.

TPS9598 **Poster Session (Board #202b), Sat, 1:15 PM-4:45 PM**

SECOMBIT (sequential combo immuno and target therapy study): A three arms prospective, randomized phase II study to evaluate the best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with metastatic melanoma and BRAF mutation. *First Author: Paolo Antonio Ascierto, Istituto Nazionale Tumori "Fondazione G.Pascale"- IRCCS, Naples, Italy*

Background: Treatment of BRAF-mutated metastatic melanoma has dramatically changed with the introduction of targeted therapy (BRAF and MEK inhibitors) and immune-checkpoint blockade (anti-CTLA4, anti-PD-1, and anti-PD-L1). Target therapy has been associated with high response rates, but short-term responses. Conversely, treatment with immune checkpoint inhibitors was found to present with lower response rates, but long-term responses. Synergism has been demonstrated when targeted therapy is combined with immunotherapy. The risk of a high rate of toxicity limits the simultaneous combination of all the four compounds (target agents and immunomodulating monoclonal antibodies). Sequencing of these different combinations seems to be more feasible; finding the right treatment sequence represents an important issue to be addressed. **Methods:** Approximately, 230 patients with untreated, histologically-confirmed advanced melanoma (measurable disease by RECIST v1.1) and carrying the *BRAF*^{V600} mutation will be randomized to Arm A [E+B until disease progression (PD), followed by I+N], or Arm B (I+N until PD, followed by E+B) or Arm C (E+B for 8 weeks, followed by I+N until PD, followed by E+B until PD). Patients will receive the combo treatments with the following schedules: target therapy, E 450mg p.o. od + B 45mg p.o. bid; immunotherapy, I 3mg/kg + N 1mg/kg Q3w x 4 cycles, followed by N 3mg/kg Q2w. The OS (time from the date of randomization until death from any cause) is primary efficacy endpoint of the study. Secondary endpoints include total PFS (time from randomization until the second progression), survival at 2 and 3 years, best overall response rate, duration of response. About 90 patients will take part in the ancillary study for the evaluation of biomarkers on the biological samples available (biopsies + blood samples). 30 Sites in Europe will concur to enroll the patients in the trial. This study is open and currently enrolling patients. Clinical trial information: NCT02631447.

TPS9599 **Poster Session (Board #203a), Sat, 1:15 PM-4:45 PM**

A randomized phase II study of vemurafenib plus cobimetinib continuous versus intermittent in previously untreated *BRAF V600*-mutation positive patients with unresectable locally advanced or metastatic melanoma. *First Author: Jose A. Lopez-Martin, Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain*

Background: Previous clinical trials have shown that vemurafenib significantly increases PFS and OS in untreated BRAFV600 mutant advanced melanoma patients. Nevertheless, disease progression occurs after a median of 6-7 months since start of vemurafenib. Several mechanisms of acquired resistance to vemurafenib result in reactivation of MAPK pathway. Upfront addition of a MEK inhibitor (MEKi) to vemurafenib delays secondary resistance to BRAFi. The combination of cobimetinib, a MEKi, plus vemurafenib as a continuous administration was approved by FDA in 2,015 in untreated metastatic BRAFV600 advanced melanoma patients based on an increase in PFS and OS achieved in a phase III trial (coBRIM trial). Preclinical models have shown that continuous vemurafenib dosing promotes the clonal expansion of drug-resistant cells, and intermittent dosing could serve to eliminate the fitness advantage of the resistant cells and delay the onset of drug-resistant disease (Das Thakur, Nature 2013). These observations and some clinical case reports support upfront evaluation of alternative dosing regimens of MAPK pathway inhibition. **Methods:** This is a randomized phase II study to explore the efficacy and safety of two schedules of administration of vemurafenib in combination with cobimetinib (continuous – 28-day cycles with vemurafenib 960 mg PO BID, Days 1-28, and cobimetinib 60 mg PO QD, Days 1-21 – and intermittent – same dose/schedule during first 12 weeks, and then, same doses with the following schedule: vemurafenib 4 *weeks on* /2 *weeks off*, and cobimetinib 3 *weeks on*/ 3 *weeks off*), in patients with untreated, BRAFV600 mutated, unresectable, measurable (RECIST 1.1), locally advanced or metastatic melanoma. Prior adjuvant immunotherapy is allowed. Primary endpoint is PFS. Secondary endpoints include: OS, ORR, pharmacokinetic and pharmacodynamic profiles and safety. Additional translational research to analyze predictive factors and mechanism of resistance will be explored. The trial is in progress; 56 of up to 116 planned pts have been recruited at the end of December 2016 (enrollment started in June 2015). Clinical trial information: NCT02583516.

TPS9600 **Poster Session (Board #203b), Sat, 1:15 PM-4:45 PM**

Multicenter phase 2 study to identify the optimal neo-adjuvant combination scheme of ipilimumab (IPI) and nivolumab (NIVO) (OpACIN-neo). *First Author: Elisa A. Rozeman, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: The outcome of high risk stage IIIb and IIIc melanoma patients is poor, with a 5 year overall survival (OS) rate of $<$ 50%. Adjuvant high dose IPI significantly improves 5 year progression free survival (PFS) and OS. In stage IV patients the combination of IPI and NIVO improves response rates (RR) and PFS compared to monotherapy, but at cost of higher toxicity. Neo-adjuvant treatment may be a favorable approach as immune checkpoint inhibition (ICI) is of greatest value at the moment of TCR triggering and therefore dependent on the amount of antigen present. The phase Ib OpACIN study comparing neo-adjuvant and adjuvant IPI and NIVO showed that neo-adjuvant treatment is feasible as all patients underwent surgery on time. The neo-adjuvant pathological RR was 80%, although 18/20 patients (90%) stopped early due to $\geq$1 grade 3 or 4 immune-related adverse events (irAEs). To date (median follow-up 45 wks), none of the 8 responders in the neo-adjuvant arm have relapsed. This raises the question whether the neo-adjuvant IPI and NIVO schedule can be adjusted to reduce toxicity but preserve efficacy. **Methods:** The aim of the multi-center phase 2 OpACIN-neo trial is to identify an optimal neo-adjuvant combination scheme of IPI and NIVO. 90 patients with resectable stage III melanoma will be randomized 1:1:1 between three combination schemes of IPI and NIVO. Patients in arm A will receive 2 courses standard regimen IPI 3mg/kg + NIVO 1mg/kg q3wks, in arm B IPI 1mg/kg + NIVO 3mg/kg q3wks, and in arm C 2 courses of IPI 3mg/kg q3wks directly followed (2-24hr) by 2 courses NIVO 3mg/kg q2wks. All patients will undergo surgery at week 6. The primary endpoints are rate of grade 3/4 irAEs, pathological RR, and radiologic RECIST 1.1. An interim analysis is planned after 13 patients have been accrued to each arm (according to the Simon 2-stage design). Major inclusion criteria are: $\geq$1 measurable lymph node metastases (according to RECIST 1.1) that can be biopsied, no history of in-transit metastases in the last 6 months, and naïve for ICI. Baseline biopsies and blood samples (week 0, 6, 12) will be taken for translational research. The first center started inclusion in December 2016, until now 2 patients have been enrolled. Clinical trial information: NCT02977052.

LBA10000 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

Long-term results of a phase II randomized controlled trial (RCT) of a psychological intervention (Conquer Fear) to reduce clinical levels of fear of cancer recurrence in breast, colorectal, and melanoma cancer survivors. *First Author: Jane McNeil Beith, Chris O'Brien Lifehouse, Camperdown, Australia*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, June 2, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

LBA10001 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

Managing cancer and living meaningfully (CALM): A randomized controlled trial of a psychological intervention for patients with advanced cancer. *First Author: Gary Rodin, Princess Margaret Cancer Centre, Toronto, ON, Canada*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, June 2, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

LBA10002 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

Web-based stress management for newly diagnosed cancer patients (STREAM): A randomized, wait-list controlled intervention study. *First Author: Viviane Hess, University of Basel and University Hospital Basel, Medical Oncology, Basel, Switzerland*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, June 2, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

10003 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

Lorazepam as an adjuvant to haloperidol for agitated delirium at the end of life: A double-blind randomized controlled trial. *First Author: David Hui, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Agitated delirium is a highly distressing neuropsychiatric syndrome common in the last days of life. The use of benzodiazepines for agitated delirium is highly controversial. We compared the effect of lorazepam versus placebo as an adjuvant to haloperidol for persistent agitated delirium. **Methods:** In this double-blind trial, we randomly assigned patients with advanced cancer admitted to an acute palliative care unit with agitated delirium despite scheduled haloperidol to either lorazepam 3 mg IV or placebo, in addition to haloperidol 2 mg IV upon the onset of agitation. The primary outcome was the Richmond Agitation Sedation Scale (RASS) over the first 8 hours, ranging from -5 (unarousable) to +4 (combative). Secondary endpoints were rescue neuroleptic use, perceived comfort, delirium-related distress, adverse effects and overall survival. 26 patients per arm provided 80% power to detect a between arm difference of 0.5 effect size in mean RASS with a=5%. We used the Wilcoxon Rank Sum test for primary comparison. **Results:** 52 of 58 (90%) patients who received the medications completed 8 h of observation. RASS decreased significantly within 30 min of treatment in both arms (Table). The lorazepam arm was associated with significantly greater reduction of RASS (Table), less rescue neuroleptics (mean haloperidol equivalent dose 1 mg v. 3 mg, P=0.02), and greater comfort as perceived by blinded caregivers (84% v. 37%, P=0.007) and nurses (77% v. 30%, P=0.005) compared to placebo. We found no significant between-group differences in delirium-related distress, adverse effects and overall survival (median 68 v. 73 h, P=0.56). **Conclusions:** The combination of lorazepam/haloperidol resulted in rapid and significant reduction of agitation compared to haloperidol alone. Our study supports the judicious use of single dose lorazepam/haloperidol for persistent agitated delirium. Clinical trial information: NCT01670097.

RASS change.

	Mean difference (95% CI)			
	Lorazepam + haloperidol (n=29)	Placebo + haloperidol (n=29)	Difference between arms	P value
0 to 30 min	-3.62 (-4.30, -2.94)	-1.62 (-2.21, -1.03)	-2.00 (-2.88, -1.12)	<0.001
0 to 8 hours	-4.12 (-4.80, -3.43)	-2.27 (-2.93, -1.61)	-1.85 (-2.78, -0.91)	<0.001

LBA10004 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

SCORAD III: Randomized noninferiority phase III trial of single-dose radiotherapy (RT) compared to multifraction RT in patients (pts) with metastatic spinal canal compression (SCC). *First Author: Peter Hoskin, Mount Vernon Cancer Centre, Middlesex, United Kingdom*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, June 2, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

10005 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

Effect of inpatient palliative care during hematopoietic stem cell transplantation (HCT) hospitalization on psychological distress at six months post-HCT. *First Author: Areej El-Jawahri, Massachusetts General Hospital, Boston, MA*

Background: Patients' experience during HCT hospitalization leads to significant psychological distress post-HCT. Inpatient palliative care integrated with transplant care improves patient-reported QOL and symptom burden during hospitalization for HCT. We assessed the impact of the inpatient palliative care intervention on patients' QOL, mood, and post-traumatic stress disorder (PTSD) at 6 months post-HCT. **Methods:** We randomized 160 patients with hematologic malignancies admitted for autologous or allogeneic HCT to an inpatient palliative care intervention (n=81) integrated with transplant care compared to transplant care alone (n=79). At baseline and 6 months post-HCT, we assessed QOL, mood, and PTSD symptoms using the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT), the Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire (PHQ-9), and the PTSD checklist, respectively. To assess symptom burden during HCT hospitalization, we used the Edmonton Symptom Assessment Scale. We utilized linear regression models controlling for baseline values to analyze the intervention effects on outcomes at 6 months. We conducted causal mediation analyses to examine whether symptom burden during HCT mediated the effect of the intervention on outcomes at 6 months. **Results:** Between 8/14 and 1/16, we enrolled 160/186 (86%) of potentially eligible patients. At 6 months post-HCT, the intervention led to improvements in depression and PTSD symptoms, but not QOL or anxiety [Table]. Improvement in symptom burden during HCT hospitalization partially mediated the effect of the intervention on patient-reported outcomes at six months post-HCT. **Conclusions:** Inpatient palliative care integrated with transplant care leads to improvements in depression and PTSD symptoms at 6 months post-HCT. Addressing symptom burden during HCT hospitalization partially accounts for the effect of the intervention on these long-term outcomes. Clinical trial information: NCT02207322.

	β	95% CI	P
FACT-BMT	2.72	-2.96, 8.39	0.346
HADS-Depression	-1.21	-2.26, -0.16	**0.024**
HADS-Anxiety	-0.61	-1.69, 0.47	0.267
PHQ-9	-1.63	-3.08, -0.19	**0.027**
PTSD	-4.02	-7.18, -0.86	**0.013**

10006 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

American Cancer Society (ACS) Nutrition and Physical Activity Guidelines after colon cancer diagnosis and disease-free (DFS), recurrence-free (RFS), and overall survival (OS) in CALGB 89803 (Alliance). *First Author: Erin Van Blarigan, University of California, San Francisco, San Francisco, CA*

Background: The ACS Nutrition and Physical Activity Guidelines for Cancer Survivors include: 1) healthy body weight; 2) physical activity; and 3) a diet high in vegetables, fruits, and whole grains. It is not known whether colon cancer patients who follow these guidelines have improved DFS, RFS, or OS. **Methods:** We conducted a prospective study among 992 stage III colon cancer patients enrolled in an adjuvant chemotherapy trial in 1999-2001. Lifestyle was assessed twice. We applied a score developed by McCullough ML et al. to quantify adherence to the ACS guidelines based on BMI; physical activity; and intake of vegetables, fruits, whole grains, and red/processed meats (range: 0-6; higher = more healthy behaviors). Alcohol is included in the ACS guidelines for cancer prevention, but not cancer survivors; we tested the score without and with alcohol using McCullough et al.'s cut points: 0 pts = >1/d for women, >2/d for men; 1 pt = no alcohol; 2 pts = >0-1/d for women, >0-2/d for men. We estimated hazard ratios (HR) and 95% confidence intervals (CI) for DFS, RFS, and OS adjusting for clinical, demographic, and lifestyle factors. **Results:** Over 7 y median follow-up, we observed 335 recurrences and 299 deaths (43 without recurrence). Compared to patients with 0-1 pt (262, 26%), patients with 5-6 pts (91, 9%) had 42% lower risk of death (HR: 0.58; 95% CI: 0.34, 0.99; p-trend: 0.01) and a trend toward improved DFS (HR: 0.69; 95% CI: 0.45, 1.06; p-trend: 0.03). When including alcohol in the score, the adjusted HR's comparing patients with 6-8 pts (162; 16%) to 0-2 pts (187; 91%) were: 0.49 for OS (95% CI: 0.32, 0.76; p-trend: 0.002), 0.58 for DFS (95% CI: 0.40, 0.84; p-trend: 0.01), and 0.64 for RFS (95% CI: 0.44, 0.94; p-trend: 0.05). **Conclusions:** Colon cancer patients with a healthy body weight who engaged in physical activity, ate a diet high in whole grains, vegetables, and fruits and low in red/processed meats, and drank moderate alcohol had longer DFS and OS than patients who did not engage in these behaviors. Support: U10CA180821, U10CA180882, U10CA180820, K07CA197077, R01CA118553, P50CA127003, R35CA197735. ClinicalTrials.gov: NCT00003835.

10007 **Oral Abstract Session, Fri, 3:00 PM-6:00 PM**

The influence of yoga on mediational relationships between sleep and cancer-related fatigue: A URCC NCORP RCT in 321 cancer patients. *First Author: Po-Ju Lin, University of Rochester Medical Center, Rochester, NY*

Background: Cancer-related fatigue (CRF) is one of the most incapacitating adverse effects of cancer and its treatments. CRF co-occurs with impaired sleep quality in cancer survivors, increasing morbidity and mortality. We have previously shown that yoga significantly lowers CRF and improves sleep quality in survivors. However, it is not clear if the effect of yoga on CRF is mediated by improvements in sleep quality. This study assessed the mediating effects of changes in sleep quality stemming from YOCAS yoga on improvements in CRF. **Methods:** We conducted a secondary analysis on data collected from a multicenter phase III randomized controlled clinical trial with 2 arms (standard care and standard care + a 4-week YOCAS yoga intervention). 321 cancer patients (96% female; mean age, 54 years; 77% had breast cancer) reported both sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), and CRF, evaluated by Multidimensional Fatigue Scale Inventory (MFSI). Causal mediation analyses were used to estimate effects of the changes in global PSQI scores and in each PSQI subscale on the relationship between yoga and CRF. **Results:** Yoga significantly improved both CRF ($p < 0.01$) and sleep quality ($p < 0.01$), compared to standard care, with total reduction in CRF by 6.5 points. Sleep quality significantly mediated the changes in CRF by 1.4 points ($p < 0.01$) in addition to the direct effect of yoga on CRF reduction (by 5.1 points; $p < 0.01$), suggesting that 22% (95% CI: 7%-54%) of the reduction in CRF was mediated through improving sleep quality. Among the PSQI subscales, daytime dysfunction had the most mediating effect of yoga on CRF. In this model, yoga directly improved CRF by 4.1 points ($p = 0.01$) and the mediating effect of yoga on CRF via daytime dysfunction was 2.4 points ($p < 0.01$), suggesting that 37% (95% CI: 23%-81%) of the improvements in CRF was mediated through decreasing daytime dysfunction. **Conclusions:** Between 22 and 37% of the improvements in CRF from yoga are due to improvements in sleep quality and reductions in daytime dysfunction. Clinicians should consider prescribing yoga for survivors experiencing CRF in combination with sleep disorders. Funding: NCI UGCA189961, R25 CA102618. Clinical trial information: NCT00397930.

10008 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Korean red ginseng to improve cancer-related fatigue in colorectal cancer patients with FOLFOX chemotherapy: A randomized, double-blind, placebo-controlled, parallel, multicenter trial, NCT02039635. *First Author: Yeul Hong Kim, Korea University College of Medicine, Seoul, Korea South*

Background: Cancer-related fatigue(CRF) is a common and severe symptom in patients with cancer. The purpose of this study is to evaluate the anti-fatigue effect of Korean Red Ginseng(Steamed *Panax ginseng* C.A. Meyer) on patients with colorectal cancer. **Methods:** 438 colorectal cancer patients in treatment with mFOLFOX-6 regimen were randomly assigned to either the Korean Red Ginseng[KRG](n = 219) or placebo(n = 219) group and received 2,000 mg/day test substances for 16 weeks. The primary endpoint was the Area Under Curve(AUC) of Brief Fatigue Inventory(BFI) over 16 weeks. The AUC and change from the baseline were calculated. The frequency and types of adverse events were determined by the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. **Results:** 438 colorectal cancer patients were enrolled from 15 institutions. Changes from the baseline in the global BFI were 78.54(Standard deviation [SD] = 16.91) in KRG group vs. 75.89(SD = 16.85) in placebo group at 16 weeks(P = 0.0363). Changes from the baseline in the Usual Fatigue were 76.15 (SD = 17.08) in KRG group vs. 73.08(SD = 17.03) in placebo group at 16 weeks (P = 0.0454). Changes from the baseline in the Mood were 80.46(SD = 17.16) in KRG group vs. 77.88(SD = 17.59) in placebo group at 16 weeks (P = 0.0086). Changes from the baseline in the Relations with Others were 82.09(SD = 17.49) in KRG group vs. 78.67(SD = 17.90) in placebo group at 16 weeks(P = 0.0080). Changes from the baseline in the Walking ability were 82.70(SD = 17.28) in KRG group vs. 80.77(SD = 16.47) in placebo group at 16 weeks(P = 0.0090). Changes from the baseline in the Enjoyment of life were 79.53(SD = 19.53) in KRG group vs. 77.51(SD = 18.02) in placebo group at 16 weeks(P = 0.0150). Toxicities per self-report and CTCAE grading did not differ statistically significantly between the groups. **Conclusions:** The data supports benefits of consuming 2,000 mg KRG water extract powder daily on CRF over 16-week period. There were no discernible toxicities associated with the treatment. More studies on mechanisms of KRG to guide its role in CRF improvement are needed. Clinical trial information: NCT02039635.

10009 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: A 10-year experience by the U.S. Food and Drug Administration. *First Author: Harpreet Singh, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Older adults are a growing segment of our oncology population, with an expected increase in cancer incidence of 67% from 2010 to 2030 in people age 65 and older. However, older adults have been proportionally underrepresented in clinical trials. We sought to analyze the age-related enrollment of cancer patients onto trials supporting registration of new drugs or new indications approved by the US Food and Drug Administration from 2005 to 2015. **Methods:** This study involved retrospective analyses of demographic data of cancer patients enrolled onto trials supporting registration from 2005-2015. The data on 224,766 cancer patients supporting 105 drug applications were analyzed according to age distributions of <65, 65-69, 70-74, 75-79, and ≥80 years. The rates of enrollment were compared with the corresponding rates in the US cancer population. The age distributions of the US cancer population were derived from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute for the year 2013 based on the 2010 US Census. **Conclusions:** Older adults were under-represented in the registration trials of new cancer therapies, especially those over age 75. Various strategies may be needed to evaluate cancer therapies for older adults in prospective clinical trials and to improve cancer care in adults over age 75. These include re-evaluating what may be considered restrictive eligibility criteria so as not to exclude older adults. Incorporating elements from geriatric assessment tools may help identify older adults most likely to benefit from treatment. More detailed labeling information that reflects the clinical experience with older adults could be considered. The FDA encourages drug sponsors as well as clinical trial cooperative groups to devise strategies to recruit patients that are reflective of their intended population.

	Clinical Trial Participants (2005-2015)	Cancer Incidence (2013)
<65	138077 (60%)	559949 (44%)
65-69	38664 (17%)	174886 (14%)
70-74	27578 (12%)	162483 (13%)
75-79	17544 (8%)	169510 (13%)
80+	9678 (4%)	209949 (16%)

10010 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

Adherence to geriatric assessment (GA)-based recommendations in older patients (pts) with cancer. *First Author: Lore Decoster, UZ Brussel, Brussels, Belgium*

Background: In the general older population, GA-guided treatment plans improve overall survival, quality of life and functional status. In geriatric oncology, studies mainly focused on screening and assessment but not on geriatric interventions and follow-up. The aim of this study was to investigate the adherence to recommendations and subsequent interventions based on GA results in older pts with cancer. **Methods:** A prospective Belgian multicenter (n = 22) cohort study included pts ≥70 years with a malignant tumor when an oncological treatment decision had to be made. Pts with an abnormal G8 (≤14/17) underwent GA and were included in this study. Recommendations for interventions were formulated based on GA results. At follow-up adherence to GA-based recommendations was documented. **Results:** From 11-2012 till 2-2015, G8 screening was performed in 8451 pts. 5838 pts with an abnormal G8 were included in the study. Geriatric recommendations were given in 79.2% of pts with a median of 2/pt (range 0-10), most frequently consultation of a dietician (73%) for malnutrition, a social worker (54.8%) for social and functional status problems and a geriatrician (42.1%) for general geriatric problems. Follow-up data were available for 4167 pts. In the group of pts where recommendations were given, at least one intervention was performed in 69% with a median of 1/pt (range 0-6), most frequently dietician (43.4%), social worker (26.1%) and geriatrician (22.6%). A total of 7569 actions were undertaken for a total of 5725 geriatric recommendations. Recommendations were most frequently adhered to for malnutrition, social status and functional status problems. The most frequent actions undertaken were nutritional support and supplements, extended home care and psychological support. **Conclusions:** This large scale Belgian study focusses on the adherence to GA based interventions in older pts with cancer and contributes to the optimization of care for these pts. We identified the domains for which geriatric interventions are most frequently recommended and adhered to and which health care professionals and referrals are essential in the multidisciplinary approach of older pts with cancer.

10011 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

New-onset congestive heart failure (CHF) and cardiovascular disease (CVD) in older colorectal cancer (CRC) survivors: A population-based study. *First Author: Kelly Kenzik, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

Background: CRC is primarily a disease of the elderly. The high burden of pre-existing comorbidities alone or in concert with cancer treatment place the older patients with CRC at increased risk of new-onset morbidities, specifically, CVD and CHF. However, the magnitude of risk of new-onset morbidity, and its association with pre-existing comorbidities or treatment remain unknown. **Methods:** Using SEER-Medicare data, we evaluated individuals diagnosed with incident stage I-III CRC at age ≥66y between 1/1/2000 and 12/31/2011 who had survived ≥2y after diagnosis (n = 57,256; 77% with colon cancer). We compared these to an age, sex-, and race-frequency matched comparison group of non-cancer Medicare patients (n = 104,731). We evaluated new-onset CHF and CVD using competing risk cumulative incidence functions and multivariable Cox regression models. **Results:** The median age at diagnosis was 77y (66-106y); 45% males; and 85% non-Hispanic white. Median follow-up was 8y (2-14y) from diagnosis of CRC. Treatment included surgery for 99%, chemotherapy for 31%, and radiation for 12%. *New-onset morbidity:* The 10y cumulative incidence of new-onset CHF and CVD were 43.6% and 58.9%, respectively. After controlling for pre-cancer comorbidities, CRC survivors were at increased risk of new-onset CHF (HR 1.29) and CVD (HR 1.74) (all $p < 0.001$) compared to controls. Patients receiving radiation (HR 1.29) or 5-FU+oxaliplatin (HR 1.09) were at increased risk of CVD compared to those without those therapies ($p < 0.001$). Pre-existing diabetes (HR 1.16) and CHF (HR 1.21) independently increased the risk of CVD ($p < 0.001$). While 5FU+oxaliplatin did not increase the risk of CHF independently (HR 0.97), diabetic patients treated with 5-FU+oxaliplatin were at 1.71-fold increased risk of developing CHF ($p < 0.001$) when compared with those without pre-existing diabetes. **Conclusions:** Older CRC survivors are at increased of developing CHF and CVD. Monitoring survivors with a history of exposure to 5FU+oxaliplatin or radiation, and improving management of pre-existing comorbidities may reduce the burden of long-term morbidity for older CRC survivors.

LBA10012 Poster Discussion Session; Displayed in Poster Session (Board #1), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Adverse health outcomes in relationship to hypogonadism (HG) after platinum-based chemotherapy: A multicenter study of North American testicular cancer survivors (TCS). *First Author: Mohammad Issam Abu Zaid, Indiana University School of Medicine, Indianapolis, IN*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, June 2, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

10013 Poster Discussion Session; Displayed in Poster Session (Board #2), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A multimodal intervention to enhance sexual function and quality of life (QOL) in hematopoietic stem cell transplant (HCT) survivors. *First Author: Sarah Fishman, Massachusetts General Hospital, Boston, MA*

Background: Although sexual dysfunction is a common long-term complication in allogeneic HCT survivors, interventions to address sexual dysfunction are lacking. **Methods:** We conducted a pilot study to assess the feasibility and preliminary efficacy of a multimodal sexual dysfunction intervention to improve sexual function in allogeneic HCT survivors. Transplant clinicians systematically screened all HCT survivors $\geq$ 3 months post-HCT for sexual dysfunction causing distress using the NCCN Survivorship Guidelines. Those who screened positive attended monthly intervention visits with trained study clinicians that focused on 1) assessing sexual dysfunction; 2) educating and empowering patients to address this topic; and 3) implementing therapeutic interventions. We used the PROMIS Sexual Function and Satisfaction Measure, Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT), and Hospital Anxiety and Depression Scale (HADS) to assess sexual function, QOL, and mood at baseline and six months post-intervention, respectively. **Results:** 32.7% (49/150) of patients screened positive for sexual dysfunction causing distress. 95.9% (47/49) of patients who screened positive agreed to participate. We demonstrated significant improvement in patients' satisfaction and interest in sex as well as sexual function including orgasm, erectile function, lubrication, and vaginal discomfort [Table]. Six of ten patients who were not sexually active prior to the intervention became sexually active post-intervention (P = 0.031). Patients reported improvement in their QOL and a trend toward lower depression [Table]. **Conclusions:** The multimodal intervention to address sexual dysfunction appears feasible with encouraging preliminary efficacy for improving sexual function, QOL, and mood in allogeneic HCT survivors. Clinical trial information: NCT02492100.

Patient outcomes:	Pre-Intervention	Post-Intervention	P- Value
Satisfaction with sex	10.52	23.61	<0.0001
Interest in sex	11.30	13.74	0.039
Orgasm	1.57	2.78	0.011
Erectile function	17.3	29.2	0.002
Lubrication	9.38	22.85	0.005
Vaginal discomfort	41.69	27.15	0.004
QOL	105.43	116.03	0.036
Depression	4.35	3.04	0.134
Anxiety	3.88	4.34	0.431

10014 Poster Discussion Session; Displayed in Poster Session (Board #3), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Longitudinal assessment of cancer-related cognitive impairment (CRCI) up to six-months post-chemotherapy with multiple cognitive testing methods in 943 breast cancer (BC) patients and controls. *First Author: Michelle Christine Janelsins, University of Rochester Medical Center, Rochester, NY*

Background: Large nationwide studies are needed to assess CRCI. **Methods:** NCORPs recruited BC patients and age-matched non-cancer controls. Computerized ((CANTAB Delayed Match to Sample (DMS), Rapid Visual Processing (RVP), Verbal Recognition Memory (VRM)), paper-based ((Controlled Oral Word Association (COWA), and Trail Making Test (TMT)) , and phone-based (category fluency, word recall, backward counting and digits backward) cognitive assessments of memory, attention, and executive function at pre-chemotherapy, post-chemotherapy, and 6 months follow-up (or time-equivalent for controls) were completed. Longitudinal mixed model (LMM)s included group, time, time*group, and adjusted for age, education, reading, anxiety, and depression. **Results:** 580 BC patients (mean age = 54) and 363 controls (mean age = 53) were assessed. In all LMMs, there was a significant group*time interaction depicting lower scores in patients compared to controls ($p < 0.005$) except for TMT ($p = 0.09$). For longitudinal change on the DMS memory test (primary aim), we observed no significant difference between groups from pre- to post-chemotherapy but did observe a significant difference from pre-chemotherapy to follow-up ($p = 0.017$) where patients significantly declined ($p = 0.005$) and controls did not change. We observed similar results for RVP. For VRM, there was a significant pre- to post-chemotherapy group difference ($p = 0.003$). For COWA, patients significantly declined and controls significantly improved reflecting a significant between group difference ($p < 0.001$) from pre- to post-chemotherapy. For TMT, both groups significantly improved with patients improving less than controls reflected by a significant between group difference ($p = 0.04$) that remained a trend at follow-up ($p = 0.06$). On all phone tests, there was a significant between group effect from both pre- to post-chemotherapy and at follow-up with patients doing less well than controls (all $p < 0.001$). **Conclusions:** This nationwide study shows CRCI in BC patients persists in multiple cognitive domains up to 6 months post-chemotherapy compared to controls. Clinical trial information: NCT01382082.

10015 Poster Discussion Session; Displayed in Poster Session (Board #4), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

New primary lung cancers after a head and neck cancer: The impact of radiation therapy and latency period on risk. *First Author: Chetan Jeurkar, Drexel University College of Medicine, Philadelphia, PA*

Background: Patients with head and neck cancer (HNC) have an increased risk of developing a new primary lung cancer (NPLC). Our objective was to assess the critical latency period after HNC when the risk for a NPLC was highest and to see if radiation therapy (XRT) had an impact on this risk. **Methods:** This was a population based study of patients with HNC in the Surveillance, Epidemiology, and End Results (SEER) database. The risk of NPLC was calculated using standardized incidence ratios (SIR) and from this, the number needed to screen (NNS) was extrapolated. The cohort was separated by delivery of XRT and latency period of the NPLC. **Results:** There were a total of 4,209 NPLC from the cohort of 85,154 HNC patients. The SIR, NNS, observed/expected number of NPLC for both the no XRT and XRT groups are shown in table 1. As compared to the no XRT group, the XRT group had higher SIR and lower NNS values across all latency periods. The highest SIR for both the no XRT and XRT groups came between 1 and 3 years. **Conclusions:** In patients with HNC, the risk of developing a NPLC is associated with receiving XRT. This risk is highest within 10 years of the initial HNC diagnosis. The NNS was especially low for the XRT group, less than 100 for most latency periods. Since low dose computed tomography scans for lung cancer screening in smokers has a NNS of 217, screening for these patients should be considered, especially within 10 years of the primary HNC diagnosis. This may contribute to better survivorship care in these patients.

SIR, observed/expected number of NPLC, and NNS for patients with a primary HNC separated by delivery of XRT.

XRT Delivery	Latency (Years)	SIR	Observed NPLC	Expected NPLC	NNS	Total Persons
No XRT	<1	2.18	142	65.04	472.0	36,327
	1-3	2.60	346	133.11	146.3	31,146
	3-5	2.41	274	113.85	153.9	24,642
	5-10	2.41	537	223.17	65.3	20,510
	10-15	1.88	278	148.01	100.0	12,997
	>15	1.80	334	186.07	52.7	7,794
	Total	2.20	1911	869.24	34.9	36,327
Beam XRT	<1	3.45	256	74.24	268.6	48,827
	1-3	5.86	694	118.44	65.6	37,744
	3-5	4.57	387	84.65	77.6	23,466
	5-10	4.04	574	141.98	40.2	17,346
	10-15	3.19	247	77.46	51.4	8,708
	>15	1.99	140	70.36	62.6	4,360
	Total	4.05	2298	567.12	28.2	48,827

Total persons with the primary HNC are also shown.

10016 Poster Discussion Session; Displayed in Poster Session (Board #5), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Impact of intensity of post-treatment surveillance on survival in colorectal cancer. *First Author: Rebecca A Snyder, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The optimal strategy for CRC post-treatment surveillance is unknown. The frequency and type of testing remains controversial, and it is unclear whether surveillance impacts rates of detection or survival. The purpose of this study was to determine if the intensity of post-treatment surveillance is associated with time to recurrence detection, treatment, or overall survival (OS). **Methods:** Primary records of a random sample of 10,636 Stage I-III CRC patients from Commission on Cancer accredited hospitals (2006-2007) were abstracted, and detailed results of surveillance testing were reviewed. Data was merged with records in the National Cancer Database (NCDB). A predicted and observed number of imaging and CEA tests per patient were determined and clustered by hospital to categorize patients into high (HI, O/E $\geq$ 1) or low intensity (LI, O/E $<$ 1) categories. **Results:** 6,279 patients underwent imaging or CEA surveillance in the 3 years after CRC treatment. Patients with HI imaging (50.6%) or CEA (51.2%) had a mean of 2.9 imaging studies and 4.7 CEA tests. Patients with LI imaging underwent a mean of 1.4 imaging studies and 1.6 CEA tests. 5-year recurrence rates did not differ based on intensity of surveillance. Stage II and III patients who underwent HI imaging and CEA testing had a slightly higher resection rate, but this did not translate into an improvement in 5-year OS. **Conclusions:** High vs. low intensity surveillance was not associated with earlier detection of recurrent disease or improved OS. HI surveillance was associated with a slightly higher resection rate, but this did not result in a survival benefit. Our findings within a national hospital registry cohort failed to demonstrate a survival benefit of HI surveillance and suggest that an effective surveillance strategy may involve less frequent testing.

	Imaging			CEA		
	LI	HI	P-value	LI	HI	P-value
Observed # tests in 3 years Mean (SD) (n = 6279)	1.4 (1.46)	2.9 (2.4)	< .001	1.7 (2.6)	4.7 (4.4)	< .001
3-year recurrence rate (n = 8542)	17.7%	17.4%	0.673	17.7%	17.4%	0.816
Resection of recurrence in 3 years (n = 3393)	3.9%	4.8%	0.05	4.2%	4.5%	0.40
Adjusted 3 and 5-yr OS (n = 8542)	87.1%,77.8%	87.3%,78.1%	HR = 0.98, p = 0.687	86.9%,77.5%	87.4%,78.4%	HR = 0.95, p = 0.301

10017 Poster Discussion Session; Displayed in Poster Session (Board #6), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Receipt of recommended surveillance with imaging in survivors of early stage non-small cell lung cancer. *First Author: Jyoti Malhotra, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Lung cancer survivors have a high risk for recurrence and second cancers and a 5-year survival of only 50%. Imaging surveillance for early cancer detection in this group is recommended for life. We measured the rates and determinants of regular surveillance imaging in non-small cell lung cancer (NSCLC) survivors. **Methods:** Using the Surveillance Epidemiology and End Results (SEER)-Medicare linked database, we identified 10680 patients with stage I and II NSCLC, age $\geq$ 66 years diagnosed from 2001-2011 and treated with surgery. Patients were censored at the time of recurrence/second cancer, loss of insurance or 3 months before death. Receipt of a CT and/or PET scan during the surveillance periods of 7 to 18, 19 to 30, 31 to 42 and 43 to 60 months from the date of surgery was assessed. Percentage of patients' receiving regular imaging up to 18, 30 and 60 months of follow-up was determined. Adjusted cox regression was used to measure the effect of receiving recommended imaging on survival. **Results:** Overall, 79% and 40% survivors had follow-up information till the end of 30-month and 60-month surveillance periods respectively. Forty nine percent survivors were male and 86% were white. With a median follow-up of 7.6 years, 71% of the survivors received imaging in the first 18 months after surgery, but only 56% and 44% of survivors continued to receive regular imaging by 30-month and 60-month of follow-up periods respectively. Survivors were less likely to receive imaging if they were older ($\geq$80 years), black, not married, had rural residence, did not receive adjuvant therapy, had stage I disease (compared to stage II) and were diagnosed in 2006 or earlier. In adjusted analysis, survivors receiving recommended imaging up to 18 months from surgery had improved survival compared to survivors who did not (HR 0.86; 95% CI 0.81-0.92). Survival benefit was also observed in survivors who had regular imaging up to 5 years from surgery (HR 0.68; 95% CI 0.60-0.76). **Conclusions:** More than half the lung cancer survivors did not receive recommended long-term surveillance imaging especially if older, black or with rural residence. Adherence to regular surveillance even at 5 years from initial surgery is associated with improved survival.

10018 Poster Discussion Session; Displayed in Poster Session (Board #7), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Mitochondrial DNA content in peripheral blood as a biomarker for cancer-related fatigue in early-stage breast cancer patients: A prospective cohort study. *First Author: Jung-Woo Chae, Department of Pharmacy, National University of Singapore, Singapore, Singapore*

Background: Cancer-related fatigue (CRF) is reported to be associated with mitochondrial dysfunction. Hence, mitochondrial DNA (mtDNA) content, a biomarker of mitochondrial dysfunction, is hypothesized to correlate with the onset of CRF. This study aimed to evaluate the association between peripheral blood mtDNA content and CRF in patients receiving chemotherapy. **Methods:** This was a prospective cohort study. Early-stage breast cancer patients (Stages I to III) receiving anthracycline or taxane-based chemotherapy were recruited. CRF was assessed using the validated Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) at two time points: baseline (T1; prior to treatment) and 6 weeks after initiation of treatment (T2). Worsening of CRF was defined as $\geq$10% increase in the overall MFSI-SF score at T2. Peripheral blood mtDNA content was measured at both time points using real-time quantitative polymerase chain reaction. Multiple logistic regression was utilized to evaluate the association between mtDNA reduction and worsening of CRF, adjusting for age, anxiety, insomnia and other clinically important covariates. **Results:** A total of 91 patients [mean age ($\pm$SD): 51.3 (9.2) years; 81.3% Chinese; 63.3% receiving anthracycline-based chemotherapy] were recruited. Proportions of patients with worsening of CRF increased from the lower to the upper quartiles of mtDNA reduction (26.1%, 30.4%, 52.2%, and 59.1% in quartiles 1, 2, 3, and 4, respectively, $P = 0.010$ for trend). Reduction of mtDNA content was significantly greater among those with worsening of CRF compared to those without CRF [mean reduction ($\pm$SD): 16.3 (23.5) vs 6.0 (17.3), $P = 0.018$]. After adjusting for covariates, every 1-unit reduction of the mtDNA content was associated with a 4% increase risk for worsening of CRF (95% CI, 1%-8%; $P = 0.016$). **Conclusions:** This is the first study to show that reduction of mtDNA content in peripheral blood is associated with onset of CRF in patients receiving chemotherapy. Further validation studies are required to confirm the findings.

10019 Poster Discussion Session; Displayed in Poster Session (Board #8), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Effect of exercise on quality of life (QoL) in 198 older patients with cancer: A URCC NCORP nationwide RCT. *First Author: Kah Poh Loh, University of Rochester Medical Center, Rochester, NY*

Background: Cancer and its treatment frequently impact QoL in patients. In older cancer patients, a small decrement in QoL is associated with significant functional impairment, disability, treatment discontinuation and decreased survival. Little is known about the role of exercise in improving QoL in older cancer patients undergoing active chemotherapy and the mechanistic association between inflammation and QoL. We conducted a secondary analysis of a nationwide phase III RCT to assess the effect of exercise on QoL in older cancer patients. **Methods:** We included 198 older cancer patients (aged $\geq$60 years) who were randomized to receive chemotherapy alone (C) or with EXCAP (Exercise for Cancer Patients). EXCAP is a home–based progressive aerobic and resistance training program. We used ANCOVA to evaluate the effect of EXCAP on QoL (measured by the Functional Assessment of Cancer Therapy-General, FACT-G, and -Cognitive Function, FACT-Cog). Baseline values, gender and chemotherapy duration were adjusted. We assessed associations between changes in QoL and changes in inflammatory cytokines. **Results:** Median age was 66.7 $\pm$ 2.3 years, 92% were female and 77% had breast cancer. In terms of chemotherapy, 3-week and 2-week regimens were used for 72% and 28%, respectively. EXCAP group had better social (p=0.02), emotional (p=0.04) and physical (p=0.03) well-being post-intervention than the C group. There was also a positive trend for improvement in functional, cognitive and overall well-being (Table 1). In the EXCAP group, improved social well-being was associated with decreases in the pro-inflammatory cytokine, IL-8 (r=0.30, p=0.03). **Conclusions:** Our analysis showed that exercise improves QoL in older cancer patients receiving active chemotherapy. Improvement in social well-being may be mediated by reducing inflammation. Physicians should consider incorporating exercise when prescribing chemotherapy for older adults with cancer. Clinical trial information: NCT00924651.

QoL Domains		EXCAP (mean $\pm$ SD)	Control (mean $\pm$ SD)	P-value
FACT-G	Overall	85.5 $\pm$ 15.6	82.1 $\pm$ 17.2	0.46
	Social	25.4 $\pm$ 4.3	23.7 $\pm$ 5.5	0.02
	Emotional	20.5 $\pm$ 3.0	19.9 $\pm$ 3.7	0.04
	Physical	20.4 $\pm$ 6.3	19.9 $\pm$ 5.5	0.03
	Functional	19.3 $\pm$ 6.0	18.7 $\pm$ 6.1	0.49
Fact-Cog	Cognition	27.3 $\pm$ 5.8	25.5 $\pm$ 7.0	0.06

10020 Poster Discussion Session; Displayed in Poster Session (Board #9), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Effect of exercise on novel biomarkers of muscle damage and cancer-related fatigue: A nationwide URCC NCORP RCT in 350 patients with cancer. *First Author: Karen Michelle Mustian, University of Rochester Medical Center, Rochester, NY*

Background: Chemotherapy may lead to systemic muscle damage. Up-regulation of developmental myosin light chain 5 (MYL5) and myosin heavy chain 8 (MYH8) genes is required for normal muscle regeneration in response to damage. However, secretion of MYL5 and MYH8 proteins into the serum suggest degradation of muscle, which, in turn, may lead to cancer-related-fatigue (CRF). In this study, we investigated (1) the effect of an exercise intervention, Exercise for Cancer Patients (EXCAP) on mRNA gene expression and serum protein levels of MYL5 and MYH8 and (2) the association of these novel biomarkers with CRF. **Methods:** Chemotherapy naïve cancer patients (N = 350; mean age = 55.7) from 39 community oncology practices throughout the U.S. affiliated with the URCC NCORP Research Base participated in this nationwide, multicenter, phase III RCT. Patients were randomized into 2 groups: (1) chemotherapy and (2) chemotherapy plus a 6-week aerobic and resistance exercise prescription-EXCAP. Gene expression and protein levels of MYL5 and MYH8, as well as CRF were assessed pre- and post-intervention from whole blood by qPCR, from serum by Luminex assays, and from patient-report by the Multidimensional Fatigue Symptom Inventory, respectively. **Results:** T-tests show MYL5, but not MYH8, mRNA levels were significantly up-regulated from pre- to post-intervention in exercisers and controls (all $p < 0.01$) with no significant group difference. Additionally, MYL5 and MYH8 serum protein levels significantly increased from pre to post in controls (all $p < 0.05$), but remained stable in exercisers. Significant group differences in these serum proteins ($p < 0.01$) suggest greater muscle degradation in non-exercisers. Pearson correlations revealed trends suggesting increases in MYL5 and MYH8 serum proteins are associated with increases in CRF ($r = 0.09$ and $r = 0.11$, respectively, all $p < 0.10$). **Conclusions:** Results suggest EXCAP exercise is protective from chemotherapy-induced muscle damage via its effects on MYL5 and MYH8, and changes in these novel biomarkers may mediate changes in CRF. Further research is needed to confirm these findings. NCI UGCA189961, R25 CA102618. Clinical trial information: NCT00924651.

10021 Poster Discussion Session; Displayed in Poster Session (Board #10), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Agreement about end-of-life (EOL) care among advanced cancer patients and their caregivers: Associations with care received. *First Author: Charles Stewart Kamen, University of Rochester Medical Center, Rochester, NY*

Background: Patients with advanced cancer and their caregivers often have different preferences regarding patients' EOL care. Disagreement in a patient-caregiver dyad can increase stress and result in suboptimal care. Understanding factors that promote agreement, as well as the effect of agreement on care received at EOL, can inform interventions to improve communication and EOL decision-making for patients and caregivers. **Methods:** 205 patients (Stage III or IV cancer plus limited prognosis) and their caregivers were recruited to a randomized controlled trial of a communication intervention for patients, caregivers, and providers (Cancer Communication Study, PI: Epstein). Before intervention, patients completed the Preferences for Life-Extending Treatment questionnaire, which asked their preference regarding experimental treatment, life support, and palliative care; caregivers were asked about patients' preferences. Binomial logistic regressions analyses modeled agreement in preferences as a function of patient and caregiver demographic characteristics and EOL care received as a function of patient-caregiver agreement. **Results:** The majority of patient-caregiver dyads agreed about experimental treatment (60.3%), life support (63.4%), and palliative care (70.7%). Dyads were more likely to agree about palliative care when patients were female (OR = 1.94, p = .03) and non-Hispanic white (OR = 2.10, p = .07) and when caregivers were college educated (OR = 2.04, p = .03). Of the 82 patients who died during study follow-up, 57 (69.5%) received EOL care congruent with their preferences. In 19 of the 38 (50%) cases where patient-caregiver dyads disagreed, caregivers' preferences predicted EOL care received. Dyadic agreement about life support was associated with increased odds of patients receiving/not receiving life support congruent with their preference (OR = 3.02, p = .02). **Conclusions:** Facilitating agreement between patients and caregivers could improve receipt of patient-centered care. A communication intervention designed to increase dyadic agreement by helping patients and caregivers discuss challenging EOL decisions might improve EOL care delivery. Clinical trial information: NCT01485627.

10022 Poster Discussion Session; Displayed in Poster Session (Board #11), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Randomized trial of a cognitive-behavioral therapy mobile app for anxiety in patients with incurable cancer. *First Author: Joseph Greer, Massachusetts General Hospital, Boston, MA*

Background: Patients with incurable cancer often experience marked anxiety that is associated with poor quality of life (QOL), high symptom burden, and complications with medical treatment. The aim of this study was to test the efficacy of a mobile app-based cognitive-behavioral therapy (CBT) intervention to treat anxiety symptoms in patients with incurable cancer. **Methods:** From 2/15 to 8/16, 145 patients with incurable cancers (e.g., advanced lung, breast, GI/GU, sarcoma, melanoma) who screened positive for at least mild anxiety symptoms (Hospital Anxiety & Depression Scale-Anxiety subscale, HADS-A > 7) were randomized 1:1 at two cancer centers to receive either the CBT mobile app for anxiety or a mobile health education program (control), delivered via tablet computers. The CBT app included 7 modules teaching skills to relax the body, reduce worry, stay present-focused, improve communication, and plan/pace activities, which patients completed over 12 weeks. To assess anxiety, mood, and QOL, we administered the Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression Scale (CGI), HADS, and Functional Assessment of Cancer Therapy-General at baseline and 12 weeks. General linear models were used to assess the effect of the intervention on patient outcomes over time. **Results:** The sample was predominantly female (73.8%) and white (91.7%), with a mean age of 56.45 (*SD*= 11.30) years. Both study groups reported significant improvements in anxiety, depression, and QOL from baseline to post-assessment (all *p*-values≤002), with no differences in the improved outcomes between groups. Secondary analyses showed interaction effects on anxiety between the intervention and baseline HAM-A scores. Among patients with higher baseline anxiety, those randomized to the CBT app had greater improvements on the HAM-A (*p*= .043), CGI (*p*= .048), and HADS-A (*p*= .001) compared to the health education control group. **Conclusions:** Patients with incurable cancer who received either a CBT mobile app intervention or mobile health education program reported improvements in anxiety, depression, and QOL. However, the CBT mobile app had better outcomes than health education for patients with higher baseline anxiety. Clinical trial information: NCT02286466.

10023 Poster Discussion Session; Displayed in Poster Session (Board #12), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Improved coping to mediate the positive effects of integrated palliative care on quality of life and depression. *First Author: Jamie M. Jacobs, Massachusetts General Hospital, Boston, MA*

Background: In a recent trial, early integrated palliative care (PC) improved quality of life (QOL) and reduced depression symptoms in patients with newly-diagnosed incurable lung and gastrointestinal (GI) cancer. The mechanisms by which PC benefits these outcomes are unclear. Therefore, we examined whether early integrated PC improved patients' coping strategies and the degree to which changes in coping mediated intervention effects on patient-reported QOL and depression symptoms. **Methods:** From 5/2011 to 7/2015, we enrolled 350 patients with newly diagnosed incurable lung or non-colorectal GI cancer in a randomized trial of early PC integrated with oncology care vs. oncology care alone at Massachusetts General Hospital. Patients completed self-report measures of QOL (Functional Assessment of Cancer Therapy-General), depression symptoms (Patient Health Questionnaire-9), and use of active and avoidant coping strategies (Brief Cope) at baseline, 12, and 24 weeks. Linear regression was used to assess the effects of the early PC intervention on active and avoidant coping strategies. A multiple mediation regression with bias-corrected bootstrapping was modeled to examine whether changes in use of coping strategies mediated intervention effects on QOL and depression symptoms. **Results:** Compared to oncology care, early integrated PC improved patients' use of active coping and reduced use of avoidant coping strategies. Improvements in 24-week QOL in patients assigned to PC were mediated by increased use of active coping strategies (indirect effect = 1.27, bootstrapped SE = 0.65, 95% CI [0.31, 2.86]), but not by decreased use of avoidant coping. Similarly, PC-related reductions in 24-week depression symptoms were mediated by increased use of active coping strategies (indirect effect = -0.39, bootstrapped SE = 0.20, 95% CI [-0.89, -0.08] but not by decreased use of avoidant coping. **Conclusions:** Patients with newly diagnosed incurable cancer who received early integrated PC showed increased use of active coping strategies, which led to improved QOL and depression symptoms. PC may improve QOL and mood by providing patients with the skills to cope effectively with life-threatening illness. Clinical trial information: NCT01401907.

10024 Poster Session (Board #13), Sat, 1:15 PM-4:45 PM

The PULSES project: Teaching the vital elements of code status discussions to oncology residents. *First Author: Oren Hannun Levine, McMaster University, Hamilton, ON, Canada*

Background: Discussions with cancer patients around cardiopulmonary resuscitation (CPR), or 'code status,' are often led by trainees in oncology, but formal education for this competency is lacking. In this study, we developed and tested a novel communication tool, the PULSES framework, for informed code status decision-making (a six-step approach summarized by the PULSES acronym [Table 1]), through an educational workshop. **Methods:** A multicentre randomized controlled trial was carried out at 3 academic cancer centres in Ontario, Canada. Residents in medical oncology (MO) and radiation oncology (RO) programs completed a workshop and an observed structured clinical exam (OSCE). Participants were randomized to complete the training before the OSCE (experimental arm) or after the OSCE (control arm). Randomization was stratified for centre and oncology discipline. Expert raters evaluated communication with two rating tools: the novel PULSES scale and the communication skills assessment form (CSAF), a validated benchmark tool that is not specific to oncology content. The primary outcome was improvement in PULSES scores. **Results:** Forty-six residents consented to participate (28 RO and 18 MO). Groups were well balanced for program and year of training. Participants in the experimental group had higher mean PULSES score than those in the control group (80.4±13.5 vs 63.4±9.7; $p < .001$; maximum score = 108). There was no significant effect for program and no significant interaction between program and training condition. Scores for the PULSES and CSAF scales were highly correlated (R = 0.864). **Conclusions:** The PULSES training improved performance among oncology residents for code status discussions. Improved communication scores were not scale-specific. The PULSES framework offers a standardized approach and can be incorporated into competency-based curricula for postgraduate oncology programs. Future work will explore whether communication training in this area impacts patient-level outcomes.

Six steps for code status communication.

P	Prognosis
U	Underlying values
L	Long term outcomes of resuscitation
S	Short term outcomes of resuscitation
E	Educated recommendation
S	Summarize and document

10025 Poster Session (Board #14), Sat, 1:15 PM-4:45 PM

Predictive value of the patient reported outcome "living with cancer" instrument on overall survival in advanced cancer patients: A tool for guiding timing of palliative care consultations. *First Author: Stuart L. Goldberg, COTA, New York, NY*

Background: The Living with Cancer (LWC) patient reported outcome (PRO) instrument evaluates distress from the point of view of the advanced cancer pt. The 7-item Likert survey measures 4 personhood domains (performance status, pain, burden [financial and family], depression) with scores ranging 0-112. In a pilot study of 433 cancer pts at a single center a score of >28 was associated with an increased likelihood of physician's (blinded) opinion of need for end-of-life care discussions (*J Palliative Med* 2016). **Methods:** The LWC instrument is a statistically validated PRO (ASCO Palliative Care Symposium 2016). LWC was administered to 1024 cancer pts receiving non-curative therapy at 7 centers (Regional Cancer Care Associates, NJ) from Sept 2015 - Oct 2016. LWC surveys were linked to the Cota database, which extracts and enriches data from EHRs. Date of survey was used as the start point in time-to-event analysis. **Results:** 290 (28%) pts expired during the study (median f/u 9.9 months). 267 (26%) pts exceeded the threshold score of 28 defined in the pilot set (28 was also independently this study's optimal cut point). Pts with an LWC score >28 had inferior 6 and 12 mo overall survival (69% and 54%) vs pts with scores <29 (88% and 73%) (log rank $p<0.001$). A Cox model demonstrated that LWC score and cancer type were significant (LWC: $p<0.001$, cancer types (compared to B): GI $p<0.001$, GU: p=0.013, T: $p<0.001$, M: p=0.334) A one point score increase in LWC resulted in a 1.8% increase in expected hazard. Among solid tumor pts with LWC >28, 20% died within the next 3 mo and 35% died within the next 6 mo, indicating appropriate timing for hospice and palliative care consults, respectively. **Conclusions:** Pt responses to the LWC instrument predict survival among advanced cancer pts and may be useful in guiding timing of palliative care consultations.

Cancer type	N	<29 6mo OS	<29 12mo OS	>28 6mo OS	>28 12mo OS	Log rank p-value
Gastrointestinal (GI)	331	84.7 %	66.0 %	60.5 %	41.0 %	<0.001
Thoracic (T)	143	74.6 %	52.3 %	52.3 %	37.6 %	0.007
Genitourinary (GU)	140	86.6 %	72.6 %	68.8 %	48.6 %	0.008
Myeloma (M)	239	96.0 %	86.0 %	87.0 %	76.2 %	0.040
Breast (B)	171	92.9 %	82.7 %	84.6 %	71.6 %	0.105

10026 Poster Session (Board #15), Sat, 1:15 PM-4:45 PM

Early specialist palliative care for all hospitalized, advanced cancer patients (ACP)? Better outcomes with "up-front" versus "on-demand" palliative care. *First Author: Monica Malec, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: Palliative care improves outcomes for cancer patients, especially those with advanced disease. Optimal timing for initiation of specialist palliative care remains undetermined. We created a Supportive Oncology inpatient service that integrates immediate "up-front" palliative care (IPC) consultation for selected ACP to supplement our usual oncologic care (UOC) service, which continued to utilize "on-demand" palliative care consultation. Here, we compare ACP populations and selected outcomes between these two versions of in-patient cancer care. **Methods:** A retrospective cohort analysis of ACP receiving either IPC or UOC between Jan 2015-Dec 2015 (N = 809). ACP were compared for age, gender, race, and ethnicity. Disease severity was determined by APR DRG weight, Risk of Mortality (ROM), and Severity score. Outcomes included examining differences between groups for: Length of stay (LOS), Cost, and 30 day readmission rate. Univariate and multivariate analysis were employed. **Results:** 468 ACP were admitted to IPC and 341 to UOC. Compared with UOC, ACP assigned to IPC were significantly younger (61.1±13.2 vs 63.3±13.0, p = 0.02); more likely female (50% vs 40%, P = 0.005); and more likely to be AA (47% vs 35%, P = 0.005). After adjusting for gender, age, race, and encounter type, ACP receiving IPC had higher ROM (52% v 47%, p = 0.03). There were no differences in APR DRG weight (p = 0.30) or Severity scores (p = 0.34). IPC had significantly lower costs ($12,050 vs $15,990, p = 0.003), less 30-day readmissions (16% vs 23%, p = 0.03), and a trend toward shorter LOS (5.6 ± 4.9 vs 6.2 ± 6.5, p = 0.10). **Conclusions:** Our data provides additional evidence for the benefits of earlier specialist palliative care consultation services, including patients traditionally identified as underserved.

10027 Poster Session (Board #16), Sat, 1:15 PM-4:45 PM

Anti-dementia and anti-hyperlipidemic medication use at end of life in elderly lung cancer patients: Analysis of SEER-Medicare data. *First Author: Min Ji Kim, MD Anderson Cancer Center, Houston, TX*

Background: Despite risk for polypharmacy, elderly cancer patients may receive drugs whose time to benefit likely exceeds life expectancy. This study aims to describe use of drugs considered potentially unnecessary, namely anti-hyperlipidemics and anti-dementia drugs, and to identify factors associated with their use in Stage 3 or 4 non-small cell lung cancer (NSCLC) patients approaching end of life. **Methods:** We identified all patients older than 65 diagnosed with primary Stage 3 or 4 NSCLC between 2006 and 2011 in the Surveillance, Epidemiology and End Results (SEER)-Medicare database. Information on drug prescriptions was extracted from Medicare Part D files. First-time hospice enrollment or death date was used as the final endpoint in analysis. The primary outcome was use of drugs of interest at 4 months before NSCLC diagnosis, 6 months and 3 months before death or hospice. Associations with demographic or other factors were tested using the Pearson $\chi 2$ test. **Results:** Of all 7983 patients, 45.1% were taking statins before diagnosis, while 40.7% and 30.9% were still taking statins at 6 and 3 months before death or hospice. Use of bile acid sequestrants, fibric acid derivatives, and cholesterol absorption inhibitors were found to decrease toward death or hospice. In contrast, anti-dementia drug use did not decrease, with 3.4% before diagnosis and 4.2% and 3.5% at 6 and 3 months before death or hospice. Approximately 30% of anti-dementia medications were newly prescribed at 6 and 3 months before study endpoint. Having a higher number of prescriptions at 3 months before death or hospice was associated with higher rates of drug use both before and after cancer diagnosis. Having a higher Charlson comorbidity index correlated with greater anti-dementia drug use before diagnosis. Demographic, socioeconomic, and treatment factors were not found to be correlated with drug use. **Conclusions:** A high prevalence of statin use persists while a notable proportion of anti-dementia drugs are newly prescribed toward death or hospice. Our findings suggest an opportunity for clinicians to re-evaluate risks and benefits of potentially unnecessary medications in elderly patients nearing end of life.

10028 Poster Session (Board #17), Sat, 1:15 PM-4:45 PM

Latino ethnicity, immigrant status, and preference for life-extending end-of-life cancer care. *First Author: Ana Isabel Tergas, Columbia University College of Physicians and Surgeons and New York-Presbyterian Hospital, New York, NY*

Background: Latino advanced cancer patients are less likely to engage in advance care planning, use hospice services, and receive end-of-life (EOL) care in line with their preferences compared to non-Latino advanced cancer patients. Little is known about how immigration status influences preference for life-extending care (LEC) at the EOL. **Methods:** Data were derived from two sequential multi-institutional, longitudinal cohort studies of patients with advanced cancer recruited from 2002 – 2008 (Coping with Cancer I [CwC-1]) and 2010 – 2015 (Coping with Cancer II [CwC-2]). Multiple logistic regression analysis was used to estimate effects of immigrant status and CwC cohort among Latinos, and effects of ethnicity and CwC cohort among US-born Latinos and non-Latino whites, on preference for LEC at the EOL. **Results:** Of the 760 studied cancer patients, 661 were US-born non-Latino (US non-L), 34 were US-born Latino (USL) and 65 were Latino immigrants (LI). LI were less educated (mean years of education: 7.8 years) than USL (11.1 years), who were in turn less educated than US non-L (13.7 years). Far fewer LI had insurance compared to USL (18.5% vs. 64.7%, respectively; $p < 0.001$), and fewer USL had insurance compared to US non-L (64.7% vs. 81.4%, respectively; $p = 0.017$). Within CwC-2, LI had higher odds of preferring LEC over comfort care compared to USL (adjusted odds ratio [AOR] = 9.4; 95% CI: 1.2, 72.4), and USL had lower odds of preferring LEC compared to US non-L (AOR = 0.3; 95% CI: 0.1, 1.0). LI from CwC-2 had higher odds of preferring LEC compared to LI from CwC-1 (AOR = 11.4; 95% CI: 2.7, 48.4), but there was no difference between USL from CwC-2 and USL from CwC-1. US non-L from CwC-2 had higher odds of preferring LEC compared to US non-L from CwC-1 (AOR = 3.9; 95% CI: 2.6, 5.9). Within CwC-1, there was no difference in LEC preference between LI and USL, nor between USL and US non-L. **Conclusions:** Immigrant status has a strong effect on preference for life-extending care among the more recent cohort of Latino cancer patients. Preference for life-extending care appears to have increased significantly over time for Latino immigrants, but remained unchanged for US-born Latinos. Latino immigrants may increasingly want life-extending care near death.

10029 Poster Session (Board #18), Sat, 1:15 PM-4:45 PM

Do elderly and young patients derive similar relative survival benefits from novel oncology drugs? A systematic review and meta-analysis. *First Author: Vanessa Sarah Arciero, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Elderly patients are commonly believed to derive less benefit from cancer drugs, even if they fulfil clinical trial eligibility. We aim to examine if novel oncology drugs provide differential treatment outcomes for elderly and young patients on clinical trials. **Methods:** A systematic review of randomized control trials (RCTs) cited for clinical efficacy evidence in novel oncology drug approvals by the Food and Drug Administration, European Medicines Agency, and Health Canada between 2006 and 2015 was conducted. Studies reporting age-based subgroup analyses for overall or progression free survival (OS/PFS), were considered. Independent reviewers extracted survival hazard ratios (HRs) and confidence intervals (CIs) for age-based subgroups. Meta-analyses based on an inverse variance random effects model were performed to examine patient subgroups < 65 and ≥ 65 years separately, and pooled HRs were compared to examine if differences in relative survival benefits existed between patient subgroups. Sensitivity analyses were conducted specific to cancer type, primary endpoint, and the type of systemic treatment. **Results:** Eighty-five RCTs, including 55,512 patients, reported age-based survival outcomes and were included. One study reported age-based toxicity and no studies age-based quality of life results. Pooled HRs [95% CIs] for patients < 65 and ≥ 65 years were 0.60 [0.56-0.65] and 0.66 [0.61-0.72], respectively with no difference between the two subgroups ($P = 0.08$). All sensitivity analyses revealed similar results. **Conclusions:** Our results suggest that elderly and young patients derive similar relative survival benefits from novel oncology drugs. In settings where there is no other direct high-level evidence of elderly patients deriving less benefit than younger patients, it is reasonable to consider offering novel oncology drugs to elderly patients who fulfil trial eligibility. There is, however, a need to report age-based toxicity and quality of life results to support patient discussions regarding the balance of treatment benefit and harm, to encourage informed individualized decision-making.

10030 Poster Session (Board #19), Sat, 1:15 PM-4:45 PM

Chemotherapy toxicity risk score (CTRS) for treatment decision in older patients with advanced solid cancer. *First Author: Tomohiro F. Nishijima, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: The decision whether to treat older patients (pts) with advanced cancer with standard (ST) or reduced therapy (RT) is complicated by heterogeneity in aging. Currently, clinical impression based largely on age and performance status, determines whether a pt is fit or unfit for ST. We evaluated the potential utility of the CTRS (Hurria JCO 2011) for treatment decision in older cancer pts. **Methods:** This is a prospective observational study of older pts (+65) receiving first-line chemotherapy for locally advanced or metastatic cancer for which combination chemotherapy is the standard of care. CTRS was calculated before therapy initiation assuming the pts received ST (combination therapy at the standard dose). Pts were categorized as high risk (CTRS $\geq$10; RT (dose reduced combination or single agent chemotherapy) deemed appropriate) or non-high risk (CTRS $<$10; ST deemed appropriate) for grade 3-5 adverse events (gr3-5 AEs). Treatment decision was left to the treating physician who was blinded to the CTRS result. We estimated the agreement in chemotherapy choice (ST vs RT) between treating physician and CTRS using the kappa statistic. **Results:** 44 pts (median 71 years) with GI (68%), GU (14%), lung (14%) or HEENT (5%) cancer were enrolled. 29 pts received ST (11 had CTRS $\geq$10 and 18 had CTRS $<$10) and 15 pts received RT (10 had CTRS $\geq$10 and 5 had CTRS $<$10). The kappa statistic showed only modest agreement in chemotherapy choice (0.26, 95%CI = -0.01 to 0.54) between physician and CTRS. Gr3-4 AEs and hospitalization due to AE occurred in 50% and 29% of 42 pts with follow-up data, respectively. There was no fatal AE. Among pts receiving ST, pts with CTRS $\geq$10 had a significantly higher incidence of gr3-4 AEs and hospitalization than those with CTRS $<$10 using Fisher's exact test (Table). In the RT group, there was no significant difference in incidence of gr3-4 AEs or hospitalization between pts with CTRS $\geq$10 and CTRS $<$10. **Conclusions:** Incorporation of CTRS in treatment decision may increase the proportion of elderly pts with advanced cancer who receive tolerable treatment.

Chemotherapy choice	CTRS	Gr3-4 AEs (%)	P value	Hospitalization (%)	P value
ST	$\geq$10 (N=10)	90	0.01	70	0.004
	$<$10 (N=17)	35		12	
RT	$\geq$10 (N=10)	30	0.33	10	0.21
	$<$10 (N=5)	60		40	

10031 Poster Session (Board #20), Sat, 1:15 PM-4:45 PM

Accrual of older adults to Canadian Cancer Trials Group (CCTG) led trials: A retrospective analysis from 1990 to 2015. *First Author: Catalina Hernandez Torres, The Ottawa Hospital, Ottawa, ON, Canada*

Background: Older adults (OA) age 65+ make up to 60% of all newly diagnosed cancers. However, only 22-32% of patients accrued in cooperative group studies in the 1990s were age 65+. In 2003, several studies suggested that clinical trial design, in particular the presence of strict exclusion criteria, was a major barrier to accrual of OA. The objective of this study was to determine: 1) whether there has been an improvement in accrual of OA to clinical trials led by the Canadian Cancer Trials Group (CCTG) over time; 2) clinical trial features associated with accrual of OA to clinical trials 3) whether exclusion criteria in trials initiated 2003 or after have been relaxed. **Methods:** All completed randomized Phase II and III CCTG-led clinical trials initiated between 1990 or later were included. Trial characteristics including tumor type, stage, treatment type, and exclusion/inclusion criteria, as well as percentage of OA age 65+ accrued were recorded. Association between percentage of OA accrued and trial characteristics were compared using the Wilcoxin rank sum test. Assessment of exclusion criteria before and after 2003 was compared using the Chi Square test or Fisher exact test. **Results:** A total of 68 trials were included. Most trials were phase III (73%), chemotherapy trials (48%), opened before 2003 (70.6%), advanced disease (73%) and lung cancer was the most common tumour site (17.6%). OA accrual remains low compared to OA diagnosed with cancer in Canada (41% vs. 56%, $p < 0.001$). There was an improvement in accrual of OA after 2003 (47.1% vs. 34.9%, $p = 0.02$). Tumour site, early stage disease, more restrictive performance status, requiring a new biopsy, and having a longer consent form, were associated with lower accrual of OA ($p < 0.05$). There was no significant loosening of exclusion with time though patients with pulmonary comorbidities were more likely to be excluded in studies initiated in 2003 or later ($p = 0.006$). **Conclusions:** OA remain under-represented in clinical trials. There has been no relaxing of exclusion criteria; however, exclusion based on comorbidities was not significantly associated with under accrual of OA in our study.

10032 Poster Session (Board #21), Sat, 1:15 PM-4:45 PM

Pre-planned safety analysis of NORDIC 9: A randomized trial comparing full dose monotherapy (S-1) with reduced dose combination therapy (S-1/oxaliplatin) in older chemo-naive patients with metastatic colorectal cancer (mCRC). *First Author: Stine Brændegaard Winther, Department of Oncology, Odense University Hospital, Odense, Denmark*

Background: More than half of the patients (pts) diagnosed with mCRC are older, but they are underrepresented in clinical trials. Data about the best treatment strategy in pts who are not candidates for standard full-dose combination therapy is scanty. Here we present a preplanned safety analysis in the NORDIC 9 trial. **Methods:** NORDIC 9 explores treatment of older mCRC pts (≥70 years) who are not candidates for full-dose combination therapy. Pts receive full dose monotherapy (Arm A: S-1 30 mg/m^2 po bid day 1-14 q3w, followed by irinotecan upon progression or reduced dose (80%) combination therapy (Arm B: S-1 20 mg/m^2 po bid day 1-14 + oxaliplatin 100 mg/m^2 iv day 1 q3w, followed by reduced dose S-1 + irinotecan q3w). Bevacizumab (7.5 mg/kg iv day 1) may be added at the discretion of the treating clinician. Geriatric screening tools (eg G-8 and VES-13) and quality-of-life are evaluated at baseline. Blood samples and tumor tissue are prospectively collected. Primary endpoint is PFS. Secondary endpoints are correlations between the geriatric screening and safety but also efficacy. **Results:** The safety analysis was performed when 50 pts had received 3 cycles. 12 pts received bevacizumab. Median age was 79 (range 70-88) years, 26 pts were male, performance status was 0 (43%), 1 (38%) or 2 (19%). Five (10%) pts discontinued therapy after only 1 cycle due to toxicity (n = 2) or PD/clinical deterioration (n = 3); 45 pts (90%) continued therapy beyond 3 cycles. Pts receiving only 1 cycle had numerically a worse G-8 and VES-13 score. Grade 3-4 non-hematological toxicity was fatigue (6%), diarrhea (10%), nausea (4%) and vomiting (6%), and was experienced by 10 pts, 6 of them received ≥3 cycles of treatment. There was no hand-foot-syndrome, cardiac or hematological grade 3-4 toxicity. Dose intensity for S-1 was 0.98 (0.7-1.0) (arm A) and 0.93 (0.6-1.0) (Arm B), respectively, and for oxaliplatin 0.99 (0.4-1.0). **Conclusions:** The safety committee recommends to continue the trial without dose adjustments according to the original design. February 2017, 118 of planned 150 pts had been included. Clinical trial information: EudraCT no 2014-000394-39.

10033 Poster Session (Board #22), Sat, 1:15 PM-4:45 PM

Patient-reported comorbidity and survival in older adults with cancer. *First Author: Grant Richard Williams, University of Alabama at Birmingham, Birmingham, AL*

Background: Our ability to optimize the care of older adults with cancer and comorbid illnesses is insufficient as most clinical trials lack systematic measurement of comorbidities. The primary purpose of this study was to evaluate the prevalence and impact of patient-reported comorbidity on survival using various comorbidity scoring algorithms. **Methods:** We utilized a unique linkage of the Carolina Senior Registry, an institutional registry (NCT01137825) that contains geriatric assessment data, with the North Carolina Central Cancer Registry to obtain mortality data. Comorbidity was assessed using a patient-reported version of the Older Americans Resources and Services Questionnaire (OARS) Physical Health subscale that includes information regarding 13 specific comorbid conditions and the degree to which each impairs function ("not at all" to "a great deal"). Multivariable Cox proportional hazard regression models were used to evaluate the association between comorbidities and all-cause mortality. **Results:** 539 patients were successfully linked to mortality data. Median age 72, 72% female, 85% Caucasian, 47% breast cancer, and 12% lung cancer. 92% of participants reported at least one comorbid condition, mean of 2.7 conditions (range 0-10), with arthritis and hypertension the most common (52 and 50%, respectively). 62% of patients with a comorbid illness reported a functional limitation related to comorbidity. Both the presence of 3 or more total comorbidities (hazard ratio (HR) 1.44, CI 1.08-1.92) and 2 or more comorbidities impacting function (HR 1.46, CI 1.09-1.95) increased mortality. After adjusting for age, cancer type, and stage, the risk of death increased 12% for each comorbid condition impacting function (HR 1.12, CI 1.02-1.24), but did not significantly increase for the number of comorbid conditions alone (HR 1.07, CI 0.99-1.15). **Conclusions:** Comorbid conditions in older adults with cancer are highly prevalent, frequently impair function, and impact survival. Comorbid conditions that impair function have a greater impact on survival than the presence of comorbidity alone. Comorbidity assessment should be incorporated in clinical trials and can be measured via a simple one-page patient-reported questionnaire.

10034 Poster Session (Board #23), Sat, 1:15 PM-4:45 PM

Immuno-oncology and the elderly: A comparative analysis of participation and toxicities of senior adults aged 65 years and above vs mid age and adolescent/young adult patients on immunotherapy-based phase I clinical trials. *First Author: Ishwaria Mohan Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Senior adults ≥ 65 yrs remain underrepresented in early phase clinical trials in particular trials with novel immunotherapies. One general limitation to enrollment is the concern for immune-related toxicities in the context of older age and comorbidities. We analyzed the enrollment and incidence of toxicities of seniors in comparison to mid age and adolescent/young adult (AYA) pts enrolled in phase 1 immunotherapy trials. **Methods:** We identified 422 consecutive pts w advanced cancer treated on immunotherapy-based phase I trials bw 04/2009-09/2015. We divided pts into 3 cohorts based on age at start of trial (AYA 15-39y, mid age 40-64y, seniors 65y+) and collected pt/disease characteristics and immune-related adverse events (irAE) including endocrinopathies, diarrhea/colitis, pneumonitis, constitutional (eg fatigue, fever, anorexia), myalgia, and dermatitis. **Results:** Of 422 patients treated, 116 were seniors (27%, median 70y), 50 AYA (12%, median 30y), 256 mid age (61%, median 56y). Most common cancers were GI (n = 108, 26%), thoracic/head/neck (n = 84, 20%), GU (n = 54, 13%), and GYN (n = 47, 11%). Median PFS was comparable in all 3 cohorts (2.4m seniors, 2.1m AYA, 2.1m mid age). The incidence of irAE was higher in elderly than mid age or AYA (low grade [G1/2] 49% vs 34% vs 34%, p 0.02; high grade [G3/4] 19% vs 11% vs 12%. p 0.14). When comparing irAE rates of seniors to AYA and mid age pts, the odds ratio of high grade events was 1.81 (95% CI 1.01, 3.24; p 0.05) and low grade events was 1.85 (95% CI 1.20, 2.85; p 0.0055). Most common G1/2 irAE among all cohorts was fatigue (n = 76, 18%), dermatitis (n = 59, 14%), fever (n = 29, 7%) and anorexia (n = 28, 7%) with seniors having a greater incidence of low grade fatigue (25% vs 15%, OR 1.84, 95% CI 1.09, 3.10, p 0.025). **Conclusions:** Senior adults accounted for < 1/3 of pts on immunotherapy-based phase I trials. When compared to mid age and AYA pts, seniors had a higher likelihood of experiencing a toxicity. Early phase immunotherapy trials may be an option for older adults but with a particular vigilance for adverse events in this population.

10035 Poster Session (Board #24), Sat, 1:15 PM-4:45 PM

A phase II trial of older adults with metastatic breast cancer (MBC) receiving nab-paclitaxel: Melding the fields of geriatrics and oncology. *First Author: Enrique Soto Perez De Celis, City of Hope, Duarte, CA*

Background: The Institute of Medicine and ASCO identified key research priorities to improve the evidence base of older adults with cancer, including the need for therapeutic phase II trials. Here we present a phase II study of *nab*-paclitaxel in older patients (pts) with MBC, incorporating geriatric oncology principles in the study design. **Methods:** Pts age ≥65 years with MBC and 0-1 chemotherapy (CT) lines received *nab*-paclitaxel (100 mg/m^2, 3 wks on, 1 wk off). Pts completed a geriatric assessment (GA) pre-CT including measures of function, comorbidity, cognition, nutrition, and psychosocial status. A CT toxicity (tox) risk score was calculated for each pt (Hurria et al. JCO 2011 and 2016). Relationships between tolerability (no. courses, hospitalizations, dose reductions, and grade (G) ≥3 tox attributed to CT) and risk score were assessed using generalized linear models, Student's t tests, and Fisher's exact test. Response rate (RR) and progression free survival (PFS) were evaluated. **Results:** 40 pts (mean age 73 [65-87]) were accrued from 06/12 to 01/16. Median no. of cycles was 6 [0-33], RR was 35% (95% CI 21-52%) and PFS was 6.5 months (95% CI 5.5-NR). 58% (n = 23) of pts had G ≥ 3 tox and 30% (n = 12) were hospitalized due to CT. G 2/3 neuropathy and G 3/4 neutropenia occurred in 10% of pts (n = 4), with no cases of febrile neutropenia. Based on the CT tox risk score, 53% (n = 21), 38% (n = 15), and 10% (n = 4) were low, intermediate, and high risk. As a continuous variable, doubling in the risk score was associated with a reduction in courses completed of 4.5 (se = 1.4, p = 0.003). Lower mean $\log_2$ risk scores were found in pts that did not require hospitalization (diff = -0.59, 95% CI -1.00, -0.18; p = 0.007), or did not have a dose reduction (diff = -0.46, 95% CI -0.85, -0.06; p = 0.02). G ≥ 3 tox was found in 38% of low, 73% of intermediate and 100% of high risk pts, with combined intermediate/high risk pts experiencing significantly more G ≥ 3 tox (OR 5.8, 95% CI 1.3-33.1; p = 0.01). **Conclusions:** This phase II trial of older pts with MBC receiving *nab*-paclitaxel incorporated geriatric principles in an oncology trial. Incorporating the GA and CT tox risk score can help weigh the risks and benefits of therapy in older adults. Clinical trial information: NCT01463072.

10036 Poster Session (Board #25), Sat, 1:15 PM-4:45 PM

Impact of hearing and visual impairment in older adults with cancer. *First Author: Enrique Soto Perez De Celis, City of Hope, Duarte, CA*

Background: Hearing and visual impairment increase the risk of psychological, functional, and cognitive deficits in older adults. However, little is known about their impact in older patients (pts) with cancer. **Methods:** This is a cross-sectional analysis of 2 prospective studies of pts ≥65 with cancer (Hurria et al. *JCO* 2011 & 2016) which identified risk factors for chemotherapy (CT) toxicity. Relationships between self-reported hearing/visual impairment (fair, poor or deaf/blind) and the need for assistance in instrumental activities of daily living (IADL, i.e. shopping), or activities of daily living (ADL, i.e. bathing); anxiety; depression and cognitive deficit (>11 on Blessed OMC test) were assessed (adjusted for age, sex, race, education, cancer type/stage, comorbidity, falls & medication). **Results:** Among 750 pts (median age 72, range 65-94) with solid tumors (28% lung, 27% GI, 30% breast/GYN; 58% stage IV), 28% (n = 213) reported 1 impairment (61% hearing, 39% visual) and 7% (n = 55) both. On multivariate analysis, impaired hearing was associated with IADL dependency, anxiety and depression. Visual impairment was associated with IADL dependency, ADL limitation and depression. Impairment in both was associated with IADL dependency, anxiety, depression and cognitive deficit. **Conclusions:** Older pts with cancer and hearing/visual impairment are at higher risk of functional, psychological and cognitive deficits. Interventions aimed at improving vision and hearing of older adults with cancer should be studied.

		IADL Dependence		ADL Limitation		Anxiety		Depression		Cognitive Deficit	
	Impairment	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Univariate	-	1		1		1		1		1	
	Hearing	2(1.3-2.9)	<.01	1.2(0.8-1.8)	.36	1.6(1.1-2.3)	.03	1.8(1.1-2.8)	.01	1.4(0.6-3.3)	.42
	Visual	2.2(1.4-3.5)	<.01	2.4(1.5-3.9)	<.01	1.6(1-2.6)	.04	3.1(1.9-5.2)	<.01	2(0.8-4.7)	.14
	Both	3.7(2-6.6)	<.01	3(1.6-5.5)	<.01	2.6(1.5-4.6)	<.01	3.6(2-6.4)	<.01	4.3(1.9-9.9)	<.01
Multivariate	-	1		1		1		1		1	
	Hearing	2(1.3-3.1)	<.01	.9(0.6-1.4)	.59	1.6(1-2.6)	.04	1.7(1-2.8)	.04	1(0.4-2.6)	.99
	Visual	2.1(1.2-3.5)	<.01	2(1.2-3.5)	.01	1.5(0.9-2.4)	.14	2.8(1.6-4.7)	<.01	1.9(0.75-5)	.18
	Both	2.9(1.5-5.5)	<.01	1.8(0.9-3.5)	.08	2.2(1.2-4)	<.01	2.6(1.4-4.9)	<.01	3.3(1.3-8.2)	<.01

10037 Poster Session (Board #26), Sat, 1:15 PM-4:45 PM

Outcomes for patients ≥75 years with localized gastroesophageal cancer: Experience from the Princess Margaret Cancer Centre. *First Author: Akina Natori, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: The optimal treatment and outcome for elderly patients (pts) with localized gastroesophageal (GE) cancer remains unclear as they are underrepresented in clinical trials. We aimed to assess survival in pts ≥75 years according to treatment received. **Methods:** A retrospective analysis was performed for all pts aged ≥75 years with GE cancer treated in 2012-2014. Frailty was measured using the Charlson comorbidity index (CCI) and ECOG performance status (PS). Overall survival (OS) and disease-free survival (DFS) were assessed via uni- and multivariable Cox proportional hazards regression, adjusting for demographics. Logistic regression analyses were used to examine factors impacting treatment choices. **Results:** Of 105 pts, median age was 81 years (range: 75-99), primary sites were esophageal (55%, with 43% squamous histology) and gastric (45%). Baseline characteristics included: PS: 0 (31%), 1 (42%), 2 (16%), 3 (10%), 4 (1%); and CCI: 0 (34%), 1 (25%), 2 (19%), ≥3 (22%). Treatment received included radiotherapy alone (RT) (31%); surgery alone (29%); surgery plus adjuvant chemotherapy (chemo) and/or RT (14%); chemoradiation alone (7%) and supportive care (18%). In univariable analyses; age < 85 (p = 0.003), PS < 2 (p = 0.03) and surgery (p < 0.001) were associated with improved OS. Chemo and RT, either alone or in combination, did not significantly improve OS. In multivariable analyses; surgery (HR 0.38, 95% CI 0.21-0.70, p = 0.002) was the only independent predictor for improved OS. Patients with good PS (p = 0.01), gastric disease site (p = 0.01) and adenocarcinoma histology (p = 0.02) were more likely to undergo surgery. **Conclusions:** At our institution, relatively few pts ≥75 years received multimodality therapy for localized GE cancers. Those pts ≥75 years who underwent surgery had excellent outcomes, but they were well-selected. Comprehensive assessment should be considered for pts ≥75 years with localized GE cancer to ensure optimal treatment selection, particularly given the potential benefit of surgery.

10038 Poster Session (Board #27), Sat, 1:15 PM-4:45 PM

A randomized control trial of outpatient occupational and physical therapy for older adults with cancer: The CARE program. *First Author: Mackenzi Pergolotti, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Limitations in functional status and reduced health status are common among older adults with cancer, yet occupational and physical therapy (OT/PT) remain underutilized (Pergolotti, et.al. *JGO,*2015). For this population, we evaluated an outpatient CAncer REhabilitation (CARE) program and compared it to usual care (UC). **Methods:** We recruited adults 65 years and older who had a diagnosis of cancer or recurrence within 5 years and had at least one functional limitation as measured by a geriatric assessment (GA). Participants were then randomized to OT/PT (CARE) or UC. CARE delivered individualized outpatient intervention; OT addressed functional activities, and PT strength/endurance needs. UC participants received a brochure on supportive care services. Primary outcome was functional status (Nottingham Extended Activities of Daily Living Scale [NEADL] (range 0-22)) and secondary outcomes were global Mental and Physical Health, and ability to participate in Social Roles (SR) and activities (Patient-Reported Outcomes Measurement Information System [PROMIS] (range 0-100)), for all measures, higher scores indicate better health. We used t-tests to compare groups. **Results:** 51 adults were randomized: median age 73 years, 55% male, 92% White, 33% with Leukemia/lymphoma, 26% Breast, 22% Colorectal, 67% in active treatment, and 37% with Stage 3 or 4. After 3 months, both groups experienced a significant decline in functional status ($p = .046$; $p = .005$), but change in functional status (-1.5 UC, -1.1 CARE, $p = .637$) , physical health status (0.0 UC, 2.4 CARE, $p = .121$) and participation in SR (.11 in UC, 3.71 CARE, $p = .088$) between UC and CARE were not significant. However, change in mental health (-1.0 in UC, 3.0 CARE, $p = .032$) significantly different between groups. **Conclusions:** CARE was associated with a significant improvement in participant's mental health status compared to a decline in UC. Results suggest CARE may influence ability to participate in social roles and activities and physical health, but further study is needed with larger sample sizes. We demonstrated that for older adults with cancer, OT/PT are promising interventions to improve mental health. Clinical trial information: NCT02306252.

10039 Poster Session (Board #28), Sat, 1:15 PM-4:45 PM

Polypharmacy and potentially inappropriate medication use in older patients with aggressive non-Hodgkin lymphoma (NHL) leads to inferior survival and increased treatment-related toxicities. *First Author: Richard Jirui Lin, NYU Langone Medical Center, New York, NY*

Background: Survival outcomes for older patients with aggressive NHL are disproportionally inferior to those of younger patients. While differences in tumor biology may play a role, older patients are often frail with comorbidities, polypharmacy, and use potentially inappropriate medications (PIM) such as anticholinergics and benzodiazepines. **Methods:** Using Cox proportional hazard and logistic regression models, we analyzed all aggressive NHL patients age ≥60 treated at our two affiliated hospitals from 2009-2014 to examine the association of polypharmacy and PIM use with progression-free survival (PFS), overall survival (OS), and treatment-related toxicities. **Results:** In this updated and final analysis, we included 171 patients with complete records from these two hospitals. They share similar demographic, clinical, and laboratory characteristics except for higher International Prognostic Index (IPI) in patients from one hospital. The median age was 70 years (range 65-77). At the time of diagnosis, 46% of patients used more than 4 medications (polypharmacy) and 47% used at least one PIM. Only 43% of patients received first-line chemotherapy of adequate relative dose intensity (>85% dosage), and 65% experienced ≥grade 3 toxicities. Polypharmacy and PIM use were associated with shortened PFS and OS by log-rank test. Most importantly, PIM use remained an independent predictor of PFS, OS, and ≥ grade 3 toxicities in multivariable analyses (Table). **Conclusions:** This is the first report of significantly adverse survival impacts of polypharmacy and PIM use in older patients with aggressive NHL, presumably from drug-drug interactions that increase toxicities and impair the delivery of adequate chemotherapy dosage. Our findings support the use of evidence-based geriatric principles to guide meticulous medication management to improve outcome disparity for these patients.

Multivariable analyses estimating the association between PIM and clinical outcomes.

Clinical outcomes	HR/OR	95% CI	P
PFS	2.81 (HR)	1.36 to 5.81	0.005
OS	3.12 (HR)	1.49 to 6.52	0.003
Toxicities ≥Grade 3	2.91 (OR)	1.42 to 5.97	0.004

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10040 Poster Session (Board #29), Sat, 1:15 PM-4:45 PM

Unmet supportive care needs of older adults with advanced cancer. *First Author: Brandon Temel, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Cancer disproportionately affects older adults, yet research defining the supportive care needs of these patients is lacking. We sought to examine associations between geriatric impairments, quality of life (QOL), and physical and psychological symptom burden in older adults with newly diagnosed incurable gastrointestinal (GI) cancer. **Methods:** We prospectively enrolled patients age ≥70 within 8 weeks of diagnosis of incurable GI cancer at Massachusetts General Hospital from 10/2015-11/2016. We used surveys to assess geriatric impairments (Vulnerable Elders Survey-13 [range 0-10, scores ≥3 identify patients with impairments), QOL (EORTC QLQ-C30 [range 0-100, higher scores indicate better QOL]), physical symptoms (Edmonton Symptom Assessment System [range 0-10, higher scores indicate greater symptom burden]) and psychological symptoms (Geriatric Depression Scale, [range 0-15, higher scores indicate greater depression symptoms]). We used descriptive statistics to determine differences in patient characteristics by the presence or absence of geriatric impairments. We used linear regression adjusted for age, employment, cancer type, and comorbidity to examine associations between geriatric impairments, QOL, and physical and psychological symptom burden. **Results:** We enrolled 50 of 58 (86%) patients approached (mean age = 78.7; 52% with pancreatic cancer). Nearly half (46%) screened positive for geriatric impairments; these patients were older (81.7 vs 76.1, $p < .01$) and had more comorbid conditions (2.4 vs 1.2, $p = .01$). On linear regression, patients with geriatric impairments reported worse QOL across all domains (General QOL: B = -28.3, $p < .01$; Physical: B = -36.8, $p < .01$; Role: B = -36.8, $p < .01$; Emotional: B = -30.1, $p < .01$; Cognitive: B = -17.8, $p = .03$; Social: B = -39.7, $p < .01$), higher depression scores (B = 5.1, $p < .01$) and worse fatigue (B = 4.6, $p < .01$), drowsiness (B = 4.0, $p < .01$), appetite (B = 3.8, $p < .01$), and pain (B = 2.7, $p = .02$). **Conclusions:** Older adults with advanced cancer experience considerable unmet supportive care needs, particularly those with geriatric impairments. Future research is needed to assess older patients for geriatric impairments and address their unique palliative and supportive care needs.

10041 Poster Session (Board #30), Sat, 1:15 PM-4:45 PM

Serum frailty biomarkers to predict overall survival in older patients with metastatic solid tumors: A substudy of prospective multi-center cohort study (KCSG PC13-09). *First Author: Se Hyun Kim, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea*

Background: To determine individualized cancer treatment for older patients, easily measurable markers that predict functional decline and mortality are needed. The purpose of this study was to confirm prognostic value of potential biomarkers of frailty in older patients with metastatic solid tumors. **Methods:** Serum samples were prospectively collected before first line chemotherapy at 11 academic centers in Korea. All patients were participants in a prospective cohort study of older patients with metastatic solid tumors (KCSG PC13-09, WHO ICTRP number: KCT0001071). Serum levels of C-reactive protein (CRP), CXCL10, SIRT1, VEGF-A, Activin A, C-terminal telopeptide of type I collagen (CTx), total 25-hydroxyvitamin D (vitD) were measured by ELISA and IL-6, Myostatin, Irisin, FGF-19, FGF-21, FGF-23 by luminex mutiplex assay. Overall survival (OS) was studied by means of Kaplan-Meier, Log Rank and Cox methods. **Results:** Serum samples from 138 patients (median age: 75, range: 70-92) were collected from Feb 2014 to Dec 2016. During a median follow up time of 13.8 months, 72 (52.6%) patients had died. Among 13 serum markers, CRP (log-rank, P=0.006), Activin A (P=0.003), and Myostatin (P=0.043) were significantly correlated with OS in univariate analyses. In a Cox regression analysis, Activin A (HR 2.36, 95% CI 1.41-3.96; P=0.001) and Myostatin (HR 2.70, 95% CI 1.24-5.84; P=0.012) were significantly associated with OS after adjustment of other clinical factors (Age, Gender, ECOG PS, BMI, Geriatric assessment, Chemotherapy response, WBC, Albumin). **Conclusions:** In older cancer patients, high serum concentration of Activin A and Myostatin are predictive of poor OS.

Multivariate analysis of prognostic factors for survival.

Factor	HR for OS (95%CI)	P-value§
ECOG PS (0-1 vs. 2-3)	2.70 (1.47-4.95)	0.001
Activin A (< 17.5 pg/mL vs. > 17.5 pg/mL)	2.36 (1.41-3.96)	0.001
Myostatin (< 480 pg/mL vs. > 480 pg/mL)	2.70 (1.24-5.84)	0.012
Chemotherapy response (CR/PR/SD vs. PD/UA)	1.87 (1.13-3.12)	0.016

§: Forward stepwise (conditional likelihood ratio) method of Cox proportional hazard regression model.

10042 Poster Session (Board #31), Sat, 1:15 PM-4:45 PM

The emotional toll of caregiving for older patients with advanced cancer: Baseline data from a multicenter geriatric assessment (GA) intervention study in the University of Rochester NCI Community Oncology Research Program (UR NCORP). *First Author: Supriya Gupta Mohile, University of Rochester Medical Center, Rochester, NY*

Background: Depression is common in caregivers (cgs) of patients (pts) with cancer. However, little is known about the association of health status of older pts with cancer with cg emotional health. **Methods:** Baseline data from a GA intervention study conducted at 68 oncology practices in the UR NCORP were analyzed. Pts aged ≥ 70 with an advanced solid tumor cancer or lymphoma with ≥ 1 GA impairment were enrolled; pts could enroll with 1 cg. Relationships between pt GA impairments (using 12 validated measures) and cg (spouses or live-in partners) emotional health including anxiety (≥ 5 on Generalized Anxiety Disorder-7 (GAD-7)), depression (≥ 2 on Patient Health Questionnaire-2), and distress (≥ 4 on distress thermometer) were evaluated in separate multivariate logistic models adjusted for pt (cancer type, treatment status) and cg (age, sex, race, education, income, comorbidity) characteristics. **Results:** Among 213 pts (mean age 76, 70-89), >50% had ≥ 5 impaired GA measures. Of the 213 cg (mean age 73, 52-91), 23% screened positive for anxiety, 16% for depression, and 40% for distress. In bivariate analyses, number of GA impairments, ≥ 1 fall, pt anxiety (≥ 5 on GAD-7) and depression (≥ 5 on Geriatric Depression Scale (GDS)) were associated with all 3 cg outcomes; pt activities of daily living (ADL) deficits were associated with cg depression and distress. In multivariate analysis, number of GA impairments was associated with cg distress. In separate models, pt ADL deficit and depression were associated with cg distress, and pt ADL deficit was associated with cg depression. GA variables were not associated with cg anxiety in multivariate analysis. **Conclusions:** A high proportion of cg of older pts with cancer report distress. GA can help identify cg at risk for poor emotional health. Interventions for cgs should address the health status of older pts with cancer.

	Cg depression		Cg distress	
Pt factors	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Number of GA impairments	1.14 (0.92-1.41)	0.22	1.19 (1.03-1.38)	0.02
ADL deficit	3.21 (1.04-9.96)	0.04	2.75 (1.15-6.60)	0.02
+GDS	0.59 (0.18-1.89)	0.37	2.40 (1.02-5.61)	0.04

10043 Poster Session (Board #32), Sat, 1:15 PM-4:45 PM

Association between glycemic control, age, and outcomes among intensively treated patients with acute myeloid leukemia (AML). *First Author: Patrick Kuhlman, Wake Forest Baptist School of Medicine, Winston-Salem, NC*

Background: Hyperglycemia and increased glycemic variability are associated with infection and increased mortality. We evaluated the relationship between glycemic control during AML induction and outcomes by age. **Methods:** We retrospectively evaluated outcomes in 262 consecutive patients (pts) with newly diagnosed AML hospitalized for intensive induction at Wake Forest Baptist Hospital (2002-2009). Data on mean blood glucose (BG) (mg/dL) during hospitalization and standard deviation (SD) of BG (measure of glycemic variability, GV), complete remission ± incomplete count recovery (CR+CRi), and overall survival (OS) were collected. Modified Charlson Comorbidity Index (CCI), diabetes, age, gender, race, cytogenetics, hemoglobin, WBC, LDH, body mass index, and insurance were used in uni- and multi-variate models. We used logistic regression to evaluate CR+CRi, and Cox proportional hazard models for OS, stratified by age (< 60 vs ≥60 yrs). **Results:** 124 pts were < 60 (median age 47, median OS 23.1 months), 138 were ≥60 yrs (median age 70, median OS 7.9 months). Older pts had higher baseline comorbidity (CCI > 1 60.1% vs 25.8%) and a higher prevalence of diabetes (20.3% vs 7.3%). The mean ±SD number of BG values obtained per patient during hospitalization was 61±71. The mean ±SD of each individual s mean BG during hospitalization was 111.6± 16.4 in younger versus 121.7±25.9 older pts. The mean SD of BG values [GV] was 26.8±18.6 in younger versus 33±22.8 in older pts. In multivariable analysis higher mean BG was associated with lower odds of CR+CRi in younger (odds ratio (OR) 0.67, 95% CI 0.48-0.93) and older pts (OR 0.78, 95% CI 0.65-0.93) per 10 mg/dL BG increase. Higher mean BG was associated with shorter OS in older adults (HR 1.12, 95% CI 1.04-1.21). Higher GV was associated with lower odds of CR+CRi in younger (OR 0.73, 95% CI 0.56-0.96) and older (OR 0.71, 95% CI 0.57-0.88), as well as shorter OS in older pts (HR 1.17, 95% CI 1.08-1.26) for each 10 mg/dL SD increase in GV. **Conclusions:** Hyperglycemia and GV during intensive induction are associated with lower CR+CRi rates (all ages) and shorter OS among older adults.Glycemic control during induction may be a modifiable factor to improve AML outcomes.

10044 Poster Session (Board #33), Sat, 1:15 PM-4:45 PM

Autologous stem cell transplant (ASCT) in myeloma to improve patient reported physical function and fatigue. *First Author: Geetika Bhatt, Ohio State University Wexner Medical Center, Columbus, OH*

Background: Patients with Multiple Myeloma (MM) report some of the poorest Health-related quality of life (HRQoL). Few studies show how ASCT influences global health outcomes as measured by a Geriatric Assessment (GA). We performed a prospective GA evaluating the dynamic changes in health pre- and post-ASCT. **Methods:** 100 pts with plasma cell dyscrasia (median (m) = 60 yrs, range (r) = 36-75 yrs) underwent GA pre-ASCT, 90 days and 1-yr post-ASCT. GA included nutritional survey, Hospital Anxiety and Depression Scale (HADS), Brief Fatigue Inventory (BFI), Medical Outcomes Study-Social Support Survey (MOS-SSS), Short Physical Performance Battery (SPPB), handgrip strength, self-reported Human Activity Profile (HAP) Maximum Activity Score (MAS) and Adjusted Activity Score (AAS). Data were analyzed using paired t-test ($p < 0.05$). **Results:** Pts reported moderate fatigue pre-ASCT (m = 4.6, r: 0-9.8) which normalized at 1-yr (m = 2.5, r: 0-7.3; p = 0.008). Self-reported pre-ASCT physical function (MAS) (m = 73, r = 20-94) improved at 1-yr (m = 75.5, r = 52-94; p = 0.014); AAS (m = 64, r = 18-94) also improved at 1-yr (m = 70.5, r = 38-91; p = 0.025). In contrast, MD-reported KPS decreased. Screens for deficits in anxiety, depression, social support, objective physical function, handgrip strength and wt loss did not change significantly at 1-yr. **Conclusions:** Our data indicate that ASCT significantly improves patient-reported fatigue and physical function, unlike MD-reported KPS.

		PRE-ASCT (n = 100)	PRE VS 90-DAY POST-ASCT (n = 36)		PRE VS. 365-DAY POST-ASCT (n = 36)	
DOMAINS		**M (r)**	**M (r)**	**p value**	**M (r)**	**p value**
Hospital Anxiety and Depression Scale		11 (1-29)	9 (0-22)	0.93	7.5 (0-24)	0.06
Brief Fatigue Inventory		4.61 (0-9.78)	2.67 (0-7.4)	0.03	2.5 (0-7.33)	0.008
Social Support (MOS-SSS)		83 (31-95)	83.5 (33-95)	0.31	84.5 (25-95)	0.44
Self-Reported activity	Maximum Activity Score	73 (20-94)	68 (45-91)	0.78	75.5 (52-94)	0.014
	Adjusted Activity Score	64 (18-94)	62.5 (28-91)	0.81	70.5 (38-91)	0.025
Objective Physical Function	Short Physical Performance Battery	10 (4-12)	11 (1-12)	0.38	10 (6-12)	0.78
	Dominant handgrip strength	31 (10-72)	30 (8-72)	0.2	30.5 (12-92)	0.45
Performance Status (%)		90 (70-100)	80 (70-100)	0.002	80 (70-100)	0.03

10045 Poster Session (Board #34), Sat, 1:15 PM-4:45 PM

Cancer-related fatigue in breast cancer survivors: A longitudinal analysis compared to matched controls. *First Author: AnnaLynn Williams, University of Rochester Medical Center, Rochester, NY*

Background: Cancer related fatigue (CRF) is commonly reported among breast cancer survivors and can negatively impact quality of life and treatment adherence. Large, prospective, longitudinal studies assessing CRF in breast cancer survivors compared to matched non-cancer controls are rare. **Methods:** Breast cancer survivors (n = 581, stage I-IIIBC, mean age 53.4) from community oncology clinics and age-matched controls (n = 364, mean age 52.6) completed the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI, scores range -24 to 96) prior to chemotherapy (T1), at chemotherapy completion (T2) and six-months after chemotherapy (T3). Linear mixed models compared trajectories of CRF over time in survivors compared to controls, adjusting for age, education, race, BMI, marital status, menopausal status, and depressive symptoms. **Results:** Survivors reported greater CRF compared to controls at all time points (mean total score T1 9.4 vs. -3.7, T2 17.0 vs. -3.3, and T3 8.5 vs. -3.1, all $p < 0.001$; all subscales $p < 0.001$). From T1 to T2 survivors experienced a significant increase in CRF as shown in the total score (mean change (MC) = 8.3; effect size (ES) = 0.4 , $p < 0.001$), and general, mental, and physical sub-scales (MC = 4.3, 2.1, 3.2 , ES = 0.7, 0.5, 0.7, respectively, all $p < 0.001$), while controls experience minimal changes (MC = 0.1-0.3, ES < 0.09, $p > 0.05$). At T3 survivors total score returned to T1 values (MC = -0.1, ES = 0.01, p = 0.461), which was, however, still greater than controls ($p < 0.001$), while general, mental, and physical CRF subscale scores remained significantly higher than T1 values (MC = 1.2, 1.7, 1.9, ES = 0.2, 0.4, 0.3, respectively, all $p < 0.001$; controls no change). Group by time interactions indicated changes over time were greater in the survivors than controls ($p < 0.001$). In multivariate analyses of survivors, age, BMI, performance status, and baseline depression significantly predicted change in CRF. **Conclusions:** These results from the largest well-controlled study to date showed that breast cancer survivors experience significantly more CRF prior to and after chemotherapy compared to healthy controls. Further research should aim to identify subgroups of survivors most susceptible to CRF.

10046 Poster Session (Board #35), Sat, 1:15 PM-4:45 PM

Utility of the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) in hematopoietic stem cell transplantation (HSCT). *First Author: Patricia B. Mumby, Loyola University Medical Center, Maywood, IL*

Background: The SIPAT is used to assess psychosocial risk in solid organ transplants but data in HSCT is lacking. We examined if pre-HSCT SIPAT scores predict mortality, morbidity, length of stay (LOS) and number of hospitalizations over a 1 year period. **Methods:** 89 adult HSCT (59% autologous, 38% allogeneic) pts from an academic medical center underwent the SIPAT pre-HSCT. Additional data were obtained on Day 0, and 3-, 6-, and 12-months. Univariable Cox proportional hazards models assessed the instantaneous risk of mortality at any given time after Day 0 as a function of baseline pt characteristics and the SIPAT score. **Results:** TheSIPAT categorized 28%, 66% and 5.7% respectively of the pts as excellent (E), good (G), and high risk (HR) candidates. One year post HSCT, 76% of E, 72% of G, and 40% of HR candidates were alive. Higher SIPAT scores were a significant predictor of mortality. Compared to E candidates, the HR candidates were 5.94 (95% CI: 1.31-26.81) times more likely to die any time after Day 0 – even after controlling for pts' comorbidity index ($p = .02$). Similarly, compared to G candidates, HR pts were 4.81 (95% CI: 1.33-17.47) times more likely to die even after controlling for pts' comorbidity index ($p = .01$). There was no difference between the G and E candidates on univariable ($p = .75$) or multivariable analysis controlling for comorbidity index score ($p = .72$). For every 1 point increase in pts' adherence score, the risk of death was expected to decline by approximately 14% ($HR = 0.86$, 95% CI: 0.78 – 0.96; $p = .01$). SIPAT items that predicted mortality were depression ($p = .02$), deceptive behavior ($p < .001$) and moderate alcohol abuse ($p < .001$). In linear regression analysis, higher SIPAT score was associated with longer LOS ($p = .04$) but not infection ($p = .23$), GVHD ($p = .40$), or number of hospitalizations ($p = .73$). Because there were only 18 mortality events, multivariable analyses were limited. Future research will examine the effect of SIPAT on time to death controlling for other pt comorbidities. **Conclusions:** We found the SIPAT was able to predict mortality and LOS in HSCT pts. This finding if validated in a multi-center manner could be an important tool for HSCT pt selection.

10047 Poster Session (Board #36), Sat, 1:15 PM-4:45 PM

Evaluation of adolescents and young adults (AYA) attitudes towards participation in cancer clinical trials. *First Author: Abha A. Gupta, Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Participation in clinical trials (CT) for AYA (< 39 years) remain the lowest of any patient group with cancer. Little is known about the personal barriers to AYA accrual. The aim of this study was to explore AYA attitudes that influence CT participation. **Methods:** A mixed methods approach included 1) qualitative: interpretive descriptive methodology guided individual semi-structured interviews with 21 AYA for factors influencing CT enrollment and 2) quantitative: AYA and non-AYA (≥ 40) matched for histology completed Cancer Treatment subscale of Attitudes toward Cancer Trials Scales (ACTS-CT) (Schuber, 2008) and 9 supplementary questions formed from interview analysis. Differences between AYA and non-AYA cohorts were analyzed using the Mann-Whitney U test and ordered logistic regression models were constructed for prediction of the effect of baseline demographics. **Results:** The major themes influencing CT participation were: (1) family/peer group opinion (2) CT impact on daily/future life (e.g. school; starting a family) and (3) illness severity/psychological readiness for CT information. Surveys were distributed to 61 AYA (median age: 29 years (17-39)); 74 non-AYA (55 (40-88)). Compared with non-AYA, AYA perceived CT to be unsafe/more difficult (Personal Barrier/Safety domain; p = 0.01). AYA were also more concerned with CT interference in their long term goals (p = 0.04). Logistic regression identified participants who had previously been offered a CT (p = 0.01) or who spoke English as their first language (80% of cohort)(p = 0.01) reported less barriers to CT. There were no differences based on age in other domains (Personal Benefits; Personal/Social Value; Trust in CT). In all participants, differences were seen in the Personal Benefits domain if respondents had children (p = 0.05) or were currently working (p = 0.04). **Conclusions:** Age-related differences in attitudes towards CT suggest that tailored approaches to CT accrual of different patient groups may be warranted. Patient-centered delivery of information regarding CT, particularly for those in whom English is a second language and who are trial-naïve, may improve accrual and warrants further prospective, randomized study.

10048 Poster Session (Board #37), Sat, 1:15 PM-4:45 PM

Prevalence of depression and anxiety in older patients with multiple myeloma in North Carolina: A population-based, claims-based assessment. *First Author: Anureet Copeland, University of North Carolina, Chapel Hill, NC*

Background: Patients (pts) with multiple myeloma (MM) experience physical symptoms and complications from disease or treatment that include bone pain, fatigue, anorexia, and insomnia. However, the prevalence of psychiatric comorbidities and their impact on short and long-term outcomes has been understudied. The aim of this analysis was to identify the prevalence of anxiety and depression in older pts with MM in the state of North Carolina. We also sought to evaluate if comorbid depression and anxiety impacted short and long-term outcomes in these patients. **Methods:** Using the University of North Carolina Integrated Cancer Information and Surveillance System (ICISS), we retrospectively identified a statewide cohort of 536 pts (ages 65-80) diagnosed with MM from 2006-2012 who had continuous enrollment in Medicare or Medicaid. Patients were identified through insurance claims by ICD-9 diagnosis codes for anxiety or depression or antidepressant medications filed at any time from 6 months prior to MM diagnosis to 12 months after MM diagnosis. **Results:** The mean age of pts in the cohort was 72 years. Pts were 68% non-Hispanic white, 42% rural, and 51% male. Of the 536 pts, 200 (37%) had a diagnosis of anxiety or depression and/or were being treated with an antidepressant. 54% of those with psychiatric comorbidity had a relevant diagnosis or medication in the 6 months prior to MM diagnosis. Of those with psychiatric comorbidities, 70% were diagnosed with fatigue and 57% were diagnosed with pain. In multivariate analysis, there was no association of psychiatric comorbidity with mortality (HR, 1.03; 95% CI, 0.83-1.28), but psychiatric comorbidity was associated with an increased likelihood of hospitalization or ER visit (RR, 1.17; 95% CI, 1.05-1.30) and increased opiate use within 1 year after diagnosis (RR, 1.66; 95% CI, 1.27-2.16). **Conclusions:** The presence of psychiatric comorbidity identifies a subset of older MM pts at risk for high symptom burden and increased health care utilization. The association of psychiatric comorbidity with increased opiate use in cancer pts may also have public health implications.

10049 Poster Session (Board #38), Sat, 1:15 PM-4:45 PM

Psychological and educational outcomes among adolescent survivors of wilms tumor: A report from the Childhood Cancer Survivor study. *First Author: Rebecca Hope Foster, St. Louis Children's Hospital, St. Louis, MO*

Background: Little is known about psychological and educational problems experienced by adolescent survivors of Wilms tumor (WT), including the impact of treatment exposures and chronic health conditions. **Methods:** Parent-reports from the Childhood Cancer Survivor Study were analyzed for 666 adolescent survivors of WT (Mean[SD] age at survey = 15.3[1.65] years; age at diagnosis = 2.8[1.77] years) and 698 siblings (15.4[1.66] years). Adjusting for race and household income, survivors were compared to siblings on the Behavior Problem Inventory and educational services. Among survivors, therapeutic exposures and chronic medical conditions (CTCAE 4.03 coding) were examined via multivariable log binomial regression adjusting for sex, race, income and age at diagnosis to calculate adjusted Relative Risk (aRR) and 95% confidence intervals (CI). **Results:** Compared to siblings, survivors were more likely to use psychoactive medication (9.4 vs. 5.1%, $p = .0002$) or be in special education for learning problems, inattention, and/or low test scores (19.1 vs. 11.1%, $p = .003$) but had similar rates of depression/anxiety, headstrong behavior, inattention, social withdrawal, and antisocial behavior (p's $> .05$). Survivors who received radiation therapy (RT) to the abdomen (aRR 1.64, CI 1.03-2.61) or abdomen and chest (aRR 1.95, CI 1.16-3.26) were more likely to be in special education for any reason than those without RT. Those with grade 2-4 cardiovascular conditions were more likely to have anxiety/depression (aRR 2.04, CI 1.26-3.30), headstrong behavior (aRR 1.95, CI 1.30-2.93), or inattention (aRR 1.58, CI 1.04-2.42) compared to survivors with grade 0/1 conditions. Survivors were more likely to be in special education if they had problems with antisocial behavior, anxiety/depression, headstrong behavior, inattention or social withdrawal (p's $< .05$). **Conclusions:** Psychological intervention may be needed for adolescent survivors of WT treated with RT to the abdomen or abdomen and chest or with higher grade cardiovascular conditions. These survivors are more likely to experience behavioral and emotional problems, which in turn increases risk for placement in special education.

10050 Poster Session (Board #39), Sat, 1:15 PM-4:45 PM

The importance of recognizing and addressing depression in patients with advanced cancer. *First Author: Risa Wong, Massachusetts General Hospital, Boston, MA*

Background: Patients with cancer often experience depression, which is associated with worse outcomes, including longer hospital length of stay (LOS). Although antidepressant medication can improve depressive symptoms in patients with cancer, it is unclear whether their use translates into better outcomes. We sought to clarify the relationship between depressive symptoms, antidepressant medication, and hospital LOS in patients with advanced cancer. **Methods:** We enrolled hospitalized patients with advanced cancer from 9/2014 to 4/2016 as part of a longitudinal data repository. We examined patients' medical records to obtain information about documented depressive symptoms in the 3 months prior to admission and use of antidepressant medication at the time of admission. Using descriptive statistics, we compared differences in patient characteristics and hospital LOS across these groups. We used linear regression to examine associations and moderation effects between depressive symptoms, use of antidepressant medication, and hospital LOS. **Results:** Of 1,036 enrolled patients (89.9% of approached), 126 (12.2%) had documented depressive symptoms in the 3 months prior to admission and 288 (27.8%) were taking an antidepressant medication at the time of admission. Patients with depressive symptoms were more likely to be on antidepressant medication at admission than those without depressive symptoms (48.4% vs 24.9%, $p < .001$). Patients taking antidepressant medication were younger (62.4 vs 64.4 years, $p = .026$) and more likely to be female (55.2% vs 47.2%, $p = .021$). Depressive symptoms were associated with longer hospital LOS (7.3 vs 6.1 days, $p = .036$), and antidepressant medication was a moderator of this relationship. Among patients not on antidepressant medication, depressive symptoms were associated with longer hospital LOS (7.9 vs 6.1 days, $p = .025$), but among those on antidepressant medication, depressive symptoms were not associated with hospital LOS (6.6 vs 6.2 days, $p = .588$). **Conclusions:** Antidepressant medication moderated the relationship between depressive symptoms and longer hospital LOS. Our results support the need to recognize and address depressive symptoms in patients with advanced cancer.

10051 Poster Session (Board #40), Sat, 1:15 PM-4:45 PM

Psychosocial effects of the relaxation response resiliency program (SMART-3RP) in patients with MGUS and smoldering multiple myeloma: A waitlist controlled randomized clinical trial. *First Author: John W. Denninger, The Benson-Henry Institute for Mind Body Medicine at Massachusetts General Hospital, Boston, MA*

Background: Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are asymptomatic clonal precursors to multiple myeloma, a hematological malignancy. Because observation is currently the standard of care, a diagnosis of MGUS or SMM can be associated with stress and worry about progression. We evaluated the efficacy of the evidence-based mind-body intervention, the Stress Management and Resiliency Training: Relaxation Response Resiliency Program (SMART-3RP) in reducing distress and stress reactivity in patients with MGUS and SMM. **Methods:** In participants diagnosed with intermediate or high risk MGUS or SMM, this randomized, waitlist controlled trial (Oct 2013 – Sep 2016) assessed distress (10-point scale) as the primary outcome and perceived stress (PSS-10), stress reactivity (MOCS-A), and mindfulness (FFMQ) as secondary outcomes and hypothesized mediators of distress reduction. We collected self-report measures at enrollment (T1), 3 months (T2), and 6 months (T3). The immediate treatment arm received the 8-session, 1.5 hour/week SMART-3RP group intervention from T1 to T2 and continued practicing skills from T2 to T3; the waitlist arm received the intervention from T2 to T3. **Results:** 93 participants (59% women) diagnosed with MGUS (n = 49) or SMM (n = 44) were randomized to immediate treatment (n = 45) or waitlist (n = 48). In an ITT analysis of immediate SMART-3RP vs. waitlist (T1-T2), we found significantly greater improvement in distress (-1.4 vs. -0.3, $p = .04$) and stress reactivity (0.39 vs. 0.02, $p < .001$), but not perceived stress (-3.9 vs. -2.2, $p = .12$) or mindfulness (2.4 vs. -0.1, $p = .17$). Improvements in stress reactivity were maintained for the immediate treatment group (T2-T3), but only partially for distress. **Conclusions:** The SMART-3RP, compared to waitlist, reduced distress in participants with intermediate or high-risk MGUS and SMM, with improvements in stress reactivity as a primary mediator of distress reduction. Participants strongly endorsed the intervention's ability to enhance coping and reduce distress. Clinical trial information: NCT01955395.

10052 Poster Session (Board #41), Sat, 1:15 PM-4:45 PM

Treatment decisions and employment of breast cancer patients: Results of a population-based survey. *First Author: Reshma Jagsi, University of Michigan Health System, Ann Arbor, MI*

Background: Many patients with breast cancer work for pay at time of diagnosis, and the treatment plan may threaten their livelihood. Given rapidly evolving policies, evidence, and treatment options, we evaluated work experiences in a contemporary population-based sample of breast cancer patients to inform initiatives to reduce the burden of cancer care. **Methods:** We surveyed women aged 20-79 years diagnosed with stages 0-II breast cancer as reported to the SEER registries of Georgia and Los Angeles in 2014-15. Of 3672 eligible women, 2502 responded (68%); we analyzed 1006 who reported working prior to diagnosis. Multivariable models evaluated correlates of missing $>$ 1 month and stopping work altogether vs missing $\leq$1 month. **Results:** In this diverse sample (48% white, 19% black, 20% Latina, 11% Asian), most pts (62%) received lumpectomy; 16% had unilateral mastectomy (8% with reconstruction); 23% had bilateral mastectomy (19% with reconstruction). One third (33%) received chemotherapy. The vast majority (84%) worked full time at diagnosis, but only 50% had paid sick leave, 39% disability benefits, and 38% flexible work schedules. Surgical treatment was strongly associated with missing $>$ 1 month of work (OR 7.8 for bilateral mastectomy with reconstruction vs lumpectomy) and with stopping altogether (OR 3.1 for bilateral mastectomy with reconstruction vs lumpectomy). Chemotherapy receipt (OR 1.3 for missing $>$ 1 month; OR 3.9 for stopping altogether) and race (OR 2.0 for missing $>$ 1 month and OR 1.7 for stopping altogether, blacks vs whites) also correlated. Those with paid sick leave were less likely to stop working (OR 0.5), as were those with flexible schedules (OR 0.3). Those with disability benefits were more likely to stop working (OR 1.6) or miss $>$ 1 month of work (OR 2.7). **Conclusions:** Working patients who received more aggressive treatments, particularly surgery, were much more likely to experience substantial employment disruptions. Given the growing choice of bilateral mastectomy by patients seeking peace of mind, particularly among young women with years of potential employment ahead, these findings suggest the importance of discussing impact of treatment decisions on employment. Funded by NCI P01CA163233.

10053 Poster Session (Board #42), Sat, 1:15 PM-4:45 PM

Fear of recurrence among cancer survivors. *First Author: Rachel B Jimenez, Massachusetts General Hospital, Boston, MA*

Background: Fear of cancer recurrence (FoCR) following definitive cancer therapy is often reported by patients, but little is known about who is most likely to be impacted, how FoCR influences emotional distress, and what interventions may mitigate patients' FoCR. We sought to determine the prevalence of FoCR among cancer survivors and to evaluate potential predictors of FoCR in this population. **Methods:** As part of a comprehensive supportive care needs assessment, we evaluated the prevalence of FoCR among patients receiving follow-up cancer care at our institution as well as factors associated with FoCR. Elevated FoCR was measured with a single item: "I worry about my cancer coming back" rated on a 4-point Likert scale (1 = "not at all" to 4 = "very much"); responses of 3 or 4 were considered positive for FoCR. Descriptive statistics were used to characterize patterns of FoCR. Chi-square and Fisher's exact tests compared differences in emotional, clinical, and demographic characteristics between participants with and without FoCR, as well as interest in and knowledge of survivorship services. **Results:** Of 636 patients who completed the survey, 318/636 (50.0%) patients had curable cancer and had either completed cancer therapy or were completing maintenance treatment. On inquiry, 167/318 (53%) reported FoCR. Those with FoCR were more likely to be female ($p < 0.002$) and under the age of 70 ($p < 0.003$). They were also more likely to be sad (25% vs. 14%, $p < 0.015$), anxious (40% vs. 21% $p < 0.0005$), feel uncertain about the future (30% vs. 14%, $p < 0.0005$), have problems managing stress (26% vs. 13%, $p < 0.003$), and were more likely to worry about dying (55% vs. 8%, $p < 0.0001$) and to fear another cancer (74% vs. 8% $p < 0.0001$). Education level, cancer type, knowledge of and interest in support services, and survivorship care plan receipt were not associated with FoCR. **Conclusions:** Patient FoCR is prevalent among more than half of survivors of cancer and is associated with emotional distress that is insufficiently addressed by survivor care planning and supportive services. Clinicians can and should screen for and address this issue. Future research is needed to develop and test interventions, beyond care plans, to address FoCR in both low risk and high risk patient populations.

10054 Poster Session (Board #43), Sat, 1:15 PM-4:45 PM

Risk tolerance and attitudes toward chemotherapy: Who chooses palliative treatment when cure is possible? *First Author: Thomas William LeBlanc, Duke Cancer Institute, Duke University Medical Center, Durham, NC*

Background: Many patients with acute myeloid leukemia (AML) face a difficult choice about whether to receive palliative chemotherapy or high-dose, potentially-curative chemotherapy that poses a risk of early death. How people weigh these factors in decision-making is unknown. We hypothesized that the possibility of cure primarily drives decision-making, regardless of treatment risk. **Methods:** We designed an electronic survey describing two treatment paths: (1) high-dose chemotherapy with possibility of cure but a 10% risk of early death, and (2) palliative chemotherapy with no chance of cure but no risk of early death. We recruited respondents via Amazon MTurk and presented 7 scenarios in random order, varying only the likelihood of cure associated with high-dose chemotherapy. Subjects rated their preferred treatment on a 4-point Likert scale. We assessed numeracy and attitudes toward chemotherapy using validated scales, and employed attention checks for quality assurance. **Results:** 100 subjects completed the survey (median age 30.5; 52 female, 85 Caucasian). 46 (46%) had at least a bachelor's degree and numeracy was generally high (median 4.75 out of 6). Respondents' preferences for intensive chemotherapy varied with likelihood of cure, however some displayed a fixed preference for either curative or palliative treatment throughout, regardless of benefit level. For example, given a 50% likelihood of cure 20 respondents (20%) still preferred palliative therapy; similarly, with only a 1% likelihood of cure 28 respondents (28%) still preferred high-dose chemotherapy. In a multivariable model, preference for palliative chemotherapy was significantly predicted by subjects' scores on the attitudes toward chemotherapy scale ($p < 0.001$), controlling for age, education, and numeracy. **Conclusions:** Contrary to our hypothesis, a significant proportion of subjects preferred palliative chemotherapy, even in scenarios where high-dose chemotherapy confers a high likelihood of cure. Pre-existing attitudes toward chemotherapy appear to drive patients' decision-making, even when treatments are potentially curative. This finding may have significant implications for risk communication in oncology.

10055 Poster Session (Board #44), Sat, 1:15 PM-4:45 PM

Randomized trial of a smartphone mobile app for adherence to oral chemotherapy. *First Author: Joseph Greer, Massachusetts General Hospital, Boston, MA*

Background: As patients with cancer are increasingly prescribed oral chemotherapy, they share greater responsibility for ensuring adherence and monitoring side effects. The aim of this study was to test the effect of a smartphone mobile app to improve adherence and symptom management in patients prescribed oral chemotherapy. **Methods:** From 2/15 to 12/16, 181 patients with diverse cancers prescribed oral chemotherapy were randomized to receive either the smartphone mobile app or standard care. The mobile app included a medication treatment plan with alerts, symptom reporting module, education library, and cancer-specific resources. The primary outcome was adherence, measured by electronic pill cap (MEMS) and self-report (Morisky Medication Adherence Scale; MMAS). To assess symptoms, mood, and satisfaction with care, participants completed the MD Anderson Symptom Inventory, Hospital Anxiety & Depression Scale (HADS); and Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction (FACIT-TS) at baseline and 12 weeks. General linear models were used to assess intervention effects on patient outcomes. **Results:** Study groups did not differ across outcome measures from baseline to week 12. Secondary analyses showed that baseline adherence (MMAS) and anxiety (HADS) were moderators of intervention effects on adherence and treatment satisfaction. Among patients who reported adherence problems, those assigned to the mobile app had better average MEMS adherence (Mean Diff = 19.30, 95% CI = 0.09-38.51, p = .05) and satisfaction with clinician explanations per the FACIT-TS (Mean Diff = 1.69, 95% CI = 0.25-3.13, p = .02) compared to standard care. Also, among patients with higher anxiety, those in the mobile app group reported better adherence on the 12-week MMAS (95.2% vs. 68.0%, OR = 0.11, 95% CI = 0.01, 0.94, p = .04) and satisfaction with interpersonal treatment per the FACIT-TS (Mean Diff = 0.76, 95% CI = 0.13-1.39, p = .02) compared to standard care. **Conclusions:** Although potentially not for everyone taking oral chemotherapy, a smartphone mobile app to improve adherence and treatment satisfaction may be useful for patients with certain risk factors, such as those struggling with adherence or anxiety. Clinical trial information: NCT02157519.

10056 Poster Session (Board #45), Sat, 1:15 PM-4:45 PM

Patterns of osteoporosis (OP) in survivors of colorectal cancer (CRC) enrolled on SWOG trials. *First Author: Afsaneh Barzi, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: There are currently 1.5 million CRC survivors in US and this number will continue to rise with advancements in treatment. The risk of OP in CRC survivors has not been well described. **Methods:** We used data from 3 SWOG CRC treatment trials, all of which were phase III and had long term follow-up. Enrollees were linked to Medicare claim files for identification of OP and fractures using HCPCS and ICD9 codes. First, we compared patterns of osteoperosis and fracture risk by sex in colorectal cancer patients. To assess whether patterns of fracture risk by sex differed between patients with vs. without colorectal cancer, we compared the difference in fracture risk by sex in colorectal cancer patients to the difference in fracture risk by sex in the general U.S. population, using data from the National Health Interview Survey (NHIS) and the National Hospital Discharge Survey (NHDS). Finally, we assessed whether absolute estimates of osteoperosis and fracture risk differed between men with colorectal cancer and men without colorectal cancer. Comparison data for men without colorectal cancer were obtained from the placebo arm of the Prostate Cancer Prevention trial (PCPT). **Results:** We linked 1233 CRC cases with Medicare claims. The median age at CRC diagnosis was marginally higher for women (65 vs 64 ys, $p = 0.03$). 47% of females, 15% of men with CRC, and 19% of men without CRC had a OP diagnosis. The female to male ratio of osteoporotic fracture in general U.S. population was 1.67, while the same ratio in CRC survivors was 2.84, an increase of 70% (p-value < 0.001). **Conclusions:** Our study indicates that the risk disparity for OP fracture for females is much greater in CRC survivors than in the general U.S. population. This may be due to more OP diagnoses for female CRC survivors, but not for male CRC survivors.

10057 Poster Session (Board #46), Sat, 1:15 PM-4:45 PM

Cardiac autonomic dysfunction in breast cancer survivors. *First Author: David Payne, Brigham and Women's Hospital Heart and Vascular Center, Boston, MA*

Background: Cardiac autonomic dysfunction (AD) has been associated with increased cardiovascular (CV) and all-cause mortality in several diseases. We evaluated the prevalence, functional and prognostic significance of cardiac AD in a cohort of breast cancer (BC) survivors referred for exercise treadmill testing (ETT). **Methods:** Cardiac AD was defined as the presence of both an elevated resting heart rate (HR $\geq$ 80 beats per minute) and abnormal HR recovery (HRR $\leq$ 12 beats per minute if active cool down, or $\leq$ 18 beats per minute if passive recovery) at 1 minute after peak exercise. Presence of cardiac AD, exercise capacity, and all-cause mortality were assessed in 448 women (age 62.6$\pm$10.0 years), 8.7 [range 4.5, 14.3] years from BC diagnosis, compared to 448 cancer-free, age- and sex-matched controls, all of whom were clinically referred for ETT. **Results:** Elevated resting HR (23.7% vs. 17.0%, $p = 0.013$), abnormal HRR (25.9% vs. 20.3%, $p = 0.048$), and cardiac AD (8.0% vs. 4.2%, $p = 0.025$) were more prevalent in BC survivors than controls. BC survivors with cardiac AD had reduced exercise capacity compared to those without AD (Table). Among controls, cardiac AD was not associated with decreased exercise capacity. Among BC survivors (age-adjusted hazard ratio 1.90 (95% CI 0.78-4.62) and controls (age-adjusted hazard ratio 4.09 (95% CI 0.49-34.18), cardiac AD was not associated with increased all-cause mortality. **Conclusions:** Among patients referred for ETT, BC survivors have an increased prevalence of cardiac AD relative to controls. Cardiac AD is associated with decreased exercise capacity, but not increased all-cause mortality, in BC survivors. Available strategies to modulate cardiac AD may improve functional capacity in BC survivors. Table: Impact of markers of cardiac AD on exercise capacity.

	Breast cancer		Controls		
	Adjusted* mean reduction (SE) in METs achieved	p value	Adjusted* mean reduction (SE) in METs achieved	p value	Interaction p value
Cardiac AD	-1.9 (0.4)	< 0.0001	-0.3 (0.5)	0.53	0.05
Elevated resting HR	-0.9 (0.3)	0.0003	-0.6 (0.3)	0.03	0.12
Abnormal HRR	-1.3 (0.3)	< 0.0001	-0.6 (0.3)	0.02	0.51

*Adjusted for age, body mass index, CV comorbidities, statin use, atrioventricular blocking drugs, ETT result. METs, metabolic equivalents achieved during ETT.

10058 Poster Session (Board #47), Sat, 1:15 PM-4:45 PM

Temporal treatments and outcomes following acute myocardial infarction among cancer survivors: A population-based study, 1995-2013. *First Author: Inna Y. Gong, University of Toronto, Toronto, ON, Canada*

Background: There is little contemporary information regarding cardiac care and mortality differences following an acute myocardial infarction (AMI) between cancer survivors (CS) and non-cancer patients (NCP). **Methods:** All patients with AMI (1995-2013) in Ontario, Canada were identified through administrative databases and stratified into CS (solid or hematologic) and NCP. Those with cancer within 1 year of AMI were excluded. We used inverse probability treatment weight of propensity scores to balance confounders. Coronary intervention use and survival following index AMI were compared between CS and NCP using Modified Poisson and Cox modeling, and their temporal trends were examined. **Results:** Of 270,089 AMI patients (62.1% men; 87.8% >65 yrs old for CS vs. 56.2% for NCP), 22,907 were CS (prostate 26%, colorectal 17%, breast 16%) and 247,182 NCP. From 1995-2013, coronary interventions usage increased similarly for both groups (Table). The overall 30-day use did not differ between CS and NCP (angiogram unadjusted 36% vs. 50%, adjusted RR 0.96, 95% CI 0.96-1.00, p=.21; percutaneous coronary interventions unadjusted 21% vs. 31%, adjusted RR 0.98, 95% CI 0.94-1.01, p=.21; bypass surgery unadjusted 5% vs. 7%, adjusted RR 0.95, 95% CI 0.87-1.04, p=.25). Unadjusted 30-day mortality following AMI decreased similarly for CS and NCP (Table). However, adjusted 30-day mortality was worse in CS (HR 1.09, 95% CI 1.04-1.15, p<0.001). Over median follow-up of 11 yrs, CS had worse survival than NCP (HR 1.22, 95% CI 1.18-1.26, p<0.0001). CS had higher risk of heart failure than NCP (HR 1.10, 95% CI 1.05-1.15, p<0.0001), while myocardial (re)-infarction and stroke were similar (HR 0.99, 95% CI 0.96-1.02, p=.46; HR 1.09, 95% CI 1.00-1.18, p=.052). **Conclusions:** Following AMI, coronary intervention use increased and early mortality decreased comparably between CS and NCP over time. However, CS had worse short-term and long-term survival, suggesting that continued emphasis on cancer and cardiovascular care is needed to improve outcomes.

	CS (%)		NCP (%)	
30-day intervention	1995	2013	1995	2013
Angiogram	12	68	17	82
PCI	3	46	5	60
CABG	3	7	4	8
30-day mortality	20	12	13	6

P for trend <.0001; P for interaction ns.

10059 Poster Session (Board #48), Sat, 1:15 PM-4:45 PM

Multicenter, randomized phase II trial of physical activity (PA), metformin (Met), or the combination on metabolic biomarkers in stage I-III colorectal (CRC) and breast cancer (BC) survivors. *First Author: Jeffrey A. Meyerhardt, Dana-Farber Cancer Institute/Partners CancerCare, Boston, MA*

Background: Observational data demonstrate an inverse relationship between PA and Met to disease outcomes in CRC & BC pts. A mechanism that these could impact cancer recurrence and mortality is hypothesized to involve insulin and related growth factors. We investigated the effects of PA, Met or the combination on metabolic biomarkers in CRC & BC pts. **Methods:** In a phase 2 RCT, stage I-III CRC & BC survivors at least 2 months from completing standard therapy (excluding hormone rx or trastuzumab) were randomized to PA, Met, PA + Met or control. Major eligibility included absence of recurrence or diabetes (glucose $<$ 160 (random) or $<$ 126 (fasting) mg/dl) and exercising $<$ 120 min/wk. The PA intervention consisted of supervised aerobic training at least 2 x /wk. Metformin dosing was 850 mg 1x/day titrated to 850 mg 2x/day after 2 wks if tolerated. Interventions were 12 weeks in duration. Fasting bloods at baseline & 12 wks were analyzed for insulin (1^{o}endpoint), leptin, IGF1, IGFBP1 & IGFBP3. **Results:** 139 pts were enrolled: 62% BC/38% CRC; 83% female; median BMI 28.3; median 2 yrs from dx; median age 56 (range 34-79). 107 pts completed assigned therapy. Pts in PA and PA + Met arms increased PA by 166 and 140 min/wk vs 30 min/wk in controls (both P<0.0001). Pts in the Met and PA + Met arms lost weight vs controls (-1.41 and -0.91 kg vs + 1.97 kg, both P <0.0001). Both interventions had impact on metabolic biomarkers (Table). **Conclusions:** PA and Met both led to significant changes in insulin and other biomarkers in CRC & BC survivors with potential synergistic effect on leptin with dual intervention. Clinical trial information: NCT01340300.

	Arm 1: PA+Met n=33	P 1 v 4 arms	Arm 2: PA n=34	P 2 v 4 arms	Arm 3: Met n=32	P 3 v 4 arms	Arm 4: Control n=29	P 2 v 1 arms	P 3 v 1 arms
Insulin (SE), mU/L	-2.47(1.07)	<0.0001	-0.08(1.06)	0.01	-1.16(1.18)	0.003	2.79(1.27)	0.03	0.11
Leptin, ng/mL	-5.09(1.21)	0.0002	-0.54(1.19)	0.33	-2.56(1.33)	0.07	-0.20(1.40)	0.0002	0.02
IGF-I, ng/mL	-1.29(2.98)	0.72	8.22(2.94)	1.00	-2.66(3.28)	0.63	-3.05(3.46)	0.0008	0.59
IGFBP1,ng/mL	-0.22(0.57)	0.02	0.09(0.56)	0.11	-1.20(0.63)	0.002	0.78(0.66)	0.16	0.83
IGFBP3,ng/mL	-178.8(82.0)	0.25	53.4(80.7)	0.95	25.9(90.2)	0.89	-96.9(94.9)	0.005	0.02

10060 Poster Session (Board #49), Sat, 1:15 PM-4:45 PM

Changes in p16INK4a (p16) expression, a biomarker of aging, in peripheral blood T-cells (PBTC) in patients receiving anthracycline (A) vs non-anthracycline (NoA) chemotherapy (CRx) for early-stage breast cancer (EBC). *First Author: Shlomit Strulov Shachar, Rambam Health Care Campus, Haifa, Israel*

Background: Age-related accumulation of senescent cells plays a causal role in some aspects of mammalian aging. We have shown that the total-body burden of senescent cells can be estimated by measuring the expression of the *p16* tumor suppressor, a canonical effector of senescence, in human CD3+ PBTC (Liu et al, *Aging Cell*, 2009). Expression of *p16* increases more than 10-fold over an adult human lifespan, and this rate of accumulation is accelerated by age-promoting exposures such as CRx or stem cell transplant (Sanoff et al, *JNCI* 2014; Wood et al, *EbioMed* 2016). Increased molecular age as evidenced by increased expression of p16 prior to CRx predicts a patient's risk of CRx toxicity independently of chronological age (DeMaria et al, Cancer Discovery, 2017).This study investigates the impact of different types of CRx (A vs NoA) regimens on PBTC *p16*expression in pts with EBC. **Methods:** EBC pts who received neoAdj or Adj CRx had blood samples drawn for *p16* assay prior to CRx initiation and again between 2 months and 1.5 years after the end of CRx. Expression of *p16* mRNA in PBTC was determined using TaqMan real-time quantitative reverse transcription PCR. T-test compared *p16*change between A and NA groups. **Results:** 70 pts were evaluable. Pt. characteristics: median age 49 (range 32-76); 52 (74%) White, 14 (20%) black, 4 unknown; 39 (56%) ER or PR+ and HER2 neg, 18 (26%) triple negative, 13 (19%) HER-2 pos (all received trastuzumab). 53 pts (76%) had A (47 AC + taxane, 6 AC no taxane) and 17 (24%) NoA (all TC). Expression of *p16* increased 2.0-fold in patients who received A-based CRx compared to 1.2-fold in NoA CRx ($p = 0.04$). There was no relationship of race, ER, PR or HER-2 status on change in *p16*expression. **Conclusions:** This study is ongoing and further results will be presented at the ASCO meeting. In this sample of EBC patients treated with A vs. NoA CRx regimens, A-based CRx is more strongly associated with increased biologic aging of T-cells compared to NoA CRx. These changes are equivalent of increased biologic aging of PBTC of 11 years (A) vs.6 years (NoA) and may have major consequences on the long-term survival of these pts.

10061 Poster Session (Board #50), Sat, 1:15 PM-4:45 PM

NeuroCog-FX study: A multicenter cohort study on cognitive dysfunction in patients with early breast cancer. *First Author: Oliver Rick, Klinik Reinhardshoehe, Bad Wildungen, Germany*

Background: Many breast cancer patients complain about cognitive dysfunction (CD) with mnestic and attentional deficits. These complaints persist even after completion of therapy in approximately one third of the patients and affects both social life and working capacity. The exact nature and genesis of CD in breast cancer patients is still not fully understood and risk factors are not yet described. **Methods:** To determine CD and risk factors, we used the computer-based neuropsychological test NeuroCog-FX during a three weeks oncological rehabilitation in breast cancer patients. Eight subtests addressed attention, working memory, verbal and figural memory, and language. Test duration was < 30 minutes. A cognitive deficit was diagnosed if at least one subtest was clearly below average (score $<$ M - 1.5 SD) of the normative age group. The data on cognitive function were correlated with the level of depression (PHQ-9 test), QoL (EORTC QLQ-30) and clinical parameters (nodal status, chemo-/radiotherapy and endocrine therapy). **Results:** From February 2013 to December 2014 a total of 476 patients were recruited in 9 oncological rehabilitation centers in Germany. NeuroCog-FX was used to examine 439 patients. Median age was 50 years (range: 24-62 years); 93% of patients had early tumor stage (T0-T2) and 67% were node-negative. Sixty-one percent of the patients received chemotherapy while 84% of the subjects underwent radiotherapy. CD was found in 59% and a moderate to severe depression in 38% of the patients. The severity of depression was correlated with slower reaction times and reduced verbal memory performance. These two cognitive parameters were also associated with a reduced global health status and a reduced physical function score on the EORTC-QLQ30 questionnaire suggesting an impact of cognitive deficits on quality of life. Cognitive function was not associated with type of treatment or node status. **Conclusions:** In this large and homogeneous cohort of breast cancer patients, CD has been shown in most of the subjects using a valid test method. CD was associated with depression and reduced quality of life. Neither tumor therapy nor other clinical parameters had a significant impact on development of CD.

10062 Poster Session (Board #51), Sat, 1:15 PM-4:45 PM

Survivorship needs after head and neck cancer treatment. *First Author: Callie Berkowitz, Duke University Medical Center, Durham, NC*

Background: Head and neck cancer (HNC) survivors experience significant sequelae of treatment, including long-term physical side effects and ongoing surveillance for recurrence and secondary malignancy. Given the complicated trajectory of HNC survivors, survivorship care plans educating patients and their caregivers about treatment and recovery may be beneficial. However, little is known about patients' knowledge gaps related to survivor issues. **Methods:** Through a prospective anonymous self-administered survey, we evaluated the baseline knowledge of HNC survivors regarding common post-treatment issues and mediating factors. Forty-one HNC patients within 3 months of completing treatment participated between July-November 2016. Descriptive statistics were used to characterize patient responses. **Results:** Patients had undergone a variety of treatment modalities: radiation (97%), chemotherapy (71%), and surgery (39%). 85% of patients had primary care providers, 56% had regular dental care, and 44% had dental insurance. 78% had caregivers. HNC survivors' correct responses to side-effect (SE) knowledge questions were lowest for items regarding hearing loss (15%), sleep (33%), tiredness (38%), and anxiety (49%). Only 28% correctly identified cancer risk with alcohol intake. 87% correctly linked tobacco products to cancer recurrence. Patients were most interested in learning via discussions with nurse or doctor (76%) followed by reading written materials (61%), and researching online (32%). Most patients desired to learn more about their cancer (73%), short-term SE (80%), and long-term SE (77%). **Conclusions:** Our study demonstrated clear gaps in knowledge and healthcare access that may inform targeted, individualized survivorship care plans. Patients had the largest knowledge deficits for alcohol use and recurrence, hearing loss after treatment, and a variety of emotional effects of cancer treatment. These topics should be addressed during delivery of survivorship care plans and surveillance encounters to improve survivorship knowledge.

10063 Poster Session (Board #52), Sat, 1:15 PM-4:45 PM

What do social media-savvy cancer survivors tell us about the completeness of survivorship care plans? *First Author: Diane Mary Radford, Cleveland Clinic, Cleveland, OH*

Background: The Commission on Cancer (CoC) standard 3.3 became effective in 1/2015 requiring the delivery of a survivorship care plan (SCP) at the completion of curative treatment. Both the CoC and ASCO have recommended minimum requirements for SCPs, which should include both a treatment summary and follow up care plan. Many cancer patients use social media (SM) as a way to obtain support and information. We have shown previously that the majority of SM savvy cancer survivors (88.2%) do not receive SCPs (*J Clin Oncol* 35, 2017 suppl 5S; abstr 104). We sought to determine the contents of the SCPs received. **Methods:** An IRB-approved survey was conducted via the online tool SurveyMonkey from 3/21/2016 to 4/2/2016. Patients were invited to participate via SM outlets reaching cancer-related communities including Twitter chats, Facebook groups, blogs, and targeted emails. **Results:** A total of 312 patients responded. 63% (194) had completed curative treatment (excluding endocrine therapy). Of these 11.8% (23) reported receiving an SCP at the end of treatment. Of 22 patients who responded, 9/22 (40.9%) found the SCP helpful, 11/22 (50.0%) somewhat helpful, and 2/22 (9.1%) not helpful. The table below shows the components of those SCPs received. **Conclusions:** Not only did a small percentage of patients receive SCPs but also no patient received a complete SCP per the CoC and ASCO recommendations. Particularly deficient was a description of late/long-term effects of treatment—only 36% received such information. Challenges exist in the delivery of complete SCPs.

Components of SCP	Yes	No	Don't know/unsure	N/A
Contact info. for providers and navigators	16/22 (72.73%)	1/22 (4.55%)	5/22 (22.73%)	0
Cancer stage provided	19/22 (86.36%)	1/22 (4.55%)	2/22 (9.09%)	0
Summary of surgery performed	19/22 (86.36%)	2/22 (9.09%)	0	1/22 (4.55%)
Summary of systemic treatment	17/22 (77.27%)	2/22 (9.09%)	1/22 (4.55%)	2/22 (9.09%)
Summary of radiation treatment	12/22 (54.55%)	1/22 (4.55%)	0	9/22 (40.91%)
Recommendations for physician follow up	18/22 (81.82%)	3/22 (13.64%)	1/22 (4.55%)	0
Recommendations for imaging follow up	13/22 (59.09%)	5/22 (22.73%)	4/22 (18.18%)	0
Description of long-term side-effects	8/22 (36.36%)	7/22 (31.82%)	7/22 (31.82%)	0

10064 **Poster Session (Board #53), Sat, 1:15 PM-4:45 PM**

Neurocognitive functions and psychological distress in young adults with cancer (YAC): A prospective, longitudinal study. *First Author: Kim Edelstein, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Non-CNS cancer and treatments are associated with neurocognitive sequelae in older adults; whether YAC (age 18-39 yrs) are protected from these effects is unknown. In YAC, cancer interferes with education and occupational attainment and is associated with psychological distress. This prospective, inception-cohort study characterizes neurocognitive functions and psychological distress in YAC. **Methods:** YAC completed a 2-hr battery of standardized neurocognitive tests and questionnaires 1.7 ± 1 months after diagnosis prior to chemotherapy (mean ± SD, T1) and 8.2 ± 1.2 (T2) and 14.2 ± 1.6 (T3) months later. Healthy YA with no cancer history (HYA) were tested at similar time points. Tests were scored using published norms, transformed to T-scores, and grouped into neurocognitive domains. **Results:** YAC (n = 108; lymphoma, breast, gyne, GI, GU, sarcoma) were grouped according to whether they required chemotherapy (n = 70) or not (n = 38), and compared to 63 HYA. At baseline, there were no group differences in neurocognitive performance, number of impaired tests, or neurocognitive complaints (Kruskal Wallis, all p-values $> .4$). About 70% of each group completed assessments at T2 and T3. Mean performance improved over time (random effects models, all p-values $< .01$), but there were no group differences or interactions between group and time. There were also no differences in proportions of participants in each group whose test scores improved (> 10 points) or declined (< 10 points) from T1 to T2 or T3. Adjusting for psychological distress, fatigue, or neurocognitive complaints did not change these results, despite higher symptoms of somatic distress, anxiety and fatigue in YAC compared to healthy YA over time (all p-values $< .03$). **Conclusions:** Before chemotherapy and up to about 14 months later, YAC have elevated distress and fatigue, but do not demonstrate the cognitive decline reported in older cancer patients. Our findings are consistent with research suggesting that aging brains are more vulnerable to neurotoxic insult. Whether the effects of cancer treatment emerge later in YAC, placing them at risk for accelerated aging as reported in older patients, remains to be examined.

10065 **Poster Session (Board #54), Sat, 1:15 PM-4:45 PM**

Pregnancy after breast cancer: Results from a prospective cohort study. *First Author: Philip Daniel Poorvu, Dana-Farber Cancer Institute, Boston, MA*

Background: Prospective data regarding fertility and pregnancy after breast cancer are limited. Many young survivors are interested future fertility, but pregnancy rates among women attempting and not attempting pregnancy have not been studied prospectively. **Methods:** As part of a multicenter cohort study, women diagnosed age ≤40 with stage 0-3 breast cancer are surveyed at baseline then annually regarding fertility interest, attempts, and pregnancies. Chi-square tests were used to compare proportions attempting and achieving pregnancy. **Results:** At least once in the 5 years (yrs) after Dx, 334/959 (35%) women reported interest in future biologic children. The percent interested was stable in the first 3 yrs then declined: 256 (27%, baseline), 244 (27%, 1 year), 209 (25%, 2 yrs), 176 (25%, 3 yrs), 106 (18%, 4 yrs), and 72 (16%, 5 yrs). Pregnancy was attempted by 104/334 (31%) of women who reported interest and 4/625 (1%) who did not. Pregnancy occurred in 118 women (12%), including 76/108 (70%) who attempted and 42/851 (5%) who did not. Attempts and achieving pregnancy were associated with younger age, partnered status, and not having children prior to Dx (table). Lower stage was associated with attempting pregnancy and ER negative disease with achieving pregnancy. **Conclusions:** A substantial number of young women become pregnant in the 5 years after a breast cancer diagnosis. Given that over 1/3 of pregnancies were among women who did not report attempting, additional attention to contraception counseling should be considered. Further evaluation of assisted reproductive technology use, pregnancy and disease outcomes in this cohort, and the POSITIVE Trial (NCT02308085) will shed light on the feasibility and safety of pregnancy after breast cancer.

	Attempted Pregnancy N (%)	X2 p-value	Achieved pregnancy N (%)	X2 p-value
Age at Dx (yrs)		<0.0001		<0.0001
≤ 30	27 (23)		32 (27)	
31-35	49 (19)		46 (18)	
36-40	32 (6)		40 (7)	
Partnered		0.02		0.02
Yes	92 (13)		100 (14)	
No	15 (7)		17 (8)	
Children prior to Dx		<0.0001		0.01
0	68 (20)		54 (16)	
≥ 1	40 (6)		64 (10)	
Stage		0.0004		0.10
0	20 (24)		17 (20)	
1	43 (13)		34 (10)	
2	35 (9)		51 (13)	
3	10 (7)		16 (12)	
ER		0.19		0.0004
Negative	35 (13)		48 (16)	
Positive	72 (10)		69 (10)	
Chemotherapy		0.16		0.30
No	39 (13)		31 (11)	
Yes	68 (10)		86 (13)	

LBA10066 **Poster Session (Board #55), Sat, 1:15 PM-4:45 PM**

Safety of pregnancy in patients (pts) with history of estrogen receptor positive (ER+) breast cancer (BC): Long-term follow-up analysis from a multicenter study. *First Author: Matteo Lambertini, Institut Jules Bordet, Brussels, Belgium*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, June 3, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

10067 **Poster Session (Board #56), Sat, 1:15 PM-4:45 PM**

Can exercise influence survival following breast cancer: Results from a randomised, controlled trial. *First Author: Sandra Christine Hayes, Queensland University of Technology, Institute of Health and Biomedical Innovation, Brisbane, Australia*

Background: Exercise for Health was a randomised, controlled trial designed to evaluate an 8-month translational exercise intervention, commencing 6-weeks post-surgery for newly diagnosed breast cancer. Outcomes for this follow-up exploratory analysis were overall- and disease-free survival. **Methods:** Consenting urban-based women (n = 194) were randomized to one of two exercise groups (intervention delivered either face-to-face or over the telephone) or a usual care group, while consenting rural/regional women (n = 143) were randomised to either the telephone-delivered exercise group or usual care group. For the purposes of these analyses, exercise groups and usual care groups were combined (exercise group, n = 207; usual care group, n = 130). Analyses were done on an intention-to-treat basis and trials were registered with the Australian New Zealand Clinical Trials Registry (ACTRN12606000233527; 12609000809235). **Results:** Participant disease and treatment characteristics were similar to the wider breast cancer population in Queensland, Australia, and 42% of the sample resided in rural or regional areas. After a median follow-up of 101 months, there were 15/130 (11.5%) survival events in the usual care group, compared with 11/207 (5.3%) events in the exercise group. Disease-free events for the usual care versus exercise group were 23/130 (17.7%) and 25/207 (12.1%), respectively. The corresponding unadjusted hazard ratio for the exercise group for overall survival was 0.45 (95% CI = 0.21-0.97; p = 0.037), and for disease-free survival was 0.66 (95% CI = 0.38-1.17; p = 0.155). **Conclusions:** Epidemiological evidence consistently shows a positive relationship between physical activity and survival post-breast cancer, but is unable to establish causality. These exploratory findings suggest that an exercise intervention delivered during and beyond conventional treatment for breast cancer and that was designed to cater for all women, irrespective of place of residence and access to medical services, has clear potential to influence survival. Clinical trial information: ACTRN12606000233527; 12609000809235.

10068 Poster Session (Board #57), Sat, 1:15 PM-4:45 PM

Chemotherapy-induced ovarian failure (CIOF) in young women with early breast cancer (EBC). *First Author: Jenny Furlanetto, German Breast Group (GBG), Neu-Isenburg, Germany*

Background: Women ≤45 years (yrs) treated with chemotherapy (CT) for EBC have a high risk of developing CIOF. Awareness of CIOF is essential for young women. **Methods:** 740 patients (pts) aged ≤45yrs treated with anthracycline or taxane-based CT for EBC from 4 German neoadjuvant/adjuvant trials were included. Blood samples were collected at baseline (N=740), end of treatment (EOT n=740), 6 (n=177), 12 (n=113), 18 (n=69), 24 (n=47) months (m) after EOT. Only samples collected in a time sequence were included. Estradiol (E2), Follicle-Stimulating Hormone (FSH) and Anti-Müllerian Hormone (AMH) were centrally assessed. CIOF was defined as FSH >12.4IU/l and E2 <52.2ng/ml and was analysed per timepoint and according to clinical and treatment-related variables. **Results:** Median age was 40yrs (range 21-45); 57.2% had BMI 18.5-<25, 41.1% ≥25; 32% had luminal, 35.9% HER2+, 32.0% triple-negative BC. Median hormone levels at baseline for pts <30yrs vs 30-40yrs vs ≥40yrs were: FSH 5.2IU/l vs 5.6IU/l vs 6.4IU/l; E2 101ng/l vs 86ng/l vs 88ng/l; AMH 2.14ng/ml vs 1.58ng/ml vs 0.53ng/ml. 85.7% of pts had CIOF at EOT, 62.2% at 6m, 54.0% at 12m, 43.5% at 18m, 38.3% at 24m. Similar results were observed in 47 pts with all timepoint samples available. Older vs younger pts had more frequently CIOF at EOT (≥40yrs 94.6%, 30-40yrs 82.0%, <30yrs 50.0%, p<0.001). CIOF at EOT was not influenced by BMI. CT agents impacted the rate of CIOF (p<0.001; Table 1). Higher rate of CIOF was associated with longer CT duration (12w 58.3%, 16-18w 94.5%, 24w 82.1%; p<0.001) and with dose-dense (ddEC-ddD, weekly PM(Cb), intense-dd (idd) EnPC) vs conventional dosed CT (P/nP-EC q3w, P, Cz) (94.5% vs 78.6%; p<0.001). **Conclusions:** The majority of young women experienced CIOF after CT for EBC. After 2 yrs 62% of the pts returned to premenopausal hormone levels. Age, CT regimen, duration and density influenced the rate of CIOF and should be taken into account when counseling young women who desire to maintain ovarian function.

CIOF according to treatment at EOT.

CT Regimen	ddEC-ddD	PMCb	iddEnPC	PM	P	nP-EC	P-EC	Cz
CIOF %	95.6	95.2	94.6	93.1	89.7	82.9	81.3	29.0

C, cyclophosphamide; Cb, carboplatin; Cz, cabazitaxel; D, docetaxel; E, epirubicin; M, doxorubicin; P, paclitaxel; nP, nab-paclitaxel.

10069 Poster Session (Board #58), Sat, 1:15 PM-4:45 PM

Fatigue and health behaviors in cancer survivors: A cross-sectional population based study. *First Author: Margarida Matias, Gustave Roussy, Université Paris-Saclay, Villejuif, France*

Background: A substantial proportion of breast, colo-rectal and prostate cancer patients (pts) can expect long term disease free survival after their primary treatment. Among those, fatigue commonly persists after diagnosis (dx) and can be debilitating. In this study, we evaluated the incidence of fatigue 2 years (y) after cancer dx and its association with health behaviors. **Methods:** We used a French population based cross-sectional study, which included a representative sample of pts from 12 cancer types (VICAN2). VICAN2 surveyed 4347 pts 2 y after dx. There is a 99% completion rate of fatigue related questions. For this study, we included 2017 pts with breast (1237), colo-rectal (348) and prostate (432) cancer without evidence of metastases at dx or relapse 2y after dx and with fatigue information. Severe fatigue was defined as average score of EORTC QLQC30 fatigue subscale ≥40 at 2y after dx. There were <1% of missing values in the evaluated covariates. Multivariate logistic regression models looked at associations of fatigue with heatlh behaviors (Δ in exercise since dx, exercise at diagnosis, body mass index (BMI), Δ since dx, smoking), age, gender, comorbidities, education, employment, cancer type, radiation, chemotherapy, hormonal therapy. **Results:** 52% of pts reported severe fatigue at 2 y after dx (median fatique score: 44, range: 0-100). 2 y after dx, 47% of pts either stopped or decrease exercise and 16% had a ≥ 10% change in BMI. Factors associated with fatigue included health behaviors (Table), but also age (adjusted odds ratio [*a*OR] for severe fatigue, 95% confidence interval [95% CI]: 0.97, 0.96-0.98), gender (*a*OR, 95 CI male vs. female: 0.5, 0.3-0.8), comorbidities (*a*OR, 95 CI yes vs. no: 2.0, 1.6-2.4) and treatment type (*a*OR, 95 CI radiation vs. no: 1.5, 1.1-2.0). **Conclusions:** Fatigue continues to be a substantial problem for cancer survivors 2 y after dx. Some factors that may contribute to persistent fatigue (health behaviors) may be amenable to interventions.

	N	% Fatigue	Adjusted odds ratio for severe Fatigue (95% confidence interval)
Δ in exercise since dx			
No	760	36	1
>than before	296	55	1.6 (1.2-2.1)
<than before or stopped	946	65	3.4 (2.7-4.3)
BMI Δ since dx			
Stable	1674	48	1
≥ or ≤10%	326	72	1.7 (1.3-2.3)

10070 Poster Session (Board #59), Sat, 1:15 PM-4:45 PM

The effect of loneliness on cancer mortality. *First Author: Simona D'ippolito, Department of Oncology, Santa Maria del Prato Hospital ULSS 1 Dolomiti, Feltre, Italy*

Background: Convergent findings indicate the need of broadening the vision of cancer beyond known prognostic factors, as many variables of different nature equally affect the course of disease. Loneliness has been found to be associated with various health outcomes, but its relationship with cancer remains unclear. Here we aimed to investigate the specific effect of loneliness and other demographic, psychological, and clinical variables on cancer mortality and to validate the Italian UCLA Loneliness Scale in cancer patients. **Methods:** This descriptive and correlational study was conducted at the Veneto Institute of Oncology in Padua. 400 patients undergoing chemotherapy from 01/2014 to 06/2015 were enrolled. The sample was stratified by sex and age (4 groups, 40-80 y). We collected demographic, clinical (site and stage of cancer, type of chemotherapy, death date), and psychosocial [self-esteem (RSE), perceived social support (MSPSS), social interaction anxiety (SIAS), personality (EPQR), and depression (BDI)] data. **Results:** GLM analyses: loneliness was higher in women than men ($F(1,398) = 7.5$, $p = .006$) and it linearly increased with age ($F(1,398) = 10.9$, $p = .001$). Loneliness was also influenced by marital status ($F(3,396) = 2.9$, $p = .037$), cohabitant offspring ($F(1,398) = 7$, $p = .008$), and educational level ($F(3,396) = 4.7$, $p = .003$), but not by clinical variables (all $ps > .05$). Correlation analyses: loneliness was inversely related to RSE ($r = -.51$), MSPSS ($r = -.52$), and extroversion ($r = -.32$), and directly related to SIAS ($r = .46$), neuroticism ($r = .43$), and BDI ($r = .44$). More importantly, a hierarchical binomial logistic regression revealed that patients' mortality was reliably predicted by gender, stage of cancer at diagnosis, time from diagnosis to UCLA collection, BDI, and UCLA (HL $\chi^2(8) = 3.53$, $p = .90$). In particular, high BDI predicted higher mortality (Wald = 11.6, $p < .001$); surprisingly, after controlling for BDI and other effects, high loneliness predicted lower mortality (Wald = 7, $p = .008$). **Conclusions:** Our results replicate prior research and reveal a surprising association between loneliness and mortality risk after partialling out the impact of, especially, depression. This suggests the role of loneliness on cancer course as an important health concern.

10071 Poster Session (Board #60), Sat, 1:15 PM-4:45 PM

Influence of patient characteristics on provider surveillance for colorectal cancer. *First Author: Joanna M. Brell, MetroHealth Medical Center Case Western Reserve University, Cleveland, OH*

Background: The majority of colorectal cancer (CRC) patients present with resectable disease and benefit from future resection of second primary CRC, local recurrence, and oligometastases. Therefore, in addition to colonoscopy one year after diagnosis, American Society of Clinical Oncology (ASCO) offers consensus recommendations to monitor serum CEA and CT scans for early detection. Limited adherence to guidelines has been reported; we explore the impact of specific patient factors related to CRC on provider prescribing in the first year. **Methods:** At a single urban safety-net hospital, electronic medical records of patients diagnosed with stages I-III CRC from 2002-2014 were reviewed with IRB approval. Chi-square tests determined extent of associations between categorical variables. Two sample t-tests compared means for continuous outcomes across groups. Cut-off for Type 1 error was alpha = 0.05. Due to minimal change in surveillance guidelines, we applied ASCO 2005 recommendations. **Results:** Records for 357 patients included 52% females and 40% African-Americans. Median age was 63 years, ever tobacco abuse was 69%. BMI > 30 found in 38%, median weight at diagnosis was 79 kg. Incidence of surveillance and associated variables are in the Table. **Conclusions:** The providers of this young, urban, almost 40% obese population were < 50% compliant with first year colonoscopy and < 60% compliant with CEA tests. Providers did significantly survey patients with co-morbidities, such as higher weight at diagnosis, in this small study. Most patients complied with orders and primary care providers were least compliant (data not shown). The data supports verification in larger study of safety-net hospitals and future comparison regarding influence of new Survivorship Care Plans on guideline adherence. To improve provider compliance, etiology of nonadherence must be addressed.

Surveillance Study	Number of Records % Completed	Variables P values < 0.05
Colonoscopy at 1st year	N = 329 46.5	Weight @ dx (0.001) Age < 55 (0.003) BMI > 30 (0.010) Ever tobacco (0.005) Hyperlipidemia (0.002)
CEA In 3-6 months of 1st year	N = 270 58.1	Weight @ dx (0.023) Stage III (0.007) Lymph nodes (0.004)
CT scan Within 1st year	N = 270 76.0	Weight @ dx (0.030) Age > 55 (0.006)

10072 Poster Session (Board #61), Sat, 1:15 PM-4:45 PM

The impact of the Affordable Care Act (ACA) on cancer survivorship. *First Author: Christine Leopold, Harvard Medical School and Harvard Pilgrim Heatlh Care Institute, Department of Population Medicine, Boston, MA*

Background: The ACA of 2010 has been recognized by the cancer community as an important step forward in insurance and payment reform, aiming to expand the number of insured patients, control costs and incentivize health care delivery system changes. In this review, we outline the ACA provisions relevant to cancer survivorship, provide available evidence for their impact, and offer insights for future research. **Methods:** We conducted a literature search in the PubMed database and grey literature. We searched the terms 'ACA and cancer survivors', which resulted in 17 articles and expanded the search to 'ACA and cancer' and found 213 articles, of which 75 were relevant for this review. We categorized the ACA provisions into three categories, 1) access to preventive care, 2) access to quality, coordinated care, and 3) coverage expansion and increased affordability. **Results:** Positive effects of the ACA were: an increased uptake of preventive services and cancer screening; a reduction in hospital admissions, increased guidelines concordance and generic prescribing through the implementation of cancer-specific Accountable Care Organizations; a reduction of unnecessary resource use (e.g. emergency visits) through the implementation of oncology patient-centered medical home models and decreases in costs though bundle payments. These results focus on the general population/cancer patients; specific studies targeting at the effects on cancer survivors are missing. In addition, evidence from literature showed that knowledge about the benefits of the ACA is low among childhood cancer survivors; while insurance coverage rates of cancer survivors, especially for childhood cancer survivors, increased. **Conclusions:** Evidence regarding the effects of the ACA on cancer survivorship care is limited, though point to greater access to preventive services and screening programs. Effects of provisions focusing on quality, coordinated care as well as coverage expansion and affordability may have beneficial effects. Whether the ACA remains or is reformed, it is critically important that decisions take into account the potential intended and unintended consequences of the ACA provisions on health outcomes and quality of life of this growing population.

10073 Poster Session (Board #62), Sat, 1:15 PM-4:45 PM

Genitourinary disease risks among 5-year ovarian cancer survivors in a population-based cohort study. *First Author: Mia Hashibe, Division of Public Health, Department of Family and Preventive Medicine, University of Utah, School of Medicine, Salt Lake City, UT*

Background: In the US, there are approximately 235,200 ovarian cancer survivors today. Five-year survival for ovarian cancer has increased from 36% for women who were diagnosed in 1975-1977 to 46% for women diagnosed between 2005-2011. Long term follow-up studies among ovarian cancer survivors are uncommon and late effects have not been well characterized in a population-based cohort. Although genitourinary complications during treatment are well known, long term impacts need to be investigated. **Methods:** A total of 602 first primary invasive ovarian cancer cases diagnosed between 1996-2012 who survived for $>$ 5 years were identified in the Utah Population Database and compared to a general population cohort of women. Genitourinary disease diagnoses were identified through ICD codes from hospital electronic medical records and statewide ambulatory surgery and inpatient data. Cox regression models were used to estimate hazard ratios for disease risks by time since cancer diagnosis with adjustments on matching factors, baseline BMI, baseline Charlson Comorbidity Index (CCI), and race. **Results:** The overall risk of genitourinary diseases for ovarian cancer patients in comparison to the general population cohort was 1.51 (95%CI = 1.30-1.74) 5-10 years after cancer diagnosis. Approximately 54.6% of ovarian cancer survivors were diagnosed with a genitourinary disease 5-10 years after cancer diagnosis. The most common genitourinary diseases among the ovarian cancer survivors were urinary tract infections (10.1%), acute renal failure (5.5%), and chronic kidney disease (4.4%). The greatest risks were observed for hydronephrosis (HR = 10.65, 95%CI = 3.68-30.80), pelvic peritoneal adhesions (HR = 5.81, 95%CI = 1.11-30.39), cystitis and urethritis (HR = 2.67, 95%CI = 1.21-6.38), and acute renal failure (HR = 2.30, 95%CI = 1.36-3.88). **Conclusions:** Ovarian cancer survivors experience increased risks of various genitourinary diseases in the 5-10 year period following cancer diagnosis. Understanding the multimorbidity trajectory among ovarian cancer survivors is of vital importance to improve their clinical care after cancer diagnosis and allow for increased attention to these potential late effects.

10074 Poster Session (Board #63), Sat, 1:15 PM-4:45 PM

Endocrine and metabolic diseases among colorectal cancer survivors in a population-based cohort. *First Author: Makenzie Hawkins, Division of Public Health, Department of Family and Preventive Medicine, University of Utah, School of Medicine, Salt Lake City, UT*

Background: Colorectal cancer is the third most common cancer among men and women in the United States. As of 2016, there were an estimated 1.4 million colorectal cancer survivors. Research on endocrine and metabolic diseases over the long term in colorectal cancer survivors is limited. Obesity is a risk factor for colorectal cancer, thus it is of interest to investigate diseases that may share this risk factor such as diabetes for long term health effects among survivors. **Methods:** A total of 7,077 colorectal cancer patients who were diagnosed between 1997 to 2012 were identified in the Utah Population Database. A general population cohort of 35,354 individuals was matched on birth year, sex, birth state and follow-up time as a comparison group. Late effects were identified using electronic medical records and statewide ambulatory and inpatient data and were assessed over three time periods of 1-5 years, 5-10 years, and $>$ 10 years. Cox proportional hazard models were used to estimate the risk of late effects after adjusting for matching factors, race, baseline body mass index, and the baseline Charlson Comorbidity Index. **Results:** Across all three time periods, late effects risk for endocrine diseases and metabolic disorders was significantly greater for colorectal cancer survivors compared to the general population cohort. Risk for diabetes mellitus with complications was significantly increased for survivors and risk was greatest for uncontrolled diabetes (HR = 5.04, 99%CI = 2.38, 10.67) and diabetes with neurological manifestations (HR = 4.10, 99%CI = 2.08, 8.26). Higher risk was also observed for thyroid disorders (HR = 3.09, 99%CI = 2.34, 4.08) and nutritional deficiencies (HR = 4.98, 99%CI = 3.47, 7.17). The risk of obesity in survivors was greatest 1-5 years post cancer diagnosis (HR = 5.04, 99%CI = 2.91, 8.75), but remained significantly increased at all follow-up time periods. **Conclusions:** Endocrine and metabolic diseases were significantly higher in colorectal cancer survivors across the follow-up periods. As the number of colorectal cancer survivors increases, understanding the long term multimorbidity trajectory is critical for improved survivorship care.

10075 Poster Session (Board #64), Sat, 1:15 PM-4:45 PM

Clinical, sociodemographic, and behavioral factors associated with cumulative burden of morbidity (CBM) among testicular cancer survivors (TCS) in the Platinum study. *First Author: Sarah L. Kerns, University of Rochester Medical Center, Rochester, NY*

Background: TCS are an important group in which to characterize late effects of cancer and its therapy given their young age at diagnosis and high cure rate. We comprehensively evaluated CBM and identified associated clinical, sociodemographic, and behavioral risk factors among TCS given cisplatin based chemotherapy in a multicenter study. **Methods:** TCS completed a comprehensive health questionnaire. Responses were grouped into 22 adverse health outcomes (AHO) and graded by severity. A CBM score was calculated based on AHO number and severity, following Geenen et al (JAMA 2007). Multivariable ordinal logistic regression examined the association of clinical, sociodemographic, and behavioral factors with CBM. Variable-based hierarchical clustering identified individual AHOs that co-occurred. **Results:** Among 1,215 TCS (median age at evaluation 38 y, range 19-68 y; time since chemotherapy 4.6 y), over 20% had a CBM score of high (17%), very high (4%) or severe (0.4%). Most TCS, however, had CBM scores of low (37%), medium (28%), very low (9%) or none (5%). In a multivariable model controlling for time since chemotherapy, older attained age (OR 1.2; 95% CI 1.1 - 1.3), being widowed/divorced/separated (OR 1.8; 95% CI 1.1 - 3.1), having less than college-level education (OR 1.7; 95% CI 1.3 - 2.2), being retired/on disability (OR 2.5; 95% CI 1.2 - 5.3), and receipt of 4 cycles of BEP vs. 4 cycles of EP or 3 cycles of BEP (OR 1.3; 95% CI 1.01 - 1.8) were associated with increased odds of a worse CBM score; vigorous exercise (OR 0.7; 95% CI 0.5 - 0.9) and non-white race (OR 0.6; 95% CI 0.4 - 0.9) were associated with decreased odds. A separate cluster analysis revealed five groups of AHOs: those known to be cisplatin-related (e.g. neuropathy, ototoxicity); metabolic abnormalities (e.g. hypercholesterolemia, diabetes); vascular damage (e.g. stroke); testicular cancer-related (e.g. hypogonadism); and other (e.g. thyroid disease). **Conclusions:** TCS with factors associated with worse CBM may be candidates for closer monitoring. If confirmed, our cluster analysis showing that groups of conditions tend to co-occur in TCS could provide guidance for survivorship care plans.

10076 Poster Session (Board #65), Sat, 1:15 PM-4:45 PM

Survivorship care plans: Recommended vs delivered care. *First Author: Karen L. Smith, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: The Committee on Cancer set a benchmark for the provision of survivorship care plans (SCP) to ≥50% of early cancer patients by the end of 2017 despite limited data indicating benefit. One hypothesis is that SCP will reduce overuse of medical care in survivors. **Methods:** We performed a retrospective review of all patients with early breast cancer (BC) who were seen by a single nurse practitioner (NP) for provision of SCP after completion of primary therapy (surgery, radiation +/- chemotherapy). We evaluated adherence to recommendations for follow-up (FU) care and testing in accordance with established guidelines. **Results:** Between August 2013 and December 2014, 152 patients received SCP after completion of primary therapy (median 2 months, range 0-27). 98% of SCP were given to patients, but only 38% were sent to primary care providers (PCP). Median FU was 23 months. Among 130 patients who did not undergo bilateral mastectomy for whom surveillance breast imaging (SBI) was recommended, 10 (8%) had 1st SBI ≥3 months earlier than time recommended (TR), 102 (78%) within 2 months of TR, 12 (9%) ≥3 months after TR, and 6 (5%) lacked confirmation of 1st SBI. Among 113 in whom 2nd SBI dates were specified, 25 (23%) had SBI ≥3 months earlier than TR, 62 (55%) within 2 months of TR, 7 (6%) ≥3 months after TR, and 18 (16%) lacked confirmation of 2nd SBI. Among 71 patients for whom first medical oncology (MO) FU visit dates are known, 64 (90%) occurred within 3 months of TR and among 81 patients for whom first radiation oncology (RO) FU visit dates are known, 67 (83%) occurred within 3 months of TR. However, among 47 patients for whom first FU visit dates with at least 2 types of providers (MO, RO and/or surgery) are known, 15 (32%) visited 2 providers within 2 months of one other. During the 1styear after completion of primary therapy, 22% underwent body imaging (CT, PET-CT, or bone scan) and 21% had liver function tests. **Conclusions:** Despite provision of a SCP to patients, PCP were often not notified and healthcare utilization exceeded recommendations. Nearly a third of patients had redundant visits, a fourth had SBI earlier than recommended, and a fifth had body imaging and lab testing. Ongoing efforts are needed to coordinate care and minimize unnecessary testing in BC survivors.

10078 Poster Session (Board #67), Sat, 1:15 PM-4:45 PM

Association of nutritional parameters and survival in parenteral nutrition-supported (PN) gastrointestinal cancer patients. *First Author: Wenli Liu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PN is a major tool in managing nutritional challenges in cancer patients. However, a clear set of clinical and biochemical indices to determine PN application in cancer patients has not been developed. We assessed the association between PN related nutritional parameters and survival in a large group of gastrointestinal (GI) cancer patients. **Methods:** 1197 consecutive GI cancer patients who received PN support between 08/01/08 – 08/01/13 were reviewed. Height, weight, plasma glucose (baseline and within 48 hours after PN initiation), surgical history, and pharmacy data including PN contents (dextrose, amino acids, and fat) and non-PN dextrose or fat in drug administration were recorded. Body mass index (BMI), Ideal body weight (IBW), PN and non-PN Calorie, and nitrogen were calculated for analysis. Data were entered into a multivariate analysis controlling for age, gender, cancer site, and medical comorbidities. **Results:** Median BMI was 25.4. 70% of the patients had unsteady weight (> 2.5% change) before PN initiation. The magnitude of weight change was inversely related to survival (HR 1.02), P < 0.001). Patients with BMI > 25 and < 7.5% weight change prior to PN initiation had the most favorable survival. Glycemic instability (maximum plasma glucose variation > 100mg/dL) was independently related to shorter survival (HR 1.53, P < 0.001). Total calorie by IBW (kcal/kg/day) (HR 0.97, P < 0.001), non-PN calorie % (HR 1.04, P < 0.001), and calorie to nitrogen ratio (kcal:g) (HR 1.02, P < 0.001) were all independently associated with overall survival. **Conclusions:** Lower BMI, weight instability, and glycemic instability were adversely associated with survival. Higher total PN calorie and amino acid support were associated with better survival. Higher non-PN calorie % was adversely related to survival. Future studies must focus on developing a set of indices incorporating independent prognostic clinical and biochemical factors in determining PN application and monitoring in cancer patients. Optimum calorie and amino acids in PN support for cancer patients also require further investigation.

10079 Poster Session (Board #68), Sat, 1:15 PM-4:45 PM

The association between mindfulness and post-operative pain in gynecologic oncology patients undergoing minimally invasive hysterectomy. *First Author: Erica Weston, Women and Infants Hospital in Rhode Island, Providence, RI*

Background: Studies demonstrate an inverse relationship between mindfulness and chronic pain. However, the relationship between mindfulness and acute post-operative pain has not yet been thoroughly investigated. The objective of this study is to determine if there is an association between pre-operative level of mindfulness and post-operative pain outcomes in women undergoing minimally invasive hysterectomy. **Methods:** For this prospective cohort study, women planning to undergo laparoscopic or robotic hysterectomy were prospectively recruited at the gynecologic oncology outpatient clinic at our institution. Baseline mindfulness was assessed at the pre-operative clinic visit using the Five Facet Mindfulness Questionnaire (FFMQ). Post-operative pain, using the Visual Numeric Rating Scale (VNRS-11), and opiate pain medication usage were evaluated via chart review and post-operative surveys completed at 1 to 2 week and 4 to 6 week post-operative clinic visits. **Results:** One hundred twenty four women completed the 6 week post-operative follow-up period, of which 80% were undergoing surgery for malignancy. Baseline mindfulness was inversely correlated with post-operative pain as measured by both the average and highest reported VNRS-11 values during the inpatient stay (r = -0.21, p = 0.019; r = -0.21, p = 0.016). At the 1 to 2 week post-operative visit, self-reported pain score was also inversely correlated with pre-operative mindfulness score (r = -0.24, p = 0.009). This relationship was not observed at the 4 to 6 week post-operative visit (r = -0.08, p = 0.403). Higher pre-operative mindfulness was also associated with lower opiate usage (r = -0.16, p = 0.077), though this relationship was not statistically significant. **Conclusions:** Higher pre-operative mindfulness is associated with more favorable post-operative pain outcomes, including lower reported numeric pain scores, in gynecologic oncology patients undergoing minimally invasive hysterectomy. This relationship provides an opportunity to target the modifiable personality characteristic of mindfulness, to improve post-operative pain in women planning gynecologic surgery.

10080 Poster Session (Board #69), Sat, 1:15 PM-4:45 PM

Exploration of risk factors for osteoporotic fracture following hematopoietic stem cell transplantation. *First Author: Huifang Lu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The incidence of fractures following hematopoietic stem cell transplantation (HSCT) ranges from 5% to 12% and the rates are up to 10 times greater than in the general population. The risk factors involved in osteoporotic fracture development following HSCT are incompletely understood. **Methods:** We conducted a retrospective cohort study of patients > 18 years that received a HSCT at MD Anderson Cancer Center, from January 1, 2001 to December 31, 2010. Patients were followed until December 31, 2013 for assessment of osteoporotic fracture occurrence using ICD-9 codes and confirmed by chart review. Cox regression model was used to identify independent risk factors for osteoporotic fractures. Factors included individual risk factors included in the World Health Organization Fracture Risk Assessment Tool FRAX and type of HSCT, type of preparatory regimen and underlying indication for HSCT. **Results:** A total of 5,170 patients received a HSCT during the 10-year study period, of which 527 (10%) patients developed an osteoporotic fracture. The median time of follow up was 3.2 years. A multivariate Cox regression model considering all clinical and malignancy specific risk factors was fitted. With the control of all other variables, the risk of developing fracture was 1.20 (95% confidence interval (CI):1.02-1.41) times higher for every 20 years increase in age at HSCT; female patients had a 1.24 (95% CI: 1.05-1.48) times higher risk compared to male patients; patients with a fracture prior to HSCT had a 2.01 (95% CI: 1.62-2.51) times higher risk compared to patients without a prior fracture; patients receiving an allogeneic HSCT had a 1.57 (95% CI: 1.20-2.05) times higher risk compared to patients receiving an autologous HSCT; and patients with multiple myeloma had a 2.62 (95% CI: 1.97-3.49) times higher risk compared to patients without multiple myeloma. **Conclusions:** Age at HSCT, gender, prior fracture status, type of HSCT, and underlying indication were identified to be statistically significantly associated with fracture. This is one of the first large scale studies assessing a comprehensive set of risk factors. To develop a risk model for fracture, we should consider these factors.

10081 Poster Session (Board #70), Sat, 1:15 PM-4:45 PM

Cardiovascular disease and preventive care among cancer survivors: A population-based study. *First Author: Kevin A. Pearlstein, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Cardiovascular disease (CVD) has been identified as a leading cause of mortality among cancer survivors, particularly long-term survivors. However, studies examining the prevalence of CVD risk factors and CVD-specific preventive care among US cancer survivors are lacking. We utilize the National Health Interview Survey (NHIS) data to address this knowledge gap. **Methods:** NHIS is an annual survey among roughly 88,000 individuals across the US, and its data are representative of US population-based estimates of health status, healthcare behavior, and healthcare utilization. 15,747 individuals surveyed from 2011 to 2015 who reported a history of cancer (except non-melanomatous skin cancer) were included in this study. Prevalence of CVD risk factors and preventive care received were calculated incorporating NHIS sample weights. A multivariable logistic regression model was used to evaluate factors associated with risk factor monitoring. **Results:** 55% of the cohort was ≥6 years out from cancer diagnosis and 53% were 65 years or older. CVD risk factors were prevalent across the entire cohort (Table). Among survivors < 50 years, 30% were active smokers, and 35% obese. Among survivors ≥65, 40% had known CVD. Among survivors with each risk factor, rates of monitoring and management of each is reported in Table. On multivariable analysis, seeing a generalist was strongly associated with monitoring of blood pressure (OR 18), cholesterol (OR 8), and fasting glucose (OR 3). **Conclusions:** This study provides the current status of preventive care among US cancer survivors, illustrating that CVD and its risk factors are common. Rates of monitoring of hypertension and hyperlipidemia are high, but there is room for improvement in interventions targeting obesity and smoking cessation.

Risk Factor	%	Management in Past Year Among Individuals with Risk Factor	%
Hypertension	53	Blood pressure check	98
Hyperlipidemia	48	Cholesterol check	94
Diabetes	18	Blood sugar check	86
Obesity	30	Moderate exercise (past month)	55
Smoking	14	Smoking cessation attempt	47

10082 Poster Session (Board #71), Sat, 1:15 PM-4:45 PM

The contribution of pre-existing cardiovascular (CV) risk factors to the risk of stroke or heart attack among non-Hodgkin lymphoma (NHL) survivors. *First Author: Talya Salz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Increased risk of myocardial infarction (MI) and cerebrovascular accident (CVA) among NHL survivors is commonly attributed to NHL treatment. The extent to which pre-existing CV risk factors also contribute to increased risk is unknown. We investigated this association among an entire national population of NHL survivors who have a full range of important CV risk factors. **Methods:** Using Danish population-based registries, we identified all adults diagnosed with primary aggressive NHL from 2000-2010 and followed them for MI and CVA from 9 months after diagnosis through 2012. MI and CVA diagnoses were ascertained from the nationwide Hospital Discharge Register and Cause of Death Register. CV risk factors (hypertension, dyslipidemia, and diabetes), vascular disease, and intrinsic heart disease prevalent at NHL diagnosis were ascertained algorithmically using the National Prescription Register and the Hospital Discharge Register. Cumulative anthracycline dose was coded continuously. Receipt of radiation was coded dichotomously for both chest and neck. Controlling for age, sex, treatment, and CV diseases, we used Cox multivariate regression to test the association between pre-existing CV risk factors and subsequent CVA or MI. **Results:** Among 2604 patients with NHL, median age was 62, and median follow-up time was 2.4 years. Overall, 131 patients were diagnosed with MI or CVA. Before NHL diagnosis, 40% of patients had at ≥1 CV risk factor, 13% had vascular disease, and 6% had intrinsic heart disease. 90% of the patients were treated with anthracyclines, 9% had received chest radiation, and 15% had received neck radiation. Patients with ≥1 CV risk factor had an increased risk of MI or CVA compared to patients with none (HR = 1.5 [95% CI = 1.1-2.2). Prevalent vascular disease, prevalent intrinsic heart disease, and NHL treatment were not associated with MI or CVA (p's > 0.05). **Conclusions:** In a large, well-characterized, and nationally representative cohort of NHL survivors, prevalent CV risk factors were associated with later CVA and MI. To prevent MI and CVA among survivors, decisions about post-treatment monitoring should take into account prevalent CV risk.

10083 Poster Session (Board #72), Sat, 1:15 PM-4:45 PM

Secondary solid tumors in patients younger than 55 with chronic lymphocytic leukemia (CLL). *First Author: Jordan Spencer Carter, Drexel University College of Medicine, Philadelphia, PA*

Background: Patients with CLL are at an increased risk of secondary solid tumors. Few studies have looked at this risk in patients < 55, despite research suggesting that this is a distinct cohort with a longer overall survival. What data does exist has yielded variable results in limited populations. In light of this, our study utilized the SEER registry to look at secondary solid tumors in patients < 55 with CLL. **Methods:** 4559 patients 15-54 years old with CLL were identified in the SEER registry between 1973 and 2013. Cancer risk was assessed using standardized incidence ratios (SIR) of observed (O) and expected (E) cancers. 95% confidence intervals (CI) were calculated assuming a Poisson distribution. Results where the CI = 1 were excluded. **Results:** 498 patients (O/E = 1.4) developed a secondary solid tumor after CLL with a mean age at diagnosis of 48.8 and 59.9 years for CLL and a second tumor, respectively. Higher than expected risk was seen in lip (O/E = 7.5), non-epithelial skin (O/E = 5.4), salivary (O/E = 4.8), mesothelioma (O/E = 4.4), melanoma (O/E = 3.1), lung (O/E = 2.4), and kidney (O/E = 1.7) cancers. Uterine cancer had a lower risk (O/E = 0.4). Stratifying the cohort by gender and race found that lip cancer in whites (O/E = 7.6) and men (O/E = 7.3), descending colon cancer (O/E = 13.3) in blacks and ureter cancer (O/E = 19.8) in women posed the highest risks. Lung cancer was the most prevalent among all groups. Secondary tumor risk was elevated in the < 1, 1-5, 5-10, and 10-15 years after diagnosis with CLL (O/E = 2.3, 1.4, 1.5, and 1.4, respectively). The cancers with the highest SIR in each period were thyroid (< 1 year, O/E = 9.2), lung (1-5 years, O/E = 3.1), nose/ear (5-10 years, O/E = 11.8), and lip (10-15 years, O/E = 15.6). In 4459 patients > 55 (O/E = 1.1), Kaposi sarcoma (O/E = 4.9), non-epithelial skin (O/E = 3.6), salivary (O/E = 2.8), melanoma (O/E = 2.1), nose/ear (O/E = 2.0), lip (O/E = 1.7), soft tissue (O/E = 1.6), lung (O/E = 1.4), kidney (O/E = 1.3), and colon cancers (O/E = 1.2) were significant. **Conclusions:** Patients < 55 have a unique tumor profile and greater risk of secondary solid tumors compared to patients > 55. This risk differs on the basis of gender, race, and survival time. Further research may help influence screening guidelines.

10084 Poster Session (Board #73), Sat, 1:15 PM-4:45 PM

Immediate-term chemotherapy-related cognitive impairment (CRCI) following administration of intravenous (IV) chemotherapy. *First Author: Omar Farooq Khan, Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada*

Background: The acute impact of chemotherapy on cognition is unknown. This study utilized performance on the psychomotor vigilance task (PVT) and trail-making test B (TMT) to assess CRCI immediately following chemotherapy administration. **Methods:** Patients aged 18-80 years receiving first-line IV chemotherapy for any stage of breast or colorectal cancer were eligible. Patients with brain metastases, neurologic disorders or allergic reactions to chemotherapy were excluded. Patient symptoms, peripheral neuropathy and Stanford Sleepiness Scale were assessed. A five-minute PVT and TMT were completed on a tablet computer pre-chemotherapy and immediately post-chemotherapy. Paired Wilcoxon Rank Sum tests were used to assess change in median PVT reaction time, TMT completion time, TMT errors and PVT lapses. A priori, an increase in median PVT reaction times by over 20 ms (approximating reaction time changes with blood alcohol concentrations of 0.04 to 0.05 g%) was considered a clinically relevant change. **Results:** 144 patients (74 breast, 70 colorectal, median age 55.5 years) were tested. Post-chemotherapy, median PVT reaction time slowed by an average of 12.4 ms ($p = 0.01$). Post-chemotherapy median PVT times slowed by over 20 ms in 59 patients (40.9%). TMT completion post-chemotherapy was faster by an average of 6.1 seconds ($p < 0.001$). No differences were seen in TMT errors ($p = 0.417$) or PVT lapses ($p = 0.845$). Change in median PVT reaction time was not associated with age, gender, number of prior chemotherapy cycles, peripheral neuropathy grade, self-reported symptoms (anxiety, fatigue or depression). Change in median PVT reaction time was also not significantly associated with use of any specific chemotherapeutic drug or class, including paclitaxel (which includes ethanol as an excipient). **Conclusions:** Median PVT reaction time was significantly slower immediately after chemotherapy compared to a pre-chemotherapy baseline, and impairment correlating to effects of alcohol was seen in 41% of patients. This effect appears independent of age, self-reported symptoms or prior chemotherapy cycles. Further studies assessing functional impact of immediate-term CRCI are warranted.

10085 Poster Session (Board #74), Sat, 1:15 PM-4:45 PM

Effect of prophylactic fentanyl buccal tablet (FBT) on exertional dyspnea in patients with cancer: A pilot double-blind, placebo-controlled, randomized trial. *First Author: David Hui, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Exertional dyspnea is one of the most common, debilitating and difficult-to-treat symptoms in cancer patients. Few clinical trials have been conducted. We tested the hypothesis that FBT, a rapid onset opioid, given prophylactically prior to exertion can improve exertional dyspnea. **Methods:** In this double-blind parallel (1:1) RCT, we asked cancer patients who were opioid-tolerant and had exertional dyspnea to complete a 6 minute walk test (6MWT) at baseline, and then randomly assigned them to either FBT proportional to 20-50% of daily dose or placebo 30 minutes before a second 6MWT. The primary outcome was a validated 11-point dyspnea NRS assessing dyspnea "now" (where 0 = none and 10 = worst possible) every minute during each 6MWT. Secondary outcomes included walk distance, vital signs and neurocognitive testing, adverse effects, and global impression. Ten evaluable patients in the FBT provided 80% power to detect an effect size as small as 1.0 using a two-sided paired t-test with a significance level of 5% to compare the change of dyspnea between the first and second walk tests. We compared the outcomes between the first and second 6MWTs using paired t-test. **Results:** Among 22 patients enrolled, 20 (91%) completed the study (9 FBT, 11 placebo). FBT was associated with a significant within-arm reduction in dyspnea NRS between 0 and 6 minutes (mean change -2.4, 95% confidence interval [CI] -3.5, -1.3) and respiratory rate (mean change -2.6, 95% CI -4.7, -0.4). Placebo was also associated with a non-statistically significant decrease in dyspnea (mean change -1.1). Between arm comparison of dyspnea scores in the second 6MWT favored FBT, albeit not statistically significant (estimate -0.25, P = 0.068). Global impression revealed more patients in the FBT group than placebo group reporting their dyspnea was at least "somewhat better" in the second 6MWT (4/9 vs. 0/11, P = 0.03). The other secondary outcomes did not differ significantly between arms. **Conclusions:** These data support our hypothesis that proportionally dosed FBT was associated with improvement in exertional dyspnea, and highlights the need for larger confirmatory trials. Clinical trial information: NCT01856114.

10086 Poster Session (Board #75), Sat, 1:15 PM-4:45 PM

Chemotherapy-induced neutropenia risk models to guide the use of myeloid stimulating factors in intermediate risk chemotherapy: A cost and practicality analysis. *First Author: Chetan Jeurkar, Drexel University College of Medicine, Philadelphia, PA*

Background: The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) have published guidelines for use of prophylactic colony stimulating factors (CSF) for patients at risk for chemotherapy induced neutropenia (CIN). Both recommend CSF if the chemotherapy regimen has a >20% febrile neutropenia (FN) risk. If the regimen is of intermediate CIN risk, the guidelines are less definitive. In this study, we looked at lung cancer patients receiving intermediate CIN risk chemotherapy and applied two risk models developed by Hosmer et al and Bozcuk et al to see if they have adjunct value to the NCCN and ASCO guidelines to more accurately predict CIN. **Methods:** This was a retrospective study of 43 patients with a diagnosis of lung cancer who were treated with chemotherapy at Drexel University from 2005-2016. Risk models developed by Hosmer et al and Bozcuk et al along with the NCCN and ASCO guidelines were applied to the cohort of patients. **Results:** The Hosmer calculator recommended giving CSF to 26 patients, the Bozuk calculator for 22 patients, the NCCN guidelines for 25 patients and the ASCO guidelines for 38 patients. Sensitivities, specificities, and pricing information for one course of filgrastim are listed for each risk model in the Table. **Conclusions:** In lung cancer patients receiving intermediate CIN risk chemotherapy, the Hosmer calculator had the best combination of sensitivity, specificity, and ease of use. The Bozcuk calculator, while accurate, was more difficult to use. The NCCN guidelines missed more patients with severe CIN while the ASCO guidelines gave CSF to the greatest number of patients. The cost for using CSF would have been highest using the ASCO guidelines. Therefore, we recommend the Hosmer calculator for lung cancer patients receiving intermediate risk CIN chemotherapy as it lends to accurate but judicious use of CSF.

Risk model	Severe CIN sensitivity	Severe CIN patients not recommended CSF	FN sensitivity	Specificity	Pricing for one course of filgrastim ($)
Hosmer	89	1	100	44	94,705.00
Bozcuk	78	2	75	56	80,135.00
NCCN	67	3	50	45	91,062.50
ASCO	97	1	100	14	138,415.00

10087 Poster Session (Board #76), Sat, 1:15 PM-4:45 PM

Impact of skeletal muscle index (SMI) loss during palliative systemic treatment (Tx) on time to progression and overall survival (OS) in metastatic colorectal cancer (mCRC) patients. *First Author: Sophie Kurk, UMC Utrecht, Utrecht, Netherlands*

Background: Evidence for a strong link between skeletal muscle depletion and poor outcomes in mCRC is growing. However, the impact of SMI changes over time on progression and OS during palliative systemic Tx is not known. The CAIRO3 study *(Simkens et al. Lancet 2015)* randomized 556 mCRC patients after 6 cycles capecitabine+oxaliplatin+bevacizumab (CAPOX-B) to maintenance CAP-B Tx (Main) vs. observation (Obs). Upon 1st disease progression (PD1), CAPOX-B or other treatment was reintroduced until 2nddisease progression (PD2). This is the first analysis using scan data of multiple time-points to investigate SMI changes during palliative systemic treatment Tx and its association with survival. **Methods:** 1227 CT-scans of a random selection of 416 CAIRO3 patients (mean age 64±9 years, Main n = 206; Obs n = 210) were analyzed for SMI (skeletal muscle area at the L3 level in cm^2/m^2). Using mixed model analysis, SMI changes were analyzed for two intervals; interval 1: from randomization to PD1, and interval 2: from PD1 to PD2. Three Cox regression models were used to study the association between SMI loss and time to PD2 and death for interval 1, and time to death for interval 2. Main and Obs groups were combined in the analyses since the p-value for interaction was not significant. Hazard ratios (HR) were reported per 2 units change in SMI. **Results:** Median times from randomization to PD1, PD2 and death were 7.7, 13.5 and 24 months resp. During interval 1 (less intensive or no Tx) patients gained SMI on average (1.2 units; *95%CI 0.6-1.8*), but 23% of patients still lost SMI. SMI loss was associated with shorter time to PD2 (HR 0.88; 0.81-0.98, *p*= .01), but not with shorter OS (HR 0.94; *0.86-1.02*, *p*= .17). During interval 2 (more intensive Tx) average SMI loss was -2.2 units (*1.5-2.8)* and 63% of patients lost SMI. SMI loss was associated with shorter OS (HR 0.73; *0.62-0.*86, *p*< .00). **Conclusions:** Loss of SMI was related to shorter time to progression during first line less intensive main Tx or obs and shorter overall survival during more intensive reinduction Tx. This large longitudinal study suggests that SMI preservation may be a therapeutic goal. Clinical trial information: NCT00442637.

10088 Poster Session (Board #77), Sat, 1:15 PM-4:45 PM

Scalp Cooling Alopecia Prevention trial (SCALP) for patients with early stage breast cancer. *First Author: Julie R. Nangia, Baylor College of Medicine, Houston, TX*

Background: Adjuvant chemotherapy decreases the risk of recurrence. However, it has distressing side effects, including alopecia. There are no randomized trials assessing modern scalp cooling to prevent alopecia, and success rates in non-randomized trials have varied. **Methods:** We conducted a multi-center randomized trial to evaluate the safety and efficacy of the Orbis Paxman Hair Loss Prevention System (OPHLPS) in reducing chemotherapy-induced alopecia. Women with stage I-II breast cancer planned to receive anthracycline- or taxane- based chemotherapy for at least four cycles were eligible and randomized in a 2:1 ratio to scalp-cooling or control. Scalp-cooling was done with the OPHLPS 30 minutes prior to, during and 90 minutes after each chemotherapy. The primary efficacy endpoints were hair preservation and device safety. We planned to enroll 235 subjects to provide 85% power to detect a 20% difference in hair preservation. Secondary endpoints included wig/scarf use and quality of life assessed by the EORTC QLQ-30, HADS and BIS. Subjects will be followed for 5 years for recurrence, overall survival, and site of recurrence. One interim analysis was planned to allow the study to stop early for efficacy after 142 subjects were enrolled and evaluable for the primary endpoint. To maintain the overall type 1 error rate, an O'Brien-Fleming spending function was used (interim boundary p = 0.0061). **Results:** This is the first randomized trial with modern scalp cooling in the world. For the interim analysis, 142 subjects were evaluable. Among them, 48 (50.5%) out of 95 in the cooling group and 0 (0%) out of 47 in the control group had hair preservation. The one-tailed p-value from the Fisher's exact test is < 0.0001, which crosses the superiority boundary (p = 0.0061). Thus on 9/26/2016 the DSMB stopped the study early. The interim analysis was presented at SABCS 2016. There are 195 subjects enrolled on this clinical trial, and the final subject will be evaluable for the primary outcome February 2017. The final analysis will be presented. **Conclusions:** Our trial showed that scalp cooling using OPHLPS is highly effective in hair retention. Paxman Coolers has applied for FDA clearance for the OPHLPS based on the results of the interim analysis. Clinical trial information: NCT01986140.

10089 **Poster Session (Board #78), Sat, 1:15 PM-4:45 PM**

Factors influencing the analgesic response over time of the oxycodone-naloxone association in painful cancer patients: GREAT study. *First Author: Oscar Corli, IRCCS - Mario Negri Institute for Pharmacological Research, Milan, Italy*

Background: The prolonged use of opioids is usually associated with the appearance of adverse events as drowsiness, constipation, nausea/vomiting, and dizziness. Some effects are self-limiting over time for the onset of tolerance while others, as constipation, persist. Clinical studies demonstrated that the association oxycodone-naloxone (OXN), reduced the constipation in the presence of unchanged analgesic efficacy. Though, the variability of the analgesic response to OXN is not explained yet. The aim of this study was to evaluate the association between the clinical and genetics factors and analgesics response at OXN. **Methods:** In this study the cancer patients with moderate to severe pain received OXN and followed for 28 days. At each visit pain intensity modifications of therapy and adverse drug reactions (ADRs) were recorded. The primary efficacy endpoint was the proportion of responders, defined as patients with a decrease of the average pain intensity from baseline to last visit ≥30% and a final average pain score≤4, measured on 0-10 numerical rating scale. Genetic tests to identify SNPs related to opioid response were performed in each patient. **Results:** 14 centers participated in the study and recruited 206 patients. Among 176 patients analyzed for a primary endpoint the mean age was 68 (SD 10); 56% were male. Average and worst pain intensity decreased from baseline to last visit from 6.2 to 2.9 and from 8.3 to 4.6 respectively. 81% of patients were responders. Digestive system tumors (p = 0.05), concomitant thyroid endocrinopathy (p = 0.023), psychological irritability (p = 0.0029) and breakthrough pain at baseline were found to decrease the risk of positive response. None of the investigated polymorphisms influenced the analgesic response. Moderate to severe intensity ADRs were mainly constipation (26%), drowsiness (19%) and dry mouth (12%). **Conclusions:** In patients with moderate to severe cancer pain, OXN showed a strong analgesic effect (about 50% pain reduction). In comparison with other studies the induced constipation appears substantially lower. Some clinical factors influence the analgesic response while none genetic polymorphisms modulate the response. Clinical trial information: NCT02293785.

10090 **Poster Session (Board #79), Sat, 1:15 PM-4:45 PM**

Phase III study of NEPA, a fixed combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV). *First Author: Li Zhang, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Co-administration of multiple antiemetics that inhibit several molecular pathways involved in emesis is required to optimize CINV control in patients receiving highly emetogenic chemotherapy (HEC). NEPA, a novel fixed combination of a highly selective NK_1 receptor antagonist (RA), netupitant (300 mg), and palonosetron (PALO 0.50 mg), a pharmacologically distinct 5-HT_3RA, has shown superior CINV prevention compared to PALO in cisplatin and AC-based settings. This study is the first head-to-head comparison of NEPA versus an aprepitant (APR)/granisetron (GRAN) regimen, with the primary objective being to demonstrate non-inferiority in preventing CINV. **Methods:** This randomized, double-blind, parallel group Phase III study conducted in an Asian population was designed to compare efficacy and safety of a single oral dose of NEPA with a 3-day oral APR/GRAN regimen in chemotherapy-naïve patients receiving cisplatin-based HEC. All patients also received oral dexamethasone (DEX) on days 1-4. The primary efficacy endpoint was complete response (CR: no emesis, no rescue medication) during the overall (0-120 h) phase. Non-inferiority was defined as a lower 95% CI greater than the non-inferiority margin set at -10%. Secondary efficacy endpoints included no emesis and no significant nausea (NSN: < 25mm on 100mm VAS). **Results:** Treatment groups were comparable for the 828 patients analyzed: predominantly male (71%); mean age 54.5 years; ECOG 0-1 (98%); lung cancer (58%). NEPA demonstrated non-inferiority to APR/GRAN for overall CR; no emesis and NSN rates favored NEPA. Most frequent study drug-related adverse events (AEs) for NEPA included constipation (8.0%) and hiccups (2.7%). The type/incidence/severity of AEs were similar for NEPA and APR/GRAN. **Conclusions:** In this first study comparing NK1RA regimens and 4 days of DEX, NEPA administered only on day 1 was non-inferior to a 3-day oral APR/GRAN regimen in preventing CINV associated with HEC.

Overall (0-120 h) % Patients	NEPA (N = 412)	APR/GRAN (N = 416)	Risk Difference % (95% CI)
CR	73.8	72.4	1.5 (-4.5, 7.5)
No Emesis	75.0	74.0	1.1 (-4.8, 6.9)
NSN	75.7	70.4	5.4 (-0.6, 11.4)

10091 **Poster Session (Board #80), Sat, 1:15 PM-4:45 PM**

Comprehensive study of risk factors for chemotherapy-induced nausea and vomiting in cancer patients receiving cisplatin-based chemotherapy: A TRIPLE pharmacogenomics study. *First Author: Hideaki Ayuhara, Tokyo Medical University Hospital, Tokyo, Japan*

Background: Chemotherapy-induced nausea and vomiting (CINV) is one of the most unpleasant adverse effects of chemotherapy. Resistance to prophylactic antiemetic treatment is problematic, with 30%–50% of patients experiencing unsatisfactory control. Younger age and female sex are well-known risk factors for CINV. Genetic polymorphisms are suggested to influence antiemetic treatment response. **Methods:** This study included a subset of patients previously enrolled in a randomised controlled trial. This study aimed to evaluate the role of pharmacogenomic polymorphisms relevant to antiemetic response in patients with cancer receiving cisplatin-based chemotherapy. The study's efficacy endpoint was the proportion of patients with complete response (CR). The study endpoint was evaluated separately in the acute ($CR_{0\text{-}24}$) and delayed ($CR_{24\text{-}120}$) phases. Thirteen polymorphisms were genotyped, and the association of these genotypes with the efficacy of prophylactic antiemetics was then investigated. Confounding variables for CR were identified using stepwise multivariate logistic regression analysis. Age and sex were included as independent variables by the forced-entry method, and the stepwise method was used to select the pharmacogenomic factors for inclusion as independent variables. **Results:** In this genetic polymorphism association study, 156 patients with solid cancer were evaluated. Multivariate logistic regression analysis revealed that *ERCC1* 8092AA (odd ratio [OR]: 11.251; 95% confidence interval [CI]: 1.741–72.712, P = 0.011) and female sex (OR = 3.630; 95% CI = 1.138–11.578, P = 0.029) were significant predictors of $CR_{0\text{-}24}$. No significant association of $CR_{24\text{-}120}$ with pharmacogenomic polymorphisms was found via multivariate logistic regression analysis. **Conclusions:** *ERCC1* polymorphism might be influenced the extent of CINV control in patients receiving cisplatin-based chemotherapy. Clinical trial information: 000009335.

10092 **Poster Session (Board #81), Sat, 1:15 PM-4:45 PM**

Morphological correlates of oxaliplatin induced peripheral neuropathy assessed by magnetic resonance neurography. *First Author: Leonidas Apostolidis, Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany*

Background: Oxaliplatin induced peripheral neuropathy (OXA-PNP) is a frequent side effect of oxaliplatin containing chemotherapy protocols. It is commonly assessed clinically via physical examination and patient reported symptoms. Research has been impeded by the lack of objective tests to quantify OXA-PNP. Neurophysiological examination is time-consuming and can only cover a selected part of the examined nerve. The aim of this study was to investigate *in-vivo* morphological correlates of OXA-PNP by magnetic resonance neurography (MRN). **Methods:** 20 patients with mild to moderate OXA-PNP and 20 matched controls were prospectively enrolled. All patients underwent a detailed neurophysiology examination prior to neuroimaging. A standardized MRN imaging protocol at 3.0 Tesla with large-coverage included the lumbosacral plexus, as well as both sciatic nerves and their branches using T2-weighted fat-saturated sequences at high resolution. Qualitative evaluation of sciatic, tibial, and peroneal nerves were performed by two readers regarding the presence, degree, and distribution of nerve lesions. Quantitative assessment included volumetry of the dorsal root ganglia (DRG) and sciatic nerve normalized T2 (nT2) signal and caliber. **Results:** Significant DRG hypertrophy in OXA-PNP patients ($207.3 \pm 47.7 mm^3$ vs. $153.0 \pm 47.1 mm^3$ in controls, p = 0.001) was found as morphological correlate of the sensory neuronopathy. Peripheral nerves only exhibited slight morphological alterations qualitatively. Quantitatively, sciatic nerve caliber was unchanged ($26.0 \pm 5.1 mm^2$ vs. $27.4 \pm 7.4 mm^2$, p = 0.19) while sciatic nerve nT2 signal was slightly and non-significantly elevated in patients (1.32 ± 0.22 vs. 1.22 ± 0.26, p = 0.19). **Conclusions:** OXA-PNP leads to morphological correlates that can be detected *in-vivo* by MRN. Significant hypertrophy of the DRG was observed, a phenomenon which has not been described in OXA-PNP previously. DRG volume should be investigated as a biomarker in other sensory peripheral neuropathies and ganglionopathies as well as in studies evaluating neuroprotective strategies for OXA-PNP.

10093 Poster Session (Board #82), Sat, 1:15 PM-4:45 PM

Two-year trends of taxane-induced neuropathy in women enrolled in a randomized trial of acetyl-l-carnitine (SWOG S0715). *First Author: Dawn L. Hershman, Columbia University Medical Center, New York, NY*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and disabling side effect of taxanes that leads to suboptimal treatment and adversely affects quality of life. Acetyl-L-Carnitine (ALC) was unexpectedly found to increase CIPN in a randomized trial. We investigated the long-term patterns of CIPN among patients enrolled in this trial. **Methods:** S0715 was a randomized, double-blind, multi-center trial comparing ALC (1000 mg TID) versus placebo for 24 weeks in women with stage I-III breast cancer undergoing taxane-based chemotherapy. The primary objective was to determine if ALC prevents CIPN as measured by the 11-item neurotoxicity (NTX) component of the FACT-Taxane scale at 12 weeks. Additional assessments were conducted at weeks 24, 36, 52 and 104. We examined the reduction of NTX score over 2 years using linear mixed models for longitudinal data, adjusting for stratification factors and the baseline NTX score. Individual assessment time-points were examined using linear regression. **Results:** SWOG S0715 registered 437 patients, of whom 409 were eligible and evaluable, including 208 assigned to receive ALC and 201 to placebo. Patterns of evaluability were similar over time by arm. The results for the primary outcome of interest, NTX, show a statistically significant ($p = 0.01$) average difference of -1.39 (95% CI: -2.47 to -0.31) between treatment groups, with the ALC group having lower scores (worse CIPN) on average than the placebo group. These differences were particularly evident at Weeks 24 ($p = 0.02$), 36 ($p = 0.04$), and 52 ($p = 0.02$). A clinically meaningful ($\geq$5 points) reduction in NTX score over baseline was observed more frequently for the ALC vs. control arm (week 24, 41% vs. 34%; week 36, 41% vs. 28%; 1 year, 41% vs. 32%; 2 years, 40% vs. 34%). For both treatment groups 2 year NTX scores were significantly different compared to baseline ($p < 0.001$). **Conclusions:** For both groups NTX scores were reduced with taxane-therapy and remained persistently low 2-years following treatment. Twenty-four weeks of ALC therapy resulted in significantly worse CIPN at weeks 24 36 and 52. Understanding the mechanism of this persistent effect may inform prevention and treatment strategies. Clinical trial information: NCT00775645.

10094 Poster Session (Board #83), Sat, 1:15 PM-4:45 PM

RCT of brief behavioral therapy (BBT-CI) for cancer-related insomnia and circadian rhythm during chemotherapy in a community oncology setting (NCORP). *First Author: Oxana Palesh, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA*

Background: Insomnia is experienced by up to 80% of cancer patients, and it frequently co-occurs with circadian rhythm disruption. The relationship is reciprocal in that disruption in circadian rhythm can cause or result from insomnia and vice versa. There are no effective brief behavioral interventions that can be delivered directly in infusion centers. We aimed to evaluate the efficacy of a novel intervention, BBT-CI, for improving sleep and circadian rhythm disruption in BC patients undergoing chemotherapy. **Methods:** In our phase II, two-arm, randomized clinical trial, 71 BC patients (mean age = 52.5) who reported moderate insomnia were randomized to: 1) BBT-CI or 2) a healthy eating behavioral control (HEAL). BBT-CI and HEAL were delivered over 6 weeks (2 face-to-face sessions + 4 phone calls) at 5 NCI-funded NCORP clinics by trained assistants. Sleep disruption was measured with the Insomnia Severity Index (ISI) and circadian rhythm with the Actiwatch-64 (Mesor, Amplitude, and Acrophase for 12- and 24-hour cycles). Participants completed the ISI at baseline and post-intervention and wore the Actiwatch for 7 days prior to each visit. **Results:** The study showed excellent feasibility and acceptability of BBT-CI as reflected by a recruitment rate of over 75% and an intervention adherence of 74%, with 75% of intervention components successfully delivered by trained community staff. ANCOVA results indicate that patients who received BBT-CI exhibited improvements in insomnia compared to HEAL at post-intervention ($p = .049$) and at 1-month follow-up ($p = .002$). Furthermore, results reveal a significant treatment effect in circadian rhythm at post-intervention for 24-hour amplitude ($p = .009$) and 12-hour Acrophase ($p = .012$) as well as a trend for Mesor in favor of BBT-CI ($p = .10$). **Conclusions:** BBT-CI demonstrated greater improvements in insomnia and circadian rhythm than HEAL. In addition, this novel intervention has shown efficacy in community oncology clinics. BBT-CI has the potential of changing clinical practice as it reduces patients' psychophysiological symptoms and burden due to its behavioral design and capacity to be delivered directly in infusion centers. Clinical trial information: NCT02002533.

10095 Poster Session (Board #84), Sat, 1:15 PM-4:45 PM

A longitudinal brain fMRI study of chemotherapy-induced peripheral neuropathy in 50 breast cancer patients. *First Author: Ian Kleckner, University of Rochester Medical Center, Rochester, NY*

Background: Over half of patients receiving taxane, platinum, and vinca alkaloid chemotherapy experience chemotherapy-induced peripheral neuropathy (CIPN), which involves numbness and neuropathic pain in the hands and feet. CIPN has no effective treatments partly because its etiology is poorly understood. We theorize that CIPN symptoms are partly caused by impairment of interoceptive brain circuitry, which processes bodily sensations via the posterior insula and anterior cingulate cortex (ACC). We investigated whether CIPN is associated with altered connectivity in interoceptive brain circuitry. **Methods:** Fifty women with breast cancer (50$\pm$9 years) reported CIPN symptoms (CIPN-20) and underwent resting fMRI one or more times: before surgery, one month after completion of chemotherapy, and one year after chemotherapy. We used an a priori seed-based investigation of connectivity between the posterior insula and ACC. We compared connectivity between 31 patients without CIPN symptoms ($\leq$10 CIPN-20-Sensory), 19 patients with CIPN symptoms ($>$ 10 CIPN-20-Sensory), and 280 healthy adults (174 women, 19.3 years) from another study. **Results:** Patients with CIPN symptoms had significantly reduced connectivity between the posterior insula and the ACC compared to patients without CIPN symptoms ($p = 0.01$, $d = 0.73$). Connectivity between the posterior insula and the ACC was negative in patients with CIPN symptoms but positive in both healthy adults and patients without CIPN symptoms. **Conclusions:** CIPN is characterized by reduced connectivity in interoceptive brain circuitry. Interoceptive networks may be a target for the development of therapies directed to prevent or treat CIPN. Future work will assess causal relationships between CIPN symptoms and reduced connectivity.

10096 Poster Session (Board #85), Sat, 1:15 PM-4:45 PM

A genome-wide association study (GWAS) meta-analysis of chemotherapy-associated cognitive impairment (CACI) in Asian early-stage breast cancer patients (ESBC). *First Author: Terence NG, Department of Pharmacy, National University of Singapore, Singapore, Singapore*

Background: Genetic variations among genes regulating neuronal function, neurotransmission and plasticity may contribute to varying risk of CACI. In order to fully elucidate the complex genetic structure underlying CACI, a GWAS meta-analysis was performed to identify genetic variants associated with CACI among ESBC patients. **Methods:** A GWAS meta-analysis of two independent cohorts totaling 266 chemotherapy-receiving ESBC patients (mean age: 51.0 $\pm$ 9.2 years; 80.8% Chinese) was performed. Patients' self-perceived cognitive function was assessed using the validated FACT-Cog (v.3). Genome-wide genotyping was performed using the Illumina HumanOmniExpress-24 version 1.1 BeadChips kits. Each beadchip contains over 700,000 genetic markers. Covariates included in the meta-analysis were the first two dimensions of the multi-dimensional scaling. **Results:** After applying stringent quality control measures and removing four population outliers, data from 546,399 SNPs were available for 84 cases and 170 controls. In the meta-analysis, two SNPs (rs6443264 and rs4686371) exceeded the suggestive threshold of $P < 1\times10^{-5}$ (Table). Following adjustment for the first two MDS dimensions in the meta-analysis, both SNPs remained as top two SNPs with $P < 1\times10^{-4}$. Both rs6443264 and rs4686371 are located in chromosome 3p25 and lie in the intronic regions encoding *OGG1* and *ARPC4* genes, respectively. Alteration of the *OGG1* gene could compromise the functions of downstream neuronal genes, and modification of the *ARPC4* gene could affect the formation of the actin-related protein 2/3 complex and impair memory formation. **Conclusions:** To the best of our knowledge, this is the first GWAS meta-analysis to identify two loci, namely rs6443264 and rs4686371 that are suggestive of genome-wide association with CACI among Asian ESBC patients.

SNP	Cohort	MAF cases	MAF controls	P	Per allele OR	95% CI
rs6443264	A	0.57	0.29	1.70×10^{-5}	3.26	1.89 to 5.64
	B	0.51	0.37	3.19×10^{-2}	1.79	1.05 to 3.08
	Meta-analysis			7.21×10^{-6}	2.41	1.64 to 3.53
rs4686371	A	0.59	0.31	1.18×10^{-5}	3.32	1.93 to 5.74
	B	0.53	0.39	4.18×10^{-2}	1.74	1.02 to 2.98
	Meta-analysis			7.99×10^{-6}	2.39	1.63 to 3.50

10097 **Poster Session (Board #86), Sat, 1:15 PM-4:45 PM**

Body weight response with anamorelin in advanced non-small cell lung cancer (NSCLC) patients with anorexia/cachexia: Pooled analysis of two phase III trials. *First Author: David Christopher Currow, IMPACT, Faculty of Health, University of Technology, Sydney, Australia*

Background: Anorexia/cachexia commonly occurs in patients with advanced NSCLC and is associated with increased morbidity and mortality. In two randomized, double-blind, placebo-controlled phase 3 trials in NSCLC patients with cachexia, the ghrelin receptor agonist anamorelin was well tolerated and significantly increased body weight, lean and fat mass, and anorexia/cachexia symptom burden over 12 weeks compared to placebo (Temel J. *Lancet Oncol*. 2016). Since an involuntary weight loss of $\geq$ 5% is an established diagnostic criterion for cancer anorexia/cachexia, an analysis was conducted to assess the proportion of patients with $\geq$ 5% increase in body weight. **Methods:** NSCLC patients [ROMANA 1 (NCT01387269; N = 484) and ROMANA 2 (NCT01387282; N = 495)] with stage III/IV disease and cachexia (BMI $<$ 20 kg/m^2 or $\geq$ 5% weight loss during prior 6 months) were randomized 2:1 to receive 100 mg once daily oral anamorelin or placebo up to 12 weeks. A pooled analysis was conducted post-hoc in the modified intent-to-treat population (N = 829) to measure the proportion of patients with $\geq$ 5% increase in body weight at the end of study (or last observation carried forward since week 6 or 9). **Results:** The percentage of patients with $\geq$ 5% increase in body weight at the end of study was significantly higher in the anamorelin arm (N = 188/552, 34.1%) compared to placebo (N = 37/277; 13.4%). Among patients with BMI $<$ 20kg/m^2 at baseline (N = 182), 47.3% (N = 53/112) of anamorelin patients had a weight increase of $\geq$ 5% compared to 17.4% (N = 12/69) in the placebo arm. In both cases the nominal p-value was lower than 0.0001. **Conclusions:** Data from two published large pivotal studies in advanced NSCLC patients with anorexia/cachexia suggest that anamorelin treatment effect size on body weight is clinically relevant, as shown by the higher response rate achieved when the stringent cut-off of $\geq$ 5% weight gain was applied. The proportion of patients with BMI $<$ 20kg/m^2 that benefited from anamorelin treatment was greater than the proportion of patients who benefited in the entire study sample, suggesting that patients with more advanced cachexia may still benefit from anamorelin treatment. Clinical trial information: ROMANA 1: NCT01387269; ROMANA 2: NCT01387282.

10098 **Poster Session (Board #87), Sat, 1:15 PM-4:45 PM**

Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. *First Author: Paolo Pedrazzoli, Medical Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

Background: The benefit of systematic use of oral nutritional supplements (ONS) in addition to nutritional counseling in head and neck cancer (HNC) patients undergoing radiotherapy (RT) has not still been properly assessed. **Methods:** In a single-center, randomized, pragmatic, parallel-group controlled trial (ClinicalTrials.gov: NCT02055833; February 2014 - August 2016), 159 newly diagnosed HNC patients suitable for to RT regardless of previous surgery and induction chemotherapy were randomly assigned to nutritional counseling in combination with omega-3 enriched ONS (N = 78) or without ONS (N = 81) from the start of RT and continuing for up to 3 months after its end. The primary endpoint was the change in body weight at the end of RT. Secondary endpoints included changes in protein-calorie intake, muscle strength, body composition and quality of life (EORTC-QLQ-C30) over the study time points and anti-cancer treatment tolerance. **Results:** In patients in whom all the variables could be assessed, counseling plus ONS (N = 67) resulted in smaller loss of body weight than nutritional counseling alone (N = 69; mean difference, 1.6 kg [95%CI, 0.5 to 2.7]; P = 0.006). Imputation of missing outcomes provided consistent findings. In the ONS-supplemented group, higher protein-calorie intake and improvement in quality of life over time were also observed (P $<$ 0.001 for all). The use of ONS reduced the need for changes in scheduled anti-cancer treatments (i.e. for RT and/or systemic treatment dose reduction or complete suspension, HR = 0.40 [95%CI, 0.18 to 0.91], P = 0.029). Nine patients reported gastrointestinal intolerance to ONS. **Conclusions:** In HNC patients undergoing RT or RT plus systemic treatment, and receiving nutritional counseling, weight loss could not be completely prevented, but the use of ONS resulted in better weight maintenance, increased protein-calorie intake, improved quality of life and better anti-cancer treatment tolerance. Clinical trial information: NCT02055833.

10099 **Poster Session (Board #88), Sat, 1:15 PM-4:45 PM**

Use of heart rate variability (HRV) biofeedback for symptom management among cancer survivors. *First Author: Mark Allen O'Rourke, Center for Integrative Oncology and Survivorship, Greenville, SC*

Background: Late effects of cancer and its treatment include pain, fatigue, stress, and depression all mediated by autonomic dysfunction. Heart Rate Variability (HRV) coherence is an established measure of autonomic dysfunction. Cancer survivors have lower HRV coherence than normal controls. HRV biofeedback (HRV-B) training improves HRV coherence, restores autonomic health, and reduces the above symptoms. This report describes a feasibility study of HRV-B in symptomatic cancer survivors. **Methods:** In a randomized, waitlist controlled, clinical trial, 179 were screened, 34 enrolled and 31 completed the protocol. Participants in the intervention arm received weekly HRV-B training up to six weeks. Outcome measures assessed at baseline (pre) and after week six (post) included HRV coherence plus Insomnia Symptom Questionnaire (ISQ), Suscro Distress Inventory (SDI), Brief Pain Inventory (BPI), Multi-Dimensional Fatigue Inventory (MFI), Perceived Stress Scale (PSS) and Beck Depression Inventory II (BDI-II). **Results:** See table below. **Conclusions:** Delivering HRV Biofeedback training to cancer survivors is feasible at our Cancer Institute. This pilot study provides preliminary evidence that HRV-B for cancer survivors improves HRV coherence and reduces insomnia, pain, fatigue, depression, and stress. The intervention has great potential and further research is indicated.

Intent to treat	HRV-B (N=17)	Waitlist Control (n=17)	P value, One tail	Intervention Trend
	Pre Post	Pre Post		
HRV Coherence	.387 .853	.396 .335	.022	Improved
PSS	17.3 12.5	19.0 17.2	.020	Improved
BDI-II	12.8 5.70	16.3 13.9	.006	Improved
MFI general	12.4 10.5	14.8 14.0	.005	Improved
MFI physical	11.6 10.5	13.4 12.4	.097	Improved trend
MFI reduced activity	9.38 6.54	10.9 9.25	.019	Improved
MFI mental	11.3 10.0	13.7 13.4	.003	Improved
BPI severity	2.71 2.18	2.66 2.61	.302	
BPI interference	2.37 1.66	3.40 3.15	.041	Improved
SDI (distress)	16.1 10.1	20.4 18.1	.007	Improved
ISQ sleep symptoms	14.6 8.4	16.5 18.1	$<$.001	Improved
ISQ daytime impair	11.2 5.4	12.6 12.6	.005	Improved

10100 **Poster Session (Board #89), Sat, 1:15 PM-4:45 PM**

Minocycline to reduce cancer pain in patients with multiple myeloma: A phase II randomized trial. *First Author: Xin Shelley Wang, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients with multiple myeloma (MM) experience substantial pain that may be from disease and/or post autologous stem cell transplant condition, and exacerbated by maintenance therapy. Minocycline is a readily available, low-cost antibiotic with anti-inflammatory properties. We conducted a phase II randomized, double-blinded, placebo controlled clinical trial to investigate the effect of minocycline in reducing patient-reported symptoms during maintenance therapy. **Methods:** Adults with MM scheduled for maintenance therapy at a single-institution were consented and randomized to receive either minocycline (100 mg twice daily) or placebo over the first 3 cycles maintenance therapy. Feasibility, toxicity, and patient-reported outcome data were prospectively collected. The MD Anderson Symptom Inventory-MM (0–10 scale) was used to assess pain and other symptoms weekly during 3 months trial. The longitudinal analysis for pain was compared between the minocycline and control groups to examine minocycline's efficacy. **Results:** From April 2013 to Aug 2016, 88 patients were enrolled and 69 (78%) were evaluable: 33 were randomized to minocycline and 36 to placebo. There were no grade 3+ study medication-related adverse events. The worst 5 symptoms on MDASI-core during the trial were fatigue, pain, numbness/tinging, drowsiness, and disturbed sleep, followed by two MM module item bone aches and muscle weakness. Demographic and disease characteristics were not significantly different between groups. Longitudinal modelling of revealed a significant reduction on pain in minocycline group than placebo group (time and treatment group interaction, estimate=-0.068, *P*=.003). The favorite pain reduction in minocycline group vs placebo arm was represented by a moderate effect size (Cohen's *d* =0.48). **Conclusions:** Minocycline during maintenance therapy for MM was feasible, had a low toxicity profile, and yielded a statistically significant positive signal on pain reduction. These preliminary results are encouraging and warrant a Phase III trial to test its efficacy. Clinical trial information: NCT01793051.

10101 **Poster Session (Board #90), Sat, 1:15 PM-4:45 PM**

Elsiglutide in the primary prevention of chemotherapy (CT)-induced diarrhea in patients with colorectal cancer (CRC) receiving 5-fluorouracil (5-FU)-based CT: A multinational, randomized, double-blind, placebo-controlled study. *First Author: Meinolf Karthaus, Hematology and Onkology, Klinikum Neuperlach, Munich, Germany*

Background: Diarrhea is a burdensome toxicity of 5-FU-based regimens and may lead to CT dose intensity reduction. We investigated the efficacy of 3 subcutaneous (s.c.) doses of elsiglutide (a GLP-2 analog) vs. placebo and vs. each other, in the primary prevention of CT induced diarrhea in patients (pts) with CRC receiving FOLFOX or FOLFIRI. **Methods:** Pts were randomized equally to receive placebo or elsiglutide 10, 20, or 40 mg s.c. on days (d)1–4 of the first 2 CT cycles and were followed up in cycle 3 for safety only. Stratification factors were CT regimen and country. Primary endpoint was the proportion of pts with diarrhea of CTC grade ≥2 in cycle 1. Changes in plasma levels of citrulline, a marker of intestinal mass, from baseline to d5 and d14 of each cycle were analyzed. With 480 pts randomized, the study had 85% power to detect a 15% difference vs. placebo for each dose at an alpha level of 0.1, assuming a 20% frequency of diarrhea CTC grade ≥2 in the placebo arm. **Results:** Treatment groups were comparable for the 484 pts (142 receiving FOLFIRI) who were randomized to receive placebo (n = 123), elsiglutide 10 mg (n = 120), 20 mg (n = 121), or 40 mg (n = 120), respectively. The proportion of pts with diarrhea CTC grade ≥2 was higher with placebo (10%) than with elsiglutide 10 mg (3%), 20 mg (5%) and 40 mg (6%); differences were not statistically significant. A similar pattern was observed in cycle 2. Differences in diarrhea frequency between placebo and elsiglutide groups were pronounced in the FOLFIRI subgroup (cycle 1: 18% with placebo, 6% with 10 mg and 20 mg; 3% with 40 mg elsiglutide). Reduction of citrulline levels was smaller with elsiglutide compared with placebo. The safety profile of all elsiglutide doses was acceptable with few related injection site reactions, mostly at the highest dose. **Conclusions:** Although a lower frequency of diarrhea CTC grade ≥2 was observed with elsiglutide, this difference was not statistically significant in pts receiving FOLFOX or FOLFIRI for CRC. Interpretation must consider the unexpectedly low reported frequency of diarrhea of grade ≥2, particularly with FOLFOX regimens. Clinical trial information: 2014-000998-39.

10102 **Poster Session (Board #91), Sat, 1:15 PM-4:45 PM**

Genomic risk prediction of aromatase inhibitor-related arthralgias (AIA) in breast cancer (BC) patients using a novel analytical algorithm (NAA). *First Author: Raquel E. Reinbolt, The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH*

Background: Many BC patients treated with aromatase inhibitors (AIs) develop AIA; 20% have symptoms severe enough to effect treatment compliance. Results of candidate gene studies to identify AIA risk are limited in scope. In this case-controlled study, we evaluated the potential of a NAA to predict AIA using germline single nucleotide polymorphism (SNP) data obtained prior to treatment initiation. **Methods:** Systematic chart review of 700 AI-treated patients with stage I-III BC between 2003-2012 identified asymptomatic patients (n = 39) and those with clinically significant AIA resulting in AI termination or therapy switch (n = 123). Germline DNA was obtained from peripheral blood cells and SNP genotyping performed using the Affymetrix UK BioBank Axiom Array to yield 695,277 SNPs. The identity of the cluster of SNPs that most closely defined AIA risk was discovered using an NAA that sequentially combined statistical filtering and a machine learning algorithm. NCBI PhenGenI and Ensemble databases were used to define gene attribution of the 200 most discriminating SNPs. Phenotype, pathway, and ontologic analyses assessed functional and mechanistic validity. **Results:** Cases and controls were similar in demographic characteristics. A cluster of 70 SNPs, correlated to 57 genes (accounting for linkage disequilibrium), was identified. This SNP group predicted AIA occurrence with a maximum accuracy of 75.93%. Strong associations with arthralgia, breast cancer, and estrogen phenotypes were seen in 19/57 genes (33%) and were functionally and ontologically consistent. **Conclusions:** Using a NAA, we identified a 70 SNP cluster that predicted AIA risk with fair accuracy. Phenotype, functional, and pathway analysis of attributed genes was consistent with clinical phenotypes. This study is the first to link a specific SNP/gene cluster to AIA risk independent of candidate gene bias. An ongoing prospective companion study will be used to validate and to expand upon results.

10103 **Poster Session (Board #92), Sat, 1:15 PM-4:45 PM**

A double blind, randomised placebo controlled trial evaluating the effect of a pholyphenolic rich plant based nail bed balm on the severity of chemotherapy-induced onycholysis. *First Author: Robert J. Thomas, Addenbrooke's Hospital, Cambridge, United Kingdom*

Background: Nail damage is common amongst patients receiving chemotherapy, especially taxanes, causing pain, distress, disfigurement, infection and restricted daily activities. Cooling the nail beds helps but there has been no published evidence for the effectiveness of nail balms, despite their popular use. We investigated whether a topical nail bed balm containing bioactive polyphenolic rich African salvia officinalis, gaultheria procumbens in a natural base of olea europaea, butyrospermun parkii, cera alba and theobroma cacao protected the nail beds via their reported anti-inflammatory, analgesic, anti-oxidant and anti-microbial properties. **Methods:** 60 patients (23 male, 37 female) were randomized to apply to their nail bed (tds) the natural balm or a petroleum balm suitably scented for a placebo control. Demographics, type and number of chemotherapy cycles did not differ between the two groups, recruited between Sept 2016-Sept 2017. At baseline and at the end of chemotherapy both patients and physicians measured outcomes of nail health. Patients completed a *Dermatology Life Quality* questionnaire and a linear severity scale; physician completed a *Nail Psoriasis Index* (NPSI) and a linear severity scale based on clinical examination and photographs. Differences were analyzed using an unpaired t-test; significance level $\alpha = 0.05$ at 95% confidence intervals (CI); probability (p). **Results:** The mean change in nail health outcomes over the course of chemotherapy were: (see table). **Conclusions:** The polyphenolics rich essential oils and plant-based waxes in this nail bed balm profoundly reduced chemotherapy related nail damage and improved nail related quality of life compared to a plain petroleum based balm. A future evaluation combining nail bed cooling and this natural balm is planned. Clinical trial information: 015-001866-24.

Nail Health Outcome	Natural balm	Placebo	Difference	CI	P value
Dermatology Life Quality (Patient)	-0.034	-6.1	6.062	4.17 - 7.95	P<0.00001
Linear Severity Scale (Patient)	+2.63	-64.1	66.72	52.97 - 80.47	P<0.00001
NSPI (Physician)	0.0	-5.71	5.71	4.29 - 7.12	P<0.00001
Linear Severity Scale (Physician)	-5.79	-66.1	60.3	45.29 - 75.32	P<0.00001

10104 **Poster Session (Board #93), Sat, 1:15 PM-4:45 PM**

Next-generation sequencing ordering trends in the cancer trajectory. *First Author: Joseph Ma, Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA*

Background: Next-generation sequencing (NGS) molecular tumor profiling is increasingly being ordered for advanced cancer patients to evaluate non-traditional therapeutic options. The timing of when NGS is ordered relative to date of diagnosis, palliative care (PC) consultation, and death remains unknown. The primary objective of this study was to examine NGS ordering patterns among cancer patients. **Methods:** This was a single center, retrospective data analysis in cancer patients at our institution between January 2011 and February 2016. Cancer patients ≥16 yrs of age were identified from a tumor registry and matched to an existing NGS tumor profiling database. Additional data were collected from an electronic medical record and compiled into a single database. Differences in the date of when NGS was ordered compared to date of diagnosis, PC consultation, and/or date of death were determined. A Mann-Whitney rank sum test examined differences in patients where NGS was ordered relative to the date of PC consultation. Logistic regression examined variables possibly associated with PC consultation. **Results:** Analysis included 1596 (807 women) cancer patients. Mean±SD age was 55.5±15.2 years, 30.8% (n = 492) of patients had metastatic disease, with breast and lung the most common cancers. The difference between date of cancer diagnosis and date of NGS order was 1053.6±1568.5 days (n = 1546). The difference between date of NGS order and date of death was 221.2.4±186.6 days. Two-hundred and fifty-one patients (15.7%) received a PC consultation, of which 82 patients had a NGS order before the PC consultation and 169 patients had a NGS order after the PC consultation. The mean difference in number of days between a NGS order before versus after a PC consultation was 147.3±216.8 vs. 179.8±169.7 days ($p < 0.005$). Four-hundred and sixty-six (29%) patients have died with 121 receiving a PC consultation. Metastatic disease, but not age and sex, was associated with PC completion (OR 1.7; 95%CI 1.27-2.21). **Conclusions:** NGS was frequently ordered near the time of death. PC consultations were completed in a minority of patients. NGS ordering in advanced cancer patients may serve as a trigger for PC consultation.

10105 Poster Session (Board #94), Sat, 1:15 PM-4:45 PM

Phase II study of the effect of the topical corticosteroid fluocinonide in patients on endocrine therapy for breast cancer or breast cancer prevention with symptoms of vaginal dryness and dyspareunia. *First Author: Evthokia A. Hobbs, Oregon Health & Science University, Portland, OR*

Background: Gynecologic symptoms and sexual dysfunction from endocrine therapy are troublesome side effects for a significant number of patients. This study explored amelioration of vaginal dryness and dyspareunia with fluocinonide cream, a strong topical corticosteroid. **Methods:** A single-arm, open-label phase II trial of topical fluocinonide 0.05% cream to improve vaginal symptoms in women on endocrine therapy in the adjuvant setting for early stage breast cancer was performed. Patients with vaginal symptoms applied topical vaginal fluocinonide 0.05% cream twice a day for two weeks then once daily for two weeks. Patients were assessed for symptoms by weekly completion of the Mayo/North Central Cancer Treatment Group Patient Pretreatment Questionnaire. The primary outcome was a change from baseline in patient-reported effects of vaginal dryness and dyspareunia on a scale from 0 (no symptoms) to 4 (very severe symptoms) from time of enrollment and at 4 weeks. Secondary outcomes were decrease in vaginal itching and total vaginal index score. Comparisons were made with Wilcoxon sign rank test with 2.5% significance level. **Results:** Thirty-four women were accrued. At 4 weeks compared with baseline, vaginal dryness improved from a median score of 2 (moderate symptoms) to 0 (no symptoms) ($P <$ .001) and dyspareunia from 3 (severe symptoms) compared with 1 (mild symptoms) (P = .002). Percentage of patients who had $>$ 2 point improvement in vaginal dryness and dyspareunia was 69.0% and 75% respectively. Secondary analysis showed decrease in vaginal itching score from 1 to 0 (P = .001) and vaginal index score of 6 to 1 (P = .002). Twenty-one patients experienced low-grade toxicities which were mostly limited to skin irritation. **Conclusions:** Fluocinonide 0.05% cream improves vaginal dryness and dyspareunia experienced by women receiving endocrine therapy and has the potential to improve quality of life of cancer survivors and compliance of endocrine therapy. Clinical trial information: NCT00297011.

10106 Poster Session (Board #95), Sat, 1:15 PM-4:45 PM

The impact of caregiver's role preference on decisional conflicts and psychiatric distresses in decision making to help caregiver's disclosure of terminal disease status. *First Author: Shin Hye Yoo, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea*

Background: A decision aid (DA) increases knowledge, decreases decisional conflicts and regrets and improves post-decision satisfaction, emotional distress. However, few DA trials have revealed whether decisional role preferences have an impact on patient-reported outcomes by decision making. The objective of this study was to investigate the impact of caregiver's decisional role preference on decisional conflicts and psychiatric distresses in decision making. **Methods:** 406 of 444 caregivers of terminally ill cancer patients enrolled onto a previous trial determining the efficacy of the decision aid about disclosure of terminal disease status were included in this analysis. The analysis outcomes were change score of decisional conflicts using the Decision Conflict Scale (DCS) and depression and anxiety using the Hospital Anxiety and Depression Scale (HADS) at 1 and 3 months from baseline. Participants were divided into 4 groups: active caregiver who received DA (active-DA), active caregiver in control group (active-control), passive caregiver who received DA (passive-DA), and passive caregiver in control group (passive-control). Linear mixed model was conducted to find out the impact of caregiver's decisional role preference on the DCS and the HADS. **Results:** Among 406 caregivers, 137 (33.7%) showed active role preference, and 269 (66.3%) showed passive role preference. In post-hoc analysis of adjusted differences of change scores between passive-DA and active-DA groups, non-significant differences were observed in DCS. However, at 3 months, change scores of HADS depression subscale increased as 4.43 (95% confidence interval (CI), 0.78-8.07; $P<$ 0.007; effect size (ES) 0.71) and those of HADS anxiety subscales increased as 4.14 (95% CI, 0.37-7.91; P= 0.021; ES 0.61) in passive-DA group than in active-DA group, showing moderate to large difference. **Conclusions:** These findings suggest that information about decision making might be provided with tailored format for how much individual wish to involve in decision making.

10107 Poster Session (Board #96), Sat, 1:15 PM-4:45 PM

The effect of pain self-management based on pain control diary on breakthrough pain. *First Author: Zu-Yan Fan, Department of Medical Oncology, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: Most patients suffer from cancer pain, especially breakthrough pain. The overall incidence of breakthrough pain is estimated to be 65%. Self-management makes patients actively participating in the use of drugs, transforming their roles and adjusting their moods in order to better cure their own diseases. Therefore, the aim of the study is to discuss the effect of reducing cancer pain patients' breakthrough pain through self-management based on pain control diary. **Methods:** From October, 2015 to October, 2016, a total of 200 patients treated with opioids for cancer pain were randomly divided into groups. Patients in the control group were given general management including the Standard "the three steps analgesic ladder treatment for cancer pain", the traditional form of health education and psychological care; While the intervention group in addition to conventional cancer pain management, self-management based on pain control diary was applied. Through repeated intensive training, patients learned how to do self-assessment, to master the feature of their own pain, problem-solving skills and formal report to their oncologists in charge. **Results:** After six weeks of intervention , 10% patients in the intervention group had suffer breakthrough pain compared with 54% patients in the control group ($P <$ 0.05). The whole processing management model is a whole process, specialization and humanization Care model for patients with advanced cancer pain management, can effectively improve patient medication compliance, reduce the cancer breakthrough pain's incidence, improve the patients,s life quality with cancer pain. The medication compliance of the intervention group was significantly higher than that of the control group(X^2= 46.606, P<0.001), and in intervention group the incidence of breakthrough pain was significantly lower than that of the control group (X^2= 44.148, P<0.001) **Conclusions:** The self management based on pain control diary is a whole process, specialization and humanization Care model for patients with advanced cancer pain management, can effectively improve patient medication compliance, reduce the cancer breakthrough pain's incidence, improve the patients's life quality with cancer pain.

10108 Poster Session (Board #97), Sat, 1:15 PM-4:45 PM

A prospective randomized controlled trial of hydrating nail solution for prevention or treatment of onycholysis in breast cancer patients who received neoadjuvant/adjuvant docetaxel chemotherapy. *First Author: Ji-Yeon Kim, Samsung Medical Center, Seoul, Republic of Korea*

Background: Onycholysis and other nail toxicities occur in approximately 20-30% of breast cancer(BC) patients receiving docetaxel(D) chemotherapy. Onycholysis, the separation of the nail plate from nail bed, is also often associated with painful paronychia decreasing patients' the efficacy of a hydrating nail solution (EVONAIL solution, Evaux Laboratories, France) for the prevention and treatment of D-induced onycholysis and nail toxicities. **Methods:** This study is a prospective randomized controlled study of hydrating nail solution for prevention or treatment of onycholysis in patients with BC receiving neo/adjuvant 3-weekly D after doxorubicin plus cyclophosphamide. In experimental arm, each patient painted hydrating nail solution on nails and periungual areas once a day till developing onycholysis grade 2 or more. After Gr 2 onycholysis development, patients painted EVONAIL twice a day regardless of treatment arms. The primary endpoint is the incidence of onycholysis Gr 2 or more and recovery rate from Gr2 onycholysis. The secondary endpoints include: the incidence of all grade onycholysis; duration from first docetaxel treatment until onycholysis symptom appearance; degree of pain from nail toxicities; the incidence of other nail toxicities. **Results:** Since Aug 2015 to May 2016, 103 patients were enrolled and completed this study (Experimental arm(E) : 51, control arm(C): 52). Of 103 patients, 25 cases of Gr1 and 22 of Gr2 onycholysis were observed (Gr1 and 2(n,(%)) : 8(15.7%) and 7(13.7%) in E, 17(32.7%) and 15(21.4%)in C, respectively). Hydrating nail solution resulted in statistically significant reduction of Gr2 onycholysis compared to C (HR = 0.39, 95% CI 0.16, 0.96; P = 0.041) and all grade onycholysis decreased in experimental arm with statistical significance (HR = 0.37, 95% CI 0.20-0.69, P = 0.002). However, the effect of onycholysis treatment was not observed. **Conclusions:** Hydrating nail solution significantly reduced the incidence of D induced onycholysis in BC patients (NCT02670603). Clinical trial information: NCT02670603.

10109 Poster Session (Board #98), Sat, 1:15 PM-4:45 PM

Chemotherapy induced nausea and vomiting in breast cancer treated with antiemetic prophylaxis as recommended by the ASCO antiemesis guidelines. *First Author: Ronda Copher, Eisai Co., Ltd., Woodcliff Lake, NJ*

Background: Current ASCO Antiemesis Guidelines recommend triple antiemetic therapy (a $5HT_3RA$, an NK1, and dexamethasone) to prevent chemotherapy (CT) induced nausea and vomiting (CINV) in patients undergoing highly emetogenic chemotherapy (HEC). This study evaluated whether this regimen resulted in reduced rates of CINV in patients diagnosed with breast cancer (BC) and initiated on HEC. The primary outcomes of interest were rates of acute and delayed CINV in patients whose antiemesis prophylaxis was or was not in accordance with the ASCO guideline (i.e., Per-guideline vs. Non-Guideline). Costs of treating CINV were also calculated. **Methods:** Patients were identified in the Premier Healthcare database, a complete geographically diverse census of inpatients and hospital-based outpatients. Adults treated for BC with HEC during the years 2012-14 were identified and stratified based on their antiemesis prophylaxis. Rates of acute (day of CT) and delayed CINV (days 2-7 post CT) were calculated following initiation of HEC. CINV was defined by ICD9 codes for nausea and vomiting or volume depletion/dehydration or use of a rescue antiemetic. Rates of CINV and health care costs were then compared between the two cohorts. **Results:** A total of 8,388 patients were included in the analysis. Of these, 5,447 (65%) had treatment Per-Guideline and 2,941 (35%) were Non-Guideline. For acute CINV, Per-Guideline patients had a significantly lower rate of CINV when compared to Non-Guideline patients (1.7% vs. 3.2%, respectively, $p < .001$). Similarly, in delayed CINV Per-Guideline patients had significantly lower rates of CINV when compared to Non-Guideline patients (15.4% vs. 19.1%, $p < .001$). Patients who experienced CINV also had significantly greater total health care costs versus those without CINV ($32,199 vs. $20,163, respectively, $p < .001$). **Conclusions:** The results showed adherence to the ASCO Antiemesis Guidelines led to lower rates of CINV and lower costs. Although defining CINV by claims may tell an incomplete story, this study suggests that following the ASCO Antiemesis Guidelines may help both patients and payers of health care costs.

10110 Poster Session (Board #99), Sat, 1:15 PM-4:45 PM

Efficacy of *Gastroplegia Patch* on treating postoperative gastroplegia: A multicenter, double-blind, randomized controlled trial. *First Author: Tian Zhou, Department of Medical Oncology, Dongfang Hospital, Beijing, China*

Background: Postoperative gastroplegia is common in digestive cancer patients and there were no effective treatments. *Gastroplegia Patch* is an external-used Chinese Herbal Medicine recipe. It has been applied clinically for more than ten years, which showed good effect. We conducted this study to verify its safety and efficacy on the symptoms of postoperative gastroplegia. **Methods:** This clinical trial was designed as a multi-center, double-blind, superior effect, randomized controlled trial. It has been registered in ISRCTN (No.18291857) before initiation and was monitored by the third party. Patient inclusion criteria: 1. Gastroenterological cancer patient who was diagnosed as post-surgery gastroplegia, could not eat and need tube feeding (parenteral nutrition or with Jejunum nutrient canal); 2. The local identification of abdomen is cold pattern, which means this kind of patient prefers heat to cold, likes hot food and hates cold ones. Eligible participants were randomized into two arms, placebo arm and *Patch* arm, respectively. Beside the basic treatments (nutrition support, gastrointestinal decompression, promoting gastric dynamics medicine), placebo or *Gastroplegia Patch* was applied in control group or *Patch* group, respectively. Placebos or the patches were allocated at two acupuncture points (*Zhongwan* and *Shenque*). The intervention course was 14 days or reached primary endpoint. The primary endpoint was able to eat without tube feeding. **Results:** All the 120 eligible participants (60 per arm) were recruited from four AAA hospitals in Beijing, China. Analysis was conducted based on intent-to-treat strategy. After the intervention, 68.33% of the participants in the Patch group were able to eat without tube feeding, which significantly higher than that of 41.67% in the control group ($p = 0.003$). It took 8 days on average in the *Patch* group to show effect, which significantly faster than that of 10 days in the control group ($p = 0.017$). The incidences of adverse events were compatible between the two arms ($p = 0.244$). **Conclusions:** *Gastroplegia Patch* is safe and effective in treating postoperative gastroplegia in gastroenterological cancer patients with cold syndrome. Clinical trial information: 18291857.

10111 Poster Session (Board #100), Sat, 1:15 PM-4:45 PM

Biomarker to cost-effectively harness the technical prowess of palliative radiation: Neutrophil lymphocyte ratio (NLR) and overall survival following palliative radiotherapy in an unselected real-world population of all tumor sites. *First Author: Santhanam Sundar, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom*

Background: Single fraction radiotherapy (RT) is standard of care for palliation of pain from bone metastases (ASTRO IJROBP 2011 79:965). But costly, complex, multi-fraction RT is quite often used for palliation of symptoms from various organs. Health care costs are burgeoning (ASCO JCO 2012 30: 1715). Costs can be constrained by judiciously reducing use of unnecessary multi-fraction RT in pts with limited life expectancy. But radiation oncologists' ability to predict survival is inaccurate. (Chow IJROBP 2005 61:870). Hence we assessed clinical utility of Neutrophil Lymphocyte ratio (NLR) - a routinely available biomarker. **Methods:** 233 patients (pts) undergoing palliative RT over a 3 month at Nottingham University Hospital. Predominant Tumour SITES: Lung 28% Breast 13% Prostate 13% Colorectal 9% Gastro-Oesophageal 5% Myeloma 5% Bladder 5%. Predominant HISTOLOGY: Adenocarcinoma 61% Squamous Cell 14%. NLR available for 158 pts. **Results:** A NLR of 4.5 was highly predictive of 90-day mortality & overall survival in an unselected real world population. (Table). No survival benefit seen for multi-fraction RT over single fraction RT across all tumour sites. On survival analysis by Cox regression, increased NLR was significant with a hazard ratio of 2.2 (95% CI 1.3 to 3.7) whereas total radiation dose, use of multiple fractions , age, serum haemoglobin, serum albumin & histology were not significant. **Conclusions:** In palliative care of advanced cancer, for pts with high NLR (>4.5), Single fraction RT should be the standard of care for palliation of symptoms.

	NLR <4.5	NLR <4.5	
Median Age	67.5	67.6	*P = 0.79 (ns)
Stage 4	94%	92%	# P = 0.63 (ns)
Site of palliative RT^x	15%	11%	# P= 0.48 (ns)
Brain	23%	31%	
Spine	26%	32%	
Chest	20%	15%	
Pelvis			
Median Haemoglobin (range)	116 (34-115)	114 (73-157)	*P = 0.48 (ns)
Median RT Dose (Gy) (range)	20 (8 – 45)	20 (8-39)	*P = 0.13 (ns)
Number of fractions (range)	5 (1-25)	5 (1-15)	*P = 0.21 (ns)
Completed RT as planned	97%	95%	# P= 0.48 (ns)
Median Overall Survival	8.14 mths	3.55 mths	^ P=0.0001
90 day mortality	29.7%	47.6%	# P= 0.02

* Mann-Whitney Test, # Chi-Square test, ^ Log Rank test

10112 Poster Session (Board #101), Sat, 1:15 PM-4:45 PM

Safety and efficacy of same-day administration of pegfilgrastim in patients (pts) receiving chemotherapy for gastrointestinal (GI) malignancies. *First Author: Robert M. Matera, Tufts University School of Medicine, Tufts Cancer Center, Boston, MA*

Background: Pegfilgrastim is typically administered 24 hours after chemotherapy per package insert; however some pts are unable or unwilling to return for this additional visit due to work or transportation especially with regimens consisting of infusional 5-FU. Same-day dosing eliminates need for this additional visit. Results from prior studies in other tumor types are inconclusive as few support same-day dosing whereas others show inferiority. Purpose of our study was to determine safety and efficacy of administering pegfilgrastim on same day as chemotherapy in pts with GI malignancies. **Methods:** A single-institution retrospective review was conducted of pts with GI malignancies who received chemotherapy and same-day pegfilgrastim (6 mg) within 1 hour of completion of chemotherapy from Jan 2014 through Jan 2017. Decision to administer pegfilgrastim was based on NCCN or ASCO recommendations. As per institutional guidelines, pts were counseled on risks of same-day pegfilgrastim prior to its administration. Data was collected on demographics, clinic notes and complete blood counts. Analyses included neutropenia, febrile neutropenia, hospitalization, use of antibiotics or bone pain. **Results:** A total of 536 chemotherapy cycles in 69 pts were analyzed. Median age was 60 years (range 32-87) with 46% of pts $\geq$ 65. Pts had an average of 4 risk factors for febrile neutropenia: advanced disease, gender, age $>$ 65 and chemotherapy regimen. Most common malignancy was colon (48%), pancreas (17%) and gastric (17%). Most commonly used regimens included mFOLFOX6 (42%), FOLFIRINOX (23%) and FOLFIRI (12%). Median absolute neutrophil count nadir for all cycles was 4538/uL (range: 1160-25168). Grade 1 and 2 neutropenia developed in 6 of 536 (1%) cycles. Bone pain reported in 3 pts (4%). There were no episodes of grade 3 or 4 neutropenia or febrile neutropenia. None had dose reductions, chemotherapy delays, hospitalizations, or antibiotic use due to neutropenia. **Conclusions:** We believe our study is the first in GI malignancies to report that same-day pegfilgrastim administration may be as effective and safe as next-day administration, benefiting pts and might reduce costs.

10113 Poster Session (Board #102), Sat, 1:15 PM-4:45 PM

A phase II RCT of high-dose vitamin D supplementation for androgen deprivation therapy (ADT)-induced bone loss among older prostate cancer (PCa) patients. *First Author: Luke Joseph Peppone, University of Rochester Medical Center, Rochester, NY*

Background: ADT is the most commonly used systemic therapy for treating locally advanced and metastatic PCa. ADT use causes hypogonadism, which can result in accelerated bone loss and fragility fractures. Vitamin D (VITD) may protect against bone loss; however it remains unclear if the recommended daily allowance (RDA) of VITD is sufficient to reduce bone loss or whether higher doses are needed. The aim of this phase II RCT was to collect preliminary data on the effect of high-dose VITD on bone mineral density (BMD) in ADT-treated PCa patients compared to the RDA of VITD. **Methods:** Older PCa patients (≥60 years old) with VITD insufficiency (< 32 ng/ml), within 6 months of starting ADT and with 6 more planned months of ADT were randomized 1:1 to high-dose VITD (hVITD; 600 IU/daily plus 50,000 IU/weekly) or RDA of VITD (rVITD; 600 IU/daily plus placebo weekly) for 24 weeks. All subjects received 100% of the RDA for calcium (1,000 mg/day). BMD was assessed at the total hip (TH) and lumbar spine (LS) via DXA at pre- and post-intervention. ANCOVA was used to test the change in BMD between groups. **Results:** 59 PCa patients were accrued (85% white; mean age = 67.6). Serum analyses confirmed high compliance in both groups (25-OH VITD change: hVITD = +32.0 ng/ml vs rVITD = +4.3 ng/ml; $p < 0.01$). The safety of hVITD was similar to rVITD (Grade I hypercalcemia: hVITD: n = 1 vs rVITD: n = 0). Bone loss was significantly reduced for the hVITD group compared to rVITD group for total hip (TH BMD% change: hVITD = −1.5% vs rVITD = −4.1%; p = 0.02), with a trend for the femoral neck (BMD% change: hVITD = −1.7% vs rVITD = −4.3%; p = 0.06) and trochanter (BMD% change: hVITD = −1.0% vs rVITD = −2.8%; p = 0.10). There was no difference between groups for LS bone loss (LS BMD% change: hVITD = −0.8% vs rVITD = −0.6%; p = 0.75). **Conclusions:** High-dose VITD supplementation produced significantly greater reductions in hip BMD loss among older PCa patients receiving ADT compared to rVITD. Clinically, higher doses of VITD may be necessary to effectively prevent ADT-induced bone loss. A definitive phase III RCT is needed to confirm these findings. Funding: NCI R21CA175793, K07CA168911 & UG1CA189961. Bio-Tech Pharmacal Inc. supplied all agents. Clinical trial information: NCT02064946.

10114 Poster Session (Board #103), Sat, 1:15 PM-4:45 PM

Multimodal therapy for cancer related fatigue in patients with prostate cancer receiving radiotherapy and androgen deprivation therapy. *First Author: Sriram Yennu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There are limited studies to evaluate treatments that target causative mechanisms of Cancer-related-fatigue (CRF) using validated tools in a defined population. The objective is to determine the feasibility, and the preliminary estimates of the effects of various combinations of standardized exercise, cognitive behavioral therapy (CBT), and methylphenidate (multimodal therapy, or MMT) on CRF as measured by AUC of Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F) subscale scores in Pts with prostate cancer receiving radiotherapy with androgen deprivation therapy. **Methods:** Prostate cancer Pts with CRF scheduled to receive radiotherapy with androgen deprivation therapy were eligible. Using a double blind (patient, investigators) randomized factorial study design, eligible Pts were randomized into 1 of the 8 arms, which included all possible combinations of the interventions (exercise, CBT, and methylphenidate) and/or their corresponding placebo treatments for a duration of 8 weeks. **Results:** 62/69 (89%) randomized Pts were evaluable. There were no differences in the demographics and baseline fatigue between groups. The adherence rates for pills, exercise and CBT were 96.5%, 67%, and 90% respectively. The study was feasible and there was no significant difference in adverse events by groups. Table 1 shows the comparison of AUC by treatment. For Pts receiving drug compared to placebo, the median FACIT-F AUC was 2328 vs 2095. The drug effect (estimate, 95% CI) in Pts who received Exercise was 596 (68.3, 1125); CBT was 354 (-121, 830); combined Exercise and CBT was -187 (-802,427); and control Exercise, control CBT was 294 (-192,781). **Conclusions:** Methylphenidate containing combinations were superior to no drug combinations. Methylphenidate + Exercise provided the best signal and should proceed to large randomized control trials. Clinical trial information: NCT01410942.

Comparison AUC (median scores and p-value) by treatment.

Interventions	AUC_ FACIT-F	AUC_ FACT-G
Methylphenidate vs Placebo	2328 vs. 2095 (p=0.0536)	4923 vs. 4532 (p=0.042)
Exercise vs control exercise	2143 vs 2285 (p=0.59)	4667 vs 4813 (p=0.37)
CBT vs control CBT	2247 vs 2197 (p=0.4)	4710 vs 4722 (p=0.84

10115 Poster Session (Board #104), Sat, 1:15 PM-4:45 PM

The impact of sleep disturbances (SD) on quality of life, psychological morbidity, and survival of advanced cancer patients (ACP) and caregivers (CG). *First Author: Fay J. Hlubocky, The University of Chicago Medicine, Chicago, IL*

Background: SD have been described as a significant symptom burden for cancer patients and their caregivers. However, in advanced cancer, the prevalence of SD and its impact on the quality of life (QOL) and psychological morbidity of ACP over time has not been described. **Methods:** A prospective cohort of ACP participating in phase I trials was assessed at baseline (T1) and one month (T2) using psychosocial instruments: cognition (MMSE); depression (CES-D), state anxiety (STAI-S), QOL(FACIT-Pal), global health (SF-36). Semi-structured interviews evaluated SD patterns including: quality/latency, habitual efficiency, daytime dysfunction. **Results:** To date,152 subjects (76 ACP and 76 CG) have been separately interviewed at T1 and T2. For the total population: median age 61 (28-78y); 51% male; 100% married; 90% Ca; 64% > HS educ; 52% GI dx; 51% income < $65,000 yr; ACP median survival 7.9 months (0.41-18.2). At T1, 57% of ACP reported experiencing SD within the past week including: 55.6% insomnia, 44% nonrestorative sleep, 49% low energy, 48% daytime somnolence. For CG, 72% reported experiencing SD: 68% insomnia, 64% nonrestorative sleep, 69% fatigue, 66% daytime somnolence. At T2, rates remained consistent over time for both ACP and CG across time with the exception of increased insomnia at 61% and 76% respectively. After controlling for pain, mood, and fatigue, ACP with self-reported SD had higher STAI-S (33 ±11 v 29 ±8 , p = 0.02) and poor global health (54 ± 19 v. 64 ± 21, p = 0.01) at T2. CG with SD had higher STAI-S anxiety (39 ± 17 v 35 ± 13, p = 0.03) and poor global health (75 ±26 v 88±16, p = .0002) at T2.Regression analyses revealed ACP with self-reported insomnia had poorer FACIT-Pal QOL (59 ± 9 v 63 ± 10, p = 0.01) over time. Prior chemotherapy was associated with ACP SD (70% v. 33%, p = 0.02). Regarding prognosis, ACP with insomnia had shorter median survival (5.5 v. 7.2 months, p = 0.01). **Conclusions:** SD are prevalent among ACP participating in clinical trials and were associated with disease progression, QOL, and anxiety. Multidisciplinary supportive care interventions designed to address SD are warranted.

10116 Poster Session (Board #105), Sat, 1:15 PM-4:45 PM

Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim for the prevention of severe neutropenia, in patients with breast cancer receiving myelosuppressive chemotherapy. *First Author: Andriy Krendyukov, HEXAL AG, Holzkirchen, Germany*

Background: In 2015, filgrastim EP2006 (Zarxio) became the first biosimilar approved by the FDA for commercial use in the US. This phase III randomized, double-blind registration study in patients with breast cancer receiving (neo)adjuvant myelosuppressive chemotherapy (TAC) compares US-licensed filgrastim, Neupogen (reference), with two groups who received alternating treatment with reference and biosimilar every other treatment cycle. **Methods:** A total of 218 patients receiving 5μg/kg/day filgrastim over 6 chemotherapy cycles were randomized 1:1:1:1 into 4 arms. Two arms received only 1 product, biosimilar or reference (unswitched), and 2 arms (switched) received alternating treatments every other cycle (biosimilar then reference or vice versa over cycles 1–6). Since the switch occurred from Cycle 2 onwards, this analysis compared pooled switched groups to the unswitched reference group for efficacy during Cycles 2–6. Safety was also assessed. Non-inferiority in febrile neutropenia (FN) rates between groups for Cycles 2–6 was shown if 95% confidence intervals (CIs) were within a predefined margin of -15%. **Results:** A total of107 patients switched treatment, and 51 patients received reference in all cycles. Baseline characteristics were similar between groups. Incidence of FN was 3.4% (switched) vs. 0% (reference) (95% CI: -9.65; 4.96), which is within the predefined non-inferiority margins. Infections occurred in 9.3% (switched) vs. 9.9% (reference). Hospitalization due to FN was low with 1 patient in Cycle 6 (switched). TEAEs related to filgrastim were reported in 42.1% (switched) vs. 39.2% (reference) (all cycles). Musculoskeletal/connective tissue disorders related to filgrastim occurred in 35.5% (switched) vs. 39.2% (reference) (all cycles), including bone pain (30.8% vs. 33.3%). No anti-drug antibodies were identified. **Conclusions:** There was no evidence of clinically meaningful differences when patients with breast cancer were switched from reference to biosimilar filgrastim, or from biosimilar to reference filgrastim. Clinical trial information: NCT01519700.

10117 Poster Session (Board #106), Sat, 1:15 PM-4:45 PM

Reducing chronic breast cancer related lymphedema utilizing a program of prospective surveillance with bioimpedance spectroscopy (BIS). *First Author: Pat W. Whitworth, Nashville Breast Center, Nashville, TN*

Background: Breast cancer related lymphedema (BCRL) represents a major side effect that can significantly impact quality of life. Current guidelines support prospective surveillance to allow for early diagnosis and treatment of BCRL at a subclinical, reversible stage. This current large, single institution experience evaluated the use of bioimpedance spectroscopy (BIS) to monitor patients for the development and treatment of BCRL. **Methods:** From April 2010 through Nov 2016, 596 patients (79.6% with high-risk features) were evaluated with BIS.Patients received a pre-operative baseline L-Dex measurement and post-operatively at regular intervals. Elevated L-Dex scores were defined as an increase of $\geq$10 points above baseline (considered subclinical BCRL). Intervention then consisted of applying an over the counter (OTC) sleeve for 4 weeks followed by re-evaluation. The need for complete decongestive physiotherapy (CDP) represented a surrogate for the development of clinically significant, chronic BCRL. **Results:** Median follow-up for all patients was 17 months. Seventy-three patients (12%) developed an elevated L-Dex score with axillary lymph node dissection (ALND) ($p < 0.001$), taxanes ($p = 0.008$), and (regional nodal irradiation (RNI) ($p < 0.001$) associated. At last follow-up, only 18 patients (3%) had unresolved clinically significant BCRL requiring CDP. Mastectomy ($p = 0.02$), ALND ($p < 0.001$), taxanes ($p = 0.05$), and RNI ($p < 0.001$) were associated with requiring CDP. **Conclusions:** Our results demonstrate that prospective monitoring using BIS, with intervention (using a simple OTC sleeve for 4 weeks) triggered by a $\geq$10-point L-Dex elevation, resulted in only a 3% rate of chronic, clinically significant BCRL. These results are lower than reported in contemporary studies and validate recent guidelines supporting prospective screening and intervention for BCRL.

10118 Poster Session (Board #107), Sat, 1:15 PM-4:45 PM

Frequency and factors predictive of aberrant drug behavior in patients presenting to outpatient supportive care center at a comprehensive cancer center. *First Author: Sriram Yennu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Opioid misuse is a growing crisis in cancer patients. Cancer patients at risk of aberrant drug behaviors (ADB) are frequently underdiagnosed in routine cancer care. The aim of this study was to determine the frequency and factors associated with ADB using the "Screener and Opioid Assessment for Patients tool" (SOAPP-14) in cancer patients seen at the outpatient supportive care center. We also examined the screening performance of Cut Down, Annoyed, Guilty, and Eye Opener (CAGE-AID) as compared to The SOAPP-14 as a gold standard. **Methods:** In this retrospective study, 1108 consecutive patients referred to supportive care clinic were reviewed. Patients were eligible if they were $\geq$18 yrs, have a diagnosis of cancer, and were on opioids for pain for atleast a week. Patients' demographics, the Edmonton Symptom Assessment Scale (ESAS), SOAPP-14, and CAGE-AID scores were analyzed. ADB+ was defined as SOAPP-14 score $\geq$7. Descriptive statistics, spearman correlation coefficient, multivariate, and ROC analysis were performed. **Results:** 703/1108 consults were eligible. A total of 153/703 (22%) were ADB +ve. SOAPP-14 scores were positively correlated with CAGE-AID $r = .38$, $p < 0.001$; male gender $r = 0.11$, $p = 0.003$; ESAS pain $r = 0.11$, $p = 0.005$; ESAS depression $r = 0.22$, $p < 0.001$; ESAS anxiety $r = 0.22$, $p < 0.001$, and ESAS financial distress $r = 0.23$, $p < 0.001$. Multivariate analysis indicated that the odds ratio for ADB +ve was 6.18 in patients with CAGE-AID+ ($p < 0.001$), 1.8 for male gender ($p = 0.007$), 1.1/pt. for ESAS anxiety ($p = 0.044$), and 1.1/pt. for ESAS financial distress ($p = 0.007$). A CAGE-AID score of 1/4 has a sensitivity of 47%, specificity of 89% positive predictive value 63.6% and negative predictive value 69.2%. **Conclusions:** Our study suggests that 22% of cancer patients on opioids presenting to supportive care center are at risk of aberrant drug behavior (ADB). Male patients with anxiety, financial distress, and prior alcoholism/illicit drug use are significant predictors of ADB's. A cut off score of $\geq$1 out 4 on CAGE-AID questionnaire allows better screening of ADB in outpatient advanced cancer patients. Further research to effectively manage these patients is needed.

10119 Poster Session (Board #108), Sat, 1:15 PM-4:45 PM

Effect of exercise on muscle immune response and mitochondrial damage and their relationship with cancer-related fatigue: A URCC NCORP study. *First Author: Anita Roselyn Peoples, University of Rochester Medical Center, Rochester, NY*

Background: Chemotherapy (CT) via inflammation and oxidative stress can cause muscle inflammatory injury, mitochondrial damage, and cancer-related fatigue (CRF). Following muscle and mitochondrial damage, various cytoplasmic and mitochondrial components are released into circulation. HLA-DQB1 gene encodes a protein involved in the activation of immune response, and is not expressed in normal muscle cells but is up-regulated under highly inflammatory states. Mitochondrial gene MT-CO2 encodes subunit 2 of complex IV, which plays a critical role in energy metabolism and mitochondrial function. We investigated the (i) influence of an exercise intervention, Exercise for Cancer Patients (EXCAP), on gene expression levels of muscle immune response and mitochondrial damage and (ii) the relationships of these genes with CRF. **Methods:** In this nationwide, multicenter, phase III RCT conducted through the URCC NCORP Research Base, cancer patients ($N = 350$; mean age = 55.7) were randomized to 2 groups: (i) CT and (ii) CT plus a 6-week individualized, home-based, aerobic and resistance exercise program (EXCAP). Gene expression and CRF were assessed pre- and post-intervention from whole blood by qPCR and from patient-report by MFSI, respectively. **Results:** T-tests revealed significant upregulation of peripheral HLA-DQB1 and MT-CO2 mRNA following CT in controls (both $p < 0.00001$) while there was less up-regulation in exercisers (both $p \leq 0.005$). ANCOVA showed a trend for significant differences between controls and exercisers for HLA-DQB1 (9.2% vs 5.4%; $p = 0.059$) and MT-CO2 (16.3% vs 12.7%; $p = 0.061$). Pearson correlations revealed that increases in HLA-DQB1 ($r = 0.21$; $p = 0.051$) and MT-CO2 ($r = 0.19$; $p = 0.025$) were significantly associated with concurrent increase in CRF in controls, but not in exercisers. **Conclusions:** CT alters muscle immune response and mitochondrial gene expression causing muscle and mitochondrial damage, which may be mediators for CRF. EXCAP is a promising intervention that may reduce both muscle and mitochondrial damage via its positive effects on HLA-DQB1 and MT-CO2. *Funding: NCI UGCA189961, R25 CA102618.* Clinical trial information: NCT00924651.

10120 Poster Session (Board #109), Sat, 1:15 PM-4:45 PM

Anticipative monitoring to improve chemotherapy induced nausea. *First Author: Reza Elaidi, Association for Innovative Therapies in Oncology, Paris, France*

Background: The PROCHE [Programme for optimisation of the chemotherapy network] initiative is an innovative oncology-monitoring program designed to reduce patient waiting time and chemotherapy wastage, ultimately improving patient care. **Methods:** Primary objective was to evaluate the incidence of nausea reported by grade (NCI-CTC AE: from 0 to 4) from 2008 to 2016. Association was quantified using Mantel-Haenszel khi^2 and exact *p-values*. Secondary objective compared the 2009-2016 patients with the control patients of 2008 period. **Results:** Between Oct 2008 and Oct 2016, 3012 patients participated in the program, representing 36 803 questionnaires completed over the whole period. Nausea was, clinically and statistically, significantly improved during the whole follow-up period with a decrease of grade 3-4 from 0.6% to 0.08% and a decrease of grade 1-2 from 29.3% to 8.2%. The already adapted nausea management in 2008 with 70% of questionnaires reported no nausea improved to 92% in 2016, with a 10% improvement the year after program initiation. As MASCC propose to change guidelines with an improvement above 10%, such an organization may impact new recommendations. **Conclusions:** Anticipating anti-cancer treatment adaptation and prevention, following guidelines and using adapted antiemetics, explain these positive results. The PROCHE initiative improves chemotherapy induced nausea.

	No adverse event (%)	Grade 1-2 (%)	Grade 3-4 (%)	
2008	70.08	29.32	0.6	p<0.0001
2009	79.12	20.57	0.31	
2010	85.71	14.07	0.23	
2011	87.57	11.87	0.56	
2012	89.53	10.39	0.09	
2013	90.60	9.36	0.04	
2014	90.39	9.61	0.00	
2015	90.61	9.39	0.00	
2016	91.68	8.23	0.08	

10121 Poster Session (Board #110), Sat, 1:15 PM-4:45 PM

Advanced cancer patients' self-reported perception of timeliness of their referral to outpatient supportive/palliative care and their survival data. *First Author: Angelique Wong, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Palliative Care referral is often thought to be delayed as judged by health professionals and caregivers. However, no studies have ever examined patients' perception of timeliness of referral. The primary objective of this study was to determine patients' perception of the timeliness of their own referral to an outpatient palliative care clinic. We also examined the association between perceived timeliness and actual timing of referral. **Methods:** In this prospective survey, patients with advanced cancer were asked to rate their perceived timeliness of referral using a 5-point Likert scale ranging from much too early to much too late within 7-35 days after their first consultation visit at Supportive Care Center. They were also asked when they felt referral to Supportive Care should occur along 4 points in their disease trajectory. Actual timing of referral was assessed based on survival from the timing of completion of the survey. **Results:** 200 advanced cancer patients were surveyed. Median age was 64, 111 (55%) were female, and 35 (18%), 32 (16%) and 26 (13%) had gastrointestinal, lung and breast cancer, respectively. The median overall survival was 8.5 months. 144 (72%) patients perceived their referral was "just in time," 42 (21%) felt it was "late/much too late," and 14 (7%) felt it was much "too early/early." 76/193 (39%) felt the referral should occur at the time of diagnosis of cancer, 32 (17%) when they start first-line chemotherapy, 46 (24%) at diagnosis of recurrent disease, 14 (7%) when there are no further treatment options, and 4 (2%) reported never. We found no significant difference in survival among patients who reported their referral was early, just in time, and late (median 9.8 vs. 8.3 vs. 9.0 months, P=0.43). **Conclusions:** Patients with advanced cancer were referred to our outpatient Supportive Care clinic a median of 8.5 months before death. A vast majority of patients perceived the timing of referral was appropriate, and many agreed that referral should occur early in the disease trajectory. The lack of association between perceived timeliness of referral and survival may be related to the ceiling effect and the small number of patients who felt their referral was late.

10122 Poster Session (Board #111), Sat, 1:15 PM-4:45 PM

Radiation for bone metastases: Reconsidering the optimal timing. *First Author: Joanna C. Yang, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Bone metastases impair function and decrease quality of life due to acute or chronic pain. The standard approach for patients with multiple bone metastases is systemic therapy and palliative radiation therapy (RT) when the metastases become symptomatic. This study aims to understand the characteristics and outcomes for inpatients admitted for painful bone metastases. **Methods:** An inpatient radiation oncology consult registry was created in 2015 to evaluate patterns of care for patients receiving RT in the inpatient setting. Of the 1151 consults requested between 7/2015 and 6/2016, 28% (n = 323) were for evaluation of symptomatic bone metastases in patients who were hospitalized for acute or chronic pain. Among this cohort, 64% (n = 208) went on to receive RT for 225 bone metastases. Sixty percent of RT courses were initiated while the patient was hospitalized. Clinical characteristics correlated with overall survival (OS) were evaluated through Cox regression analysis. **Results:** The median follow up for the 208 patients who received RT was 4 months (0.1-9 months). Patient median age was 61 (10-92 years), and the median KPS was 70 (20-90). The most common sites treated were spine (50%), joints such as hip and shoulder (11%), long bones including femur and humerus (11%), and pelvis (10%). Sixty-one percent (n = 138) of the treated metastases were diagnosed $\geq$4 months prior to RT. The median survival after receiving palliative RT was 4 months (0-19 months). Among the 141 patients who had died at the time of analysis, 92 (65%) died within 2 months, and 128 (91%) within 6 months. Eighteen patients (9%) discontinued RT to transition to hospice care. OS after RT is significantly correlated with KPS ($p < 0.0001$) at the time of consult but not with patient age or site of treated disease. **Conclusions:** In this select group of inpatients who were evaluated for palliation of symptomatic bone metastases, we found a short OS after RT. The majority of metastases were present for $\geq$4 months prior to RT. This study suggests that earlier RT for high-risk metastases should be considered to prevent development of symptomatic disease that requires hospitalization. Risk factors for development of painful bone metastases are being studied prospectively at our institution.

10123 Poster Session (Board #112), Sat, 1:15 PM-4:45 PM

Trastuzumab-related subclinical cardiotoxicity in patients with early stage HER2-positive breast cancer: A retrospective single-center cohort study. *First Author: Olexiy Aseyev, Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada*

Background: Trastuzumab-based therapy (TT) is standard treatment for HER2-positive breast cancer (HBC). Subclinical cardiotoxicity (SCTx), defined as asymptomatic decline in left ventricular ejection fraction (LVEF) > 10% to < 50%, has been reported in up to 30 % of HBC patients (pts) receiving TT. Objectives included: determine prevalence of SCTx; associated risk factors (RF); and completion rates of TT in pts with HBC referred to a cardio-oncology clinic (COC). **Methods:** HBC patients receiving TT referred to the Ottawa Hospital COC were included. Demographics, TNM staging, performance status, stage, cardio-vascular (CV) RF (history of heart disease, hypertension, smoking, dyslipidemia, and diabetes), cardiac medications (CM) (ACE-inhibitors, beta-blockers), baseline LVEF, previous cancer therapy, baseline anthracycline exposure, previous radiation therapy (RT) (including mediastinal RT) were collected. LVEF was evaluated by ECHO or MUGA. Rate of successful completion of TT among pts with SCTx was determined. Risk ratio (RR) and logistic regression analysis was performed. **Results:** 240/408 BC pts referred to the COC (2008-2016) had HBC and 163/240 (68%) were referred with SCTx while on TT. 139/163 (85 %) pts with SCTx recovered after COC assessment: 77/163 (47%) pts were prescribed CMs. A significantly higher proportion of recovery was observed in pts who did not require CM (0.92 vs 0.78, p = 0.012; RR = 0.85, 95%CI:0.74-0.91). A total of 129/163 (79%) pts who experienced SCTx finished a full course of TT. Regression analysis found baseline LVEF, diabetes, and diastolic blood pressure as significant RFs for SCTx. There were no independent predictors for recovery after asymptomatic drop in LVEF while on TT. Diabetes (OR:2.97, 95%CI:1.3-6.8) and left chest wall RT (OR:2.4, 95%CI:1.1-5.6) significantly increased risk of permanent TT interruption in pts with asymptomatic drop in LVEF. **Conclusions:** The majority of HBC pts who experience SCTx can safely complete a full course of TT; many without use of CMs. While CV RFs were associated with increased risk of SCTx, this did not impact CV recovery after asymptomatic drops in LVEF.

TPS10124 Poster Session (Board #113a), Sat, 1:15 PM-4:45 PM

A multicenter phase 4 geriatric assessment directed trial to evaluate gemcitabine +/- nab-paclitaxel in elderly pancreatic cancer patients (GrantPax). *First Author: Johannes Betge, Department of Medicine II, University Hospital Mannheim, Heidelberg University, Mannheim, Germany*

Background: *Nab*-paclitaxel/gemcitabine (*nab*-P/gem) is an effective 1st line regimen for metastatic pancreatic ductal adenocarcinoma (mPDAC). Elderly mPDAC patients (pts) may as well benefit from *nab*-P/gem. Geriatric assessments to evaluate the functional reserve of these pts may allow individualization of treatment. Therefore, the aim of this study is to determine whether comprehensive geriatric assessments (CGAs) can predict the benefit from combined *nab*-P/gem therapy for elderly mPDAC pts in 1st line. A stratified treatment approach shall result in patient groups with a stable or improving CGA performance during the 1st cycle of treatment. **Methods:** GrantPax (NCT02812992) is a multicenter, open label phase 4 interventional trial with stratified parallel treatment groups (n = 45 per arm). The hypothesis is that individualized assessment directed treatment algorithms identify elderly pts ($\geq$70 yrs), who benefit from combined *nab*-P/gem therapy. The study uses a CGA to stratify pts as GOGO, SLOWGO or FRAIL. Depending on test outcome, pts receive chemotherapy (GOGO: *nab*-P/gem; SLOWGO: gem mono) or best supportive care (FRAIL). After 1st cycle of chemotherapy (4 wks) a CGA and safety assessment will be performed to assign pts to their definite treatment arm. The primary objective is that CGA-stratified pts do not decline in their CGA performance in response to chemotherapy, measured as a loss of 5 points or less in Barthels activities of daily living (ADL1 vs. ADL2 during CGA core assessment). The expected proportion of pts with ADL decline in each treatment group is 6%. Under this assumption it shall be shown with 80% power at one-sided significance level alpha of 0.05 that the proportion of pts with functional decline is less than 20% (n = 43 per group; ADL decline: n = 2 per group). Secondary endpoints are CGA scores during the course of therapy (CGA1-4), response rates, safety, survival rates, duration of treatment, cumulative dose, quality of life and discrepancy between CGA strata estimation by the investigator and true CGA assessment. GrantPax is the first trial realizing a CGA-driven treatment to individualize cancer therapy for elderly pts. Clinical trial information: NCT02812992.

TPS10125 Poster Session (Board #113b), Sat, 1:15 PM-4:45 PM

UNICANCER: Prospective cohort study of treatment related chronic toxicities in patients with localized breast cancer (CANTO). *First Author: Ines Maria Vaz Duarte Luis, Gustave Roussy, Université Paris-Saclay, Villejuif, France*

Background: Corresponding with improved survival among breast cancer patients an awareness of the long term effects of cancer treatments has increased. There is now a call for better coordination of care and management of these patients to focus on their survivorship. This study will identify factors associated with the development and persistence of long term toxicities in patients treated for Stage I-III breast cancer. In addition, it will characterize their incidence as well as, psychological, social and economic impacts. **Methods:** This is a prospective cohort study enrolling newly diagnosed invasive cT0-cT3, cN0-3, M0 breast cancer patients of 26 French comprehensive cancer centers. All patients will be followed for a minimum of 5 years. Patients will be assessed at diagnosis, 3-6 (M0), 12 (M12), 36 (M36), 48 (M48), 60 (M60), months after treatment completion. Treatment completion is defined as completion of primary surgery, chemotherapy or radiotherapy, whichever comes last. Adjuvant trastuzumab, endocrine therapy or participation in clinical trials can be ongoing. CANTO collects an extensive list of clinical, treatment, and toxicity data including validated patient reported outcomes questionnaires *(Hospital Anxiety and Depression scale [HADS], Scheier et Carver's Questionnaire, Life Orientation Test-Revised [LOT-R], Beck Depression Inventory [BDI-SF], European Organization for Research and Treatment-QOL questionnaire for breast cancer [EORTC QLQC30-BR23], EORTC-FA13, 12 Item Short Form Survey [SF12], Global physical activity questionnaire [GPAQ]6, impact of cancer questionnaire [IOCv2], economic and social questionnaires).* Blood collection is available for all patients at diagnosis, M0, M12, M36 and M60. Genotyping will be performed in all samples. Biologic substudies are ongoing (e.g, microbiotic and cognitive substudy). CANTO aggregates a multidisciplinary team of French investigators and created a dedicated national network. Enrolment started in 2012 and by December 2016, 10030 patients were already enrolled, with a goal of 12.000 patients. Clinical trial information: NCT01993498.

TPS10126 Poster Session (Board #114a), Sat, 1:15 PM-4:45 PM

A phase II-III, multicenter, randomized, open study evaluating the feasibility and efficacy of a supervised home-based standard physical exercise program for metastatic cancer patients receiving oral targeted therapy: The UNICANCER SdS 01 QUALIOR study (ID-RCB: 2015-A01922-47). *First Author: Florence Joly Lobbedez, Centre François Baclesse, Caen, France*

Background: Fatigue is a frequent side effect with oral targeted therapies (OTT). Physical activity has been reported to improve fatigue and quality of life (QoL). However, few studies focused on metastatic cancer patients and mainly among patients treated with chemotherapy. Furthermore, recent guidelines recommend evaluation and optimization of standardized exercise programs. The aim of our study is to evaluate home-based standard physical exercise program (SPEP) for metastatic cancer patients treated with OTT. **Methods:** This phase II-III study will randomize (2:1) patients starting first-line OTT for metastatic cancer between an individualized SPEP supervised by a personal coach, and recommended physical exercises via a booklet. Eligible patients will have received $\leq$2 lines of metastatic chemotherapy, ECOG PS $\leq$2, controlled pain (VAS $<$ 3/10), and life expectancy $\geq$3 months. The phase II part (120 patients) will evaluate the feasibility of a 3-month SPEP using the rate of patients performing $\geq$50% of SPEP (2-stage Fleming: one-sided α = 5%; β = 85%). An interim analysis is planned after the phase II. The phase III will compare the efficacy of an SPEP as opposed to recommendations to reduce fatigue and/or improve physical well-being (PWB) dimensions of QoL (evaluated with FACT-G and FACT-F questionnaires). To show a difference of $\geq$5 points in PWB and 2.5 for fatigue (α = 2.5%; β = 80%), 312 patients are required in the phase III trial. . Secondary objectives include: PFS, OS, other dimensions of QoL, tolerability and observance of OTT, change in body composition, physical benefits, and a medico-economic study. The SPEP was developed by specialized coaches involved in physical activity and cancer. The study has Ethic committee approval and accrual is planned in 18 French centers in April 2017, for 30 months. This is the first randomized trial dedicated to patients with metastatic cancer treated with OTT evaluating the feasibility and the efficacy of a well design home based SPEP on fatigue and physical well-being.

TPS10127 Poster Session (Board #114b), Sat, 1:15 PM-4:45 PM

A pilot RCT of sarcopenia-focused prehabilitation in pancreas cancer. *First Author: Elizabeth Hile, Oklahoma University Health Sciences Center/ Stephenson Cancer Center, Oklahoma City, OK*

Background: Now the 3rd leading cause of US cancer deaths, pancreatic cancer (PanC) incidence is rising. Surgery is the only chance at cure, but sarcopenia (low muscle mass, strength, function) can eliminate surgical and chemotherapy options, and independently predicts poor outcomes. Strengthening (Str) with protein combats sarcopenia of aging, and pre-op exercise (prehab) benefits other cancer survivors. But the impact of Str in a brief pre-Whipple window, and a host with PanC-mediated catabolism, is unknown. We aim to quantify the post-op QoL impact of adding Str to our standard clinical aerobic instruction before Whipple for pancreatic head and related cancers. **Methods:** Pilot RCT of 130 PanC survivors age 30+ randomized (stratified by neo-chemo) to 2 home-based prehab arms: Standard/NPRE = aerobic + protein, or Sarcopenia/SPRE = Standard + Str. To explore PanC-sarcopenia as moderating Str's impact, a 3rd pre-malignancy Whipple group (p-mal, n=50) also receives SPRE. All participants get protein and exercise instruction personalized to baseline status, adherence diaries, actigraphy, and phone follow-up in pre-op period only. Endpoints are QoL (primary) as Functional Assessment of Cancer Therapy (FACT), performance as 6 Minute Walk (6MW) & Short Physical Performance Battery (SPPB); and self-reported symptoms & activities of daily living (ADL). Assessments at baseline, 1-3 days pre-op, and post-op week 4 & month 4 (primary) are blind. Sarcopenia measures are clinical (dynamometry, bioimpedance, CT body composition) and preclinical (ZIP4/ catabolic mediators in blood, muscle, tumor & duodenum). Analyses: QoL change at post-op month 4 will be compared across PanC arms (SPRE & NPRE) with mixed-models before Baron-Kenny and Preacher/Hayes' mediator analyses. To explore impact of PanC catabolic host environment on Str, outcomes will be compared by SPRE group (PanC & p-mal). To our knowledge, this is the first PanC prehab RCT with sarcopenia focus, comprehensive mechanistic approach, and high dose (60 min daily)/short duration (2-3 week) intervention. With local feasibility established, we continue to accrue (n=30), and seek multicenter collaboration to target NCI funding. Clinical trial information: pending - in submission.

TPS10128 Poster Session (Board #115a), Sat, 1:15 PM-4:45 PM

Testing a behavioral intervention to improve adherence to adjuvant endocrine therapy (AET). *First Author: Gretchen Genevieve Kimmick, Duke University Medical Center, Durham, NC*

Background: Adjuvant endocrine therapy (AET) is a crucial component of treatment used to prevent recurrence and reduce mortality for women with hormone receptor positive breast cancer. Poor adherence to AET is a significant problem, with rates of non-adherence ranging from 28% to 59%. Non-adherence to AET contributes to increased medical costs and increased mortality. Symptoms (e.g., pain, hot flashes, sleep problems, vaginal dryness) associated with AET are related to non-adherence and early discontinuation of treatment. Our goal is to test the efficacy of a novel self-management intervention (SMAET) that teaches patients skills for enhancing adherence to AET and coping with AET-related symptoms. **Methods:** Trial participants will be recruited from a tertiary care medical center and community clinics that are located in medically underserved areas. Target enrollment is 400 patients. Prospective participants must meet the following criteria: diagnosis of Stage I to III breast cancer; hormone receptor positive tumor; local definitive cancer treatment complete; within 12 months of beginning AET; have at least 18 months of AET recommended; and at least 21 years of age. We will test the effects of the SMAET intervention (n = 200) by comparing it to a general health education intervention (n = 200; attention control). The SMAET protocol includes 7 sessions providing systematic training in coping skills for managing symptoms that interfere with adherence and 3 maintenance calls delivered over 6 months by a nurse via the phone. The intervention also includes interactive voice messaging that is tailored based on real-time adherence data. The primary study outcome, adherence to AET, will be assessed in real-time for 18 months using wireless smart pill bottles (i.e., bottle opening and percent of pills remaining). Symptom interference will be examined as a secondary outcome and will be assessed over 18 months. If effective, the intervention may reduce the burden of AET use. Clinical trial information: NCT02707471.

TPS10129 Poster Session (Board #115b), Sat, 1:15 PM-4:45 PM

A randomized phase II/III study comparing stereotactic body radiotherapy (SBRT) versus conventional palliative radiotherapy (CRT) for patients with spinal metastases (NCT02512965). *First Author: Arjun Sahgal, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Innovative radiotherapy technology and modern imaging capabilities enable the use of Stereotactic Body Radiotherapy (SBRT) to treat patients with spinal metastases to optimize tumour control and palliation compared to standard conventional radiotherapy. No randomized clinical trial evidence exists directly comparing the two treatment strategies. **Methods:** SC.24 is a Canadian Cancer Trials Group randomized phase II/III study comparing standard conventional radiotherapy (20 Gy/5fr) to SBRT (24 Gy/2fr) in patients with solid tumours and MRI documented, painful spinal metastases suitable for RT. The primary accrual objective for the phase II portion of the study was met in January 2017 and the study continues as a randomized phase III study with a primary outcome measure of complete pain response at 3 months post radiotherapy. Secondary objectives include: measurement of complete pain response at 6 months; radiation site progression free survival at 3 and 6 months; adverse event profile, health related QOL and compliance with RT QA measures. Biobanking for future correlative studies is included in study design. Statistical design: The statistical assumptions for the phase III study include estimated complete pain response rates of 10% and 30% for the CRT and SBRT treatment arms respectively. Using a two sided alpha = 0.05 and power = 80% the sample size for the phase III study is 152, taking into account a 5% drop out rate. Conduct to Date: Study activation: July 2015. Accrual to date: 58. Supported by CCSRI grant 021039 Clinical trial information: NCT02512965.

LBA10500 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Temporal trends in chronic disease among survivors of childhood cancer diagnosed across three decades: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Todd M. Gibson, St. Jude Children's Research Hospital, Memphis, TN*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 PM (EDT) on Friday, June 2, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

10501 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Age-associated vulnerability to treatment-related late cardiotoxicity: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: James Edward Bates, University of Florida, Gainesville, FL*

Background: Cardiovascular disease (CVD) is the most common non-cancer cause of death in long-term survivors of pediatric cancer. We investigated the role of age at diagnosis in modifying treatment-related late CVD risk in the CCSS population. **Methods:** We evaluated CTCAE grade 3 – 5 CVD events occurring ≥5 years after diagnosis in 23,465 5-year survivors of pediatric cancer diagnosed 1970-1999. We estimated the rates of developing any CVD, including coronary artery disease (CAD) or heart failure (HF). Modifications of treatment effects by age at diagnosis were analyzed using piecewise exponential models adjusting for current age, race, and smoking. **Results:** At a median age of 28.4 years (range 5.6 –58.3) and follow up of 20.2 years (5 – 39.3), 239 CAD and 359 HF events occurred. The cumulative incidence of CVD, CAD, and HF were 4.8% (95% CI: 4.3-5.3), 2.4% (95% CI: 2.2-2.9), and 2.5% (95% CI: 2.2-2.9) by 30 years from diagnosis. Mean cardiac radiotherapy (CRT) doses of ≥10 Gy were associated with a progressively increasing risk of CVD (10 - < 20 Gy: RR 3.6, 95% CI 2.1 – 6.2, $p < 0.01$; 20 - < 30 Gy: RR 4.4, 95% CI 2.7 – 7.2, $p < 0.01$; ≥30 Gy: RR 7.5, 95% CI 4.9 – 11.5, $p < 0.01$) relative to those receiving no CRT. In those receiving a low mean CRT dose (0.1 - < 10 Gy), younger children had higher rates of CVD (0 – 4 years: RR = 2.2, 95% CI = 1.0 – 4.6, $p = 0.04$; > 4 - ≤13 years: RR = 2.1, 95% CI = 1.1 – 4.1, $p = 0.03$) compared to those > 13 years, an effect not seen at higher doses. Among survivors exposed to anthracycline doses ≥250 mg/m2, those age 0 – 4 at diagnosis had increased risk of both CAD (RR = 4.9, 95% CI 1.5 – 16.3, $p = 0.01$) and HF (RR = 3.0, 95% CI 1.6 – 5.0, $p < 0.01$). Cisplatin exposure ≥300 mg/m2 was associated with increased risk of any CVD (RR = 1.8, CI = 1.2 – 2.6, $p < 0.01$), primarily attributable to increased risk of HF (RR = 2.3, 95% CI = 1.5 - 3.5, $p < 0.01$). **Conclusions:** Among long-term survivors of pediatric cancer, increasing CRT dose is associated with increased risk for CVD in a dose-response relationship. Young children are at higher risk for CVD after low-dose CRT or high-dose anthracycline exposure. Cisplatin exposure significantly increases risk for CVD. These findings should inform future treatment and surveillance protocols.

10502 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

A high-risk genetic profile for premature menopause (PM) in childhood cancer survivors (CCS) exposed to gonadotoxic therapy: A report from the St. Jude Lifetime Cohort (SJLIFE) and Childhood Cancer Survivor Study (CCSS). *First Author: Russell J Brooke, St. Jude Children's Research Hospital, Memphis, TN*

Background: CCS are at increased risk of therapy-related PM but contribution of genetic factors is unknown. **Methods:** Using Affymetrix 6.0 SNP array, treatment exposures [cumulative alkylating agents (AA), ovarian radiotherapy (RT) dose] and clinically-assessed PM status (menopause < 40 years), a genome-wide association analysis was conducted using logistic regression in SJLIFE. A cluster of most statistically significant SNPs on chr4 was further examined, stratifying by ovarian RT and AA. Replication was performed using self-reported PM in CCSS. **Results:** PM was diagnosed in 30 of 805 SJLIFE female survivors. A loci of 13 SNPs in 4 linkage disequilibrium blocks (mean $r^2 = 0.51$) in the upstream regulatory region of Neuropeptide Receptor 2 (*NPY2R*) was identified with a minimum p-value of 3.3×10^{-7} (all $< 10^{-5}$). ENCODE gene expression, motifs, and chromatin remodeling data suggest these SNPs alter transcription factor binding sites, potentially disrupting neuroendocrine events necessary for ovulation. Among CCS exposed to ovarian RT, homozygous carriers of a risk profile (RP) defined by 4 of the 13 SNPs, found in over half of the survivors with clinically-diagnosed PM and 1 in 7 in the general population, significantly increased PM risk (odds ratio (OR) 25.8, $p = 5.4 \times 10^{-5}$) (Table). This finding was replicated using self-reported PM status of 1644 survivors in CCSS (OR 4.2, $p = 4.6 \times 10^{-4}$). Prediction of clinically-diagnosed PM (in the SJLIFE discovery cohort) improved by adding the RP to the model with age and treatment (area under ROC curve 0.84 vs. 0.93, p=0.011). **Conclusions:** The common RP is associated with PM risk in pediatric cancer survivors and may have potential for clinical application.

SJLIFE discovery and CCSS replication.

Treatment		SJLIFE			CCSS		
Ovarian RT	AA≥8 g/m^2	N (Clinically-diagnosed PM %)	RP OR (95% CI)	Exact P-value	N (Self-reported PM %)	RP OR (95% CI)	Wald P-value
No	No	490 (0.4)	5.9 (0.3-56.1)	0.099	1026 (2.0)	0.5 (0.1-2.3)	0.40
No	Yes	202 (2.5)	11.4 (1.8-72.5)	0.040	284 (9.2)	0.7 (0.1-2.4)	0.43
Yes	Yes&No	113 (20.4)	25.8 (6.2-137.4)	5.4×10^{-5}	334 (10.5)	4.2 (1.9-9.3)	4.6×10^{-4}

10503 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Molecular alterations to predict survival and response to chemotherapy of pediatric low-grade glioma. *First Author: Michal Zapotocky, The Hospital for Sick Children, Toronto, ON, Canada*

Background: RAS/MAPK pathway mutations have been identified as the major drivers of pediatric low-grade glioma (pLGG). The impact of these alterations on outcome and response to therapy is still unknown. **Methods:** We performed a large population based study of all pLGG diagnosed from 1985-2015. Detailed treatment and very long term outcome data was collected on all patients. Known pLGG-related alterations were detected using NanoString and QX200™Droplet Digital™PCR. Molecular data was correlated with outcome and response to chemotherapy. **Results:** In our cohort of 614 patients, BRAF was found to be altered in 57% and wild-type (WT) in 43% of patients without neurofibromatosis 1 (NF1). Among BRAF-WT we identified H3.3K27M, FGFR1-TACC1, MYBL1 and other alterations. Molecular alterations stratified pLGG into several risk groups. Ten-year progression free survival (PFS) was 72.3% for NF1, 69.5% for KIAA1549-BRAF, 53.5% for BRAF-WT, 30.3% for BRAF-V600E and 0% for H3.3K27M mutations ($p < 0.0001$). Similarly, overall survival (OS) at 10 years delineated difference between excellent survival of KIAA1549-BRAF and NF1 compared to BRAF-V600E and BRAF-WT ($p = 0.0005$). Interestingly, all patients with FGFR1-TACC1 and MYBL1 were alive despite observed progressions. Strikingly, response to chemotherapy determined by changes in tumor size at 6 months of therapy correlated with pLGG alteration. Objective response to first line chemotherapy was observed in 46% of patients with KIAA1549-BRAF and 35% of NF1. In contrast, only 15% BRAF-V600E and 18% BRAF-WT responded and 41% tumors grew after six months of chemotherapy. Moreover, 5-year PFS after chemotherapy was strikingly low for BRAF-V600E and BRAF-WT (25% and 31.9% respectively) compared to KIAA1549-BRAF (50%) and NF1 (76.7%) ($p = 0.001$). This translated to decreased OS for BRAFV600E and BRAF-WT patients ($p = 0.042$). **Conclusions:** Our study provides evidence that molecular alterations dictate the outcome of pLGG. KIAA1549-BRAF harbors excellent prognosis and choice of therapy should be made in favor of less toxic agents to minimize deleterious late effects. In contrast, poor prognosis is associated with lack of response to chemotherapy in BRAF-V600E and BRAF-WT tumors.

10504 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

A phase II prospective study of selumetinib in children with recurrent or refractory low-grade glioma (LGG): A Pediatric Brain Tumor Consortium (PBTC) study. *First Author: Jason R. Fangusaro, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL*

Background: A greater understanding of the Ras-MAP kinase-signaling pathway in pediatric low-grade glioma (LGG) paired with the availability of potent selective inhibitors has enhanced the ability to target this pathway with therapeutic intent. **Methods:** The PBTC conducted a multi-institutional phase II study (NCT01089101) evaluating selumetinib (AZD6244, ARRY-142886), a MEK I/II inhibitor, in children with recurrent/refractory LGG assigned to 6 strata and treated at 25 mg/m^2/dose PO BID for up to two years. Here we present the data from three of these strata. The remaining strata are still accruing patients. **Results:** Stratum I included children with non-NF-1 and non-optic pathway recurrent/refractory pilocytic astrocytoma (PA) harboring BRAF aberrations (BRAF V600e mutation or the BRAF-KIAA 1549 fusion). Eight of 25 (32%) patients achieved a partial response (PR) with 2-year PFS of 66+/-11%. Two of 7 (29%) patient tumors with a BRAF V600e mutation and 6/18 (33%) with a BRAF KIAA-1549 fusion had a PR. Stratum 3 enrolled NF-1-associated LGG. Tissue for tumor BRAF evaluation was not required for eligibility. Ten of 25 (40%) achieved PR with a 2-year PFS of 96+/-4%. Only one patient progressed while on treatment. Stratum 4 included children with non-NF-1 optic pathway/hypothalamic LGG. Tissue for tumor BRAF evaluation was not required for eligibility. Two of 16 (12.5%) had a PR with a 2-year PFS of 65+/-13%. The BRAF aberration status of the responders in strata 3 and 4 is mostly unknown. All responses were confirmed centrally and seven patients remain on treatment. The most common toxicities were grade 1/2 CPK elevation, diarrhea, hypoalbuminemia, elevated AST and rash. Rare grade 3/4 toxicities included elevated CPK, rash, neutropenia, emesis and paronychia. **Conclusions:** Selumetinib was effective in treating children with recurrent/refractory LGG, including those with NF-1 associated LGG and PA harboring BRAF V600e mutation or BRAF-KIAA 1549 fusion. Larger prospective studies are necessary to determine the future, specific role of this agent in treating children with LGG harboring specific molecular aberrations. Clinical trial information: NCT01089101.

10505 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

ACNS1221: A phase II study for the treatment of non metastatic desmoplastic medulloblastoma in children less than 4 years of age—A report from the Children Oncology Group. *First Author: Lucie Lafay-Cousin, Alberta Children's Hospital, Calgary, AB, Canada*

Background: Nodular desmoplastic medulloblastoma and medulloblastoma with extensive nodularity (ND/MBEN) have been associated with a more favorable outcome in younger children. However, treatment-related neurotoxicity remains a significant concern in this vulnerable group of patients. **Methods:** We prospectively conducted a single-arm multicenter trial of conventional chemotherapy for non-metastatic ND/MBEN, based on a modified HIT SKK2000 regimen excluding the use of intraventricular methotrexate (MTX) injection, with the aim to achieve a similar outcome with reduced treatment related neurotoxicity. The design required 37 patients and targeted a 2-year PFS of $\geq$ 90%. Secondary objectives included evaluation of feasibility of timely central pathology review, prospective evaluation of the cohort's molecular profile and neurocognitive outcomes. **Results:** Between 12/2013 and 07/2016, 26 patients were enrolled, including 16 males and 10 females, diagnosed at a median age of 19.7 months (7.1-42.9 months). Four patients had residual disease at baseline. There were 19 ND and 7 MBEN medulloblastoma, confirmed by central pathology review. All cases were reviewed within 10 days by at least 2 of the 3 neuropathologists. The study was closed early following interim analysis due to a higher than expected relapse rate. At last follow-up, 7 patients had relapsed (3 local, 2 distant and 2 combined) at a median time of 9.7 months from diagnosis (range, 9.5-13.7 months). One patient subsequently died of disease. The current median follow-up for the 25 survivors is 1 year (range, 0.2-1.9 years) and the 1 year PFS rate is 66.2% (SE 12.2%). Based on the currently available information, older age ($p = 0.07$) and ND histology ($p = 0.009$) appear to be associated with worse PFS. To date none of the patients with MBEN histology have relapsed. **Conclusions:** The proposed modified regimen of chemotherapy without intraventricular MTX failed to achieve the desirable 2 y PFS of 90%, leading to premature closure of the study. Ongoing molecular characterization of the cohort may help uncover patients who may still benefit from this regimen. Clinical trial information: NCT02017964.

10506 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Intensive multi-modality therapy for extra-ocular retinoblastoma (RB): A Children's Oncology Group (COG) trial (ARET0321). *First Author: Ira J. Dunkel, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Metastatic RB is associated with a poor prognosis. Previous small series suggested that intensified systemic chemotherapy with or without radiation therapy (RT) may improve outcomes in this population. COG opened this prospective, multi-institutional, international trial to study the effectiveness of this approach. **Methods:** Patients with regional extra-ocular RB (stage 2 or 3) were treated with 4 cycles of intensive conventional chemotherapy (vincristine 0.05 mg/kg/day, cisplatin 3.5 mg/kg/day, cyclophosphamide 65 mg/kg x 2 days, etoposide 4 mg/kg x 2 days) followed by involved-field RT (4500 cGy). Two strata of patients with metastatic RB [stage 4a: distant metastases not involving the central nervous system involvement (CNS); and stage 4b (CNS metastases)/trilateral RB)] were treated with 4 cycles of the same chemotherapy. Patients with $\geq$ partial response then received 1 cycle of high-dose carboplatin (Calvert formula with AUC = 7/day, maximum 16.7 mg/kg/day) on days -8 to -6, thiotepa (10 mg/kg/day), & etoposide (8.3 mg/kg/day) on days -5 to -3 with autologous hematopoietic stem cell rescue on day 0. Patients with metastatic RB who did not achieve an adequate response to chemotherapy also received RT. **Results:** Sixty subjects (20 in each stratum) were enrolled; 57 were eligible and included in the analyses (based on data current to June 30, 2016). Toxicity was significant as expected and there were 2 therapy related deaths. Event-free survival (EFS) at 36 months was 87.7% (90% CI 65.4 to 96.0%) for subjects with stage 2 or 3 disease, 79.3% (90% CI 54.2 to 91.6%) for subjects with stage 4a disease and 8.0% (90% CI 1.0 to 25.1%) for subjects with stage 4b/trilateral disease. The observed results significantly improved the EFS in each stratum compared with historical results used for planning the study. **Conclusions:** This is the first prospective, multi-institutional, international study to show that intensive multi-modality therapy is highly effective for patients with regional extra-ocular RB and metastatic RB not involving the CNS. More effective therapy is required for patients with CNS RB. Clinical trial information: NCT00554788.

10507 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Effect of chimeric antigen receptor-modified T (CAR-T) cells on responses in children with non-CNS extramedullary relapse of CD19+ acute lymphoblastic leukemia (ALL). *First Author: Mala Kiran Talekar, Cancer Immunotherapy Program, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Anti-CD19 CAR-T cell therapies have shown high efficacy in inducing durable marrow responses in patients with relapsed/refractory CD19+ ALL. We now report on outcome of 10 patients with extramedullary (EM) involvement of ALL treated with CAR-T, including 5 patients who had EM disease at time of infusion. **Methods:** We identified patients treated on pediatric phase 1/2a trials of murine (CTL019) or humanized (CTL119) anti-CD19 CAR-T cells for isolated EM or BM/EM relapse of ALL. EM relapse was defined as involvement of non-CNS site by imaging +/- pathology within 12 months (mos) of infusion. Post infusion, patients had diagnostic imaging done at 1, 3, 6, 9, and 12 mos. **Results:** Among 97 patients receiving CAR-T, ten (CTL019, n=6; CTL119, n=4) were identified who had EM involvement on average 2.3 mos (range 0-9 mos) prior to infusion; including 5/10 at time of infusion. Sites of EM relapses included testes, sinus, parotid, bone, uterus, kidney and skin, and 5 patients had multiple sites of EM involvement. Patients ranged from 2-4 relapses of their ALL pre-CAR-T. Two had isolated EM relapse (sites were parotid and multifocal bony lesions in one; testis and sinus in second). All 10 patients had undergone hematopoietic stem cell transplantation prior to EM relapse, 2 had received radiation directed to the EM site prior to CAR-T. Five patients evaluated by serial imaging had objective responses: 2 had resolution of EM disease by day 28; 2 had resolution by 3 mos; 1 had continued decrease in size of uterine mass at 3 and 6 mos and underwent hysterectomy at 8 mos with no evidence of disease on pathology. In the 4 patients with prior history of skin or testicular involvement, there was no evidence by exam at day 28. One patient had progressive EM disease within 2 weeks of CAR-T cell infusion and died at 6 weeks. Three relapsed with CD19+ disease [1 skin/medullary- died at 38 mos post CAR-T; 2 medullary (1 died at 17 mos, 1 alive at 28 mos)]. The remaining 6 are alive and well at median follow-up of 10 mos (range 3-16 mos) without recurrence of disease. **Conclusions:** Single agent CAR-T immunotherapy can induce potent and durable responses in patients with EM relapse of their ALL. Clinical trial information: NCT01626495, NCT02374333.

10508 Oral Abstract Session, Sat, 1:15 PM-4:15 PM

Expansion of HER2-CAR T cells after lymphodepletion and clinical responses in patients with advanced sarcoma. *First Author: Meenakshi Hegde, Texas Children's Cancer Center, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX*

Background: Outcome for patients with advanced sarcoma is extremely poor and treatment options are limited. Encouragingly, in our phase 1 dose-escalation trial (Ahmed et al, JCO 2015), systemic administration of up to $1x10^8/m^2$ autologous HER2-CAR T cells in patient with HER2+ sarcoma was safe. While T cells did not expand, 4/19 evaluable patients are alive 37-61 months post infusion without evidence of disease. The goal of this study was to evaluate if lympohodepleting chemotherapy can safely induce the expansion of HER2-CAR T cells. **Methods:** In a phase 1 clinical study, NCT00902044, we administered $1x10^8/m^2$ autologous HER2-CAR (with a CD28.zeta signaling domain) T cells to patients with refractory/metastatic HER2+ sarcoma after lymphodepletion. **Results:** Six patients with refractory/metastatic HER2+ sarcoma (4 osteosarcoma, 1 rhabdomyosarcoma, 1 synovial sarcoma) with a median age of 16 (range: 4 to 55) received up to 3 infusions of $1x10^8$ cells/m^2 CAR T cells after lymphodepletion with either fludarabine (Flu; n = 3) or Flu and cyclophosphamide (Flu/Cy; n = 3). Flu and Flu/Cy induced lymphopenia with an absolute lymphocyte count (ALC) of $<$ 100/ml at the day of the T-cell infusion. Only Flu/Cy induced neutropenia (absolute neutrophil count [ANC] $<$ 500/ml) for up to 14 days. 4/6 patients developed grade 1-2 cytokine release syndrome (CRS) within 24 hours of CAR T-cell infusion that resolved completely with supportive care within 3 days of onset. T cells expanded in 5/6 patients (median 89-fold (range: 41 to 2,893) with a median peak expansion on day 7 (range: 5 to 28). CAR T cells could be detected by qPCR in 6/6 patients at 6 weeks post infusion. One patient with rhabdomyosarcoma metastatic to the bone marrow had a complete responses (CR), 2 had stable disease (SD), and 3 had progressive disease (PD). Two patients are alive with a median overall survival of 14.2 months. **Conclusions:** Infusion of autologous HER2-CAR T cells after lymphodepletion is safe, and can be associated with objective clinical benefit in patients with advanced HER2+ sarcoma. These findings warrant further evaluation in a phase 2b study as a single agent or in combination with other approaches. Clinical trial information: NCT00902044.

10509 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

The INFORM personalized medicine study for high-risk pediatric cancer patients. *First Author: Barbara Christine Worst, German Cancer Research Center (DKFZ), Heidelberg, Germany*

Background: Relapses from high-risk tumors pose a major clinical challenge in pediatric oncology. The German INFORM registry (INdividualized therapy FOr Relapsed Malignancies in children) addresses this problem using integrated next-generation sequencing to rapidly identify patient-specific therapeutic targets. **Methods:** Whole-exome, low-coverage whole-genome and RNA sequencing is complemented with microarray-based DNA methylation profiling. Identified alterations are discussed and prioritized according to biological significance and potential druggability in a weekly molecular tumor board. **Results:** To date, 214 tumor samples of high-risk pediatric cancer patients have been profiled from 47 German centers, with 39% being sarcomas, 30% brain tumors, 13% neuroblastoma and 18% hematological or other malignancies. Turnaround time from tissue arrival to molecular results was 21 calendar days on average. In 14/214 patients (7%) we identified an underlying germline predisposition syndrome. In several cases there were discrepancies between the original histological diagnosis and our molecular findings, especially in brain tumors. We detected one or more potentially druggable alterations in 147/214 (69%) cases. Tyrosine kinases, the PI3K/mTOR pathway, MAPK pathway, and cell-cycle as well as transcriptional regulators were commonly affected. Based on these findings, targeted therapeutics were incorporated into the therapy regime in one-third of patients, with anecdotal reports of marked responses, including a patient with a pleomorphic sarcoma, where we detected a previously undescribed RAF-fusion, showing a partial remission upon RAF-inhibition. **Conclusions:** In summary, real-time comprehensive profiling of pediatric tumors provides valuable diagnostic information and identifies potential therapeutic targets. In parallel, the implementation of a systematic program for reverse-translational evaluation is ongoing. Recently, this nationwide effort has expanded to include patients from other countries. We will also recruit patients to the complementary eSMART and INFORM2 biomarker-driven, phase I/II combination trial series, to provide unprecedented access to targeted therapies in Europe.

10510 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

A pediatric phase I study of larotrectinib, a highly selective inhibitor of the tropomyosin receptor kinase (TRK) family. *First Author: Theodore Willis Laetsch, The University of Texas Southwestern, Children's Health, Dallas, TX*

Background: Larotrectinib is the first selective small-molecule inhibitor of TRKA, B, and C in clinical development. Data from the adult phase I trial demonstrate prolonged responses in patients (pts) with TRK fusions and a favorable tolerability profile. **Methods:** This multicenter, rolling 6 phase I study enrolled pts with refractory solid or CNS tumors aged $\geq$ 1 month – 21 years. Pts were dosed orally BID on a continuous 28-day schedule either by capsule or solution. Pharmacokinetic (PK)-directed intra-subject dose escalation was permitted, with exposures targeting the adult recommended Phase II dose (RP2D) of 100 mg BID. The primary objective was to define the MTD / RP2D; secondary objectives included PK and efficacy using RECIST v1.1. **Results:** As of December 31, 2016, 17 pts (12 with TRK fusions, 5 without TRK fusions) with a median age of 5.2 years (0.4 – 18.3) were enrolled to 3 dose levels. Pts were enrolled with fusions of all 3 NTRK genes: *NTRK1* (n=6), *NTRK2* (n=1), and *NTRK3* (n=5) in heterogeneous tumor diagnoses: infantile fibrosarcoma (IFS) (n=6), other sarcoma (n=4), and papillary thyroid cancer (n=2). Most common AEs regardless of attribution were vomiting, diarrhea, and fatigue. While 8 (47%) pts experienced grade 3-4 AEs, none were attributed to larotrectinib. No DLTs were observed and an MTD was not established. Both formulations delivered dose-dependent PK comparable to the adult RP2D at dose level 3. 12 pts (10 with TRK fusions, 2 without TRK fusions) remain on treatment with median follow-up of 2.8 months (0.7 – 8.4). Among TRK fusion pts, the vast majority have achieved confirmed RECIST responses regardless of tumor diagnoses. No responses were seen in pts without TRK fusions (n=4). 5 pts discontinued therapy, including 2 with TRK fusions: 1 pt with IFS had sufficient response to allow tumor resection, and 1 pt with IFS progressed with a documented acquired resistance mutation. **Conclusions:** Larotrectinib has demonstrated a favorable tolerability profile and histology-independent efficacy in pediatric pts harboring TRK fusions. Updated safety and efficacy data will be presented, including the RP2D, response rate, duration of response, and use of larotrectinib in the pre-surgical setting. Clinical trial information: NCT02637687.

10511 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase II trial of dasatinib (DAS) in pediatric patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP). *First Author: Lia Gore, University of Colorado School of Medicine/Children's Hospital Colorado, Aurora, CO*

Background: Safe and effective treatment options for newly diagnosed (ND) or imatinib (IM) resistant/intolerant (R/I) pediatric CML pts are limited, and a large prospective study is needed. DAS has proven safety and efficacy in adults with ND or IM-R/I CML and is now being evaluated in a phase II trial of pediatric pts. **Methods:** CA180-226/NCT00777036 is an open-label nonrandomized prospective study of pts aged $<$18 y in 3 cohorts: (1) CML-CP R/I to IM treated with DAS tablets 60 mg/m^2 QD, (2) IM-R/I CML-AP/BP or Ph+ ALL (enrollment closed early due to poor response), and (3) ND CML-CP treated with DAS tablets 60 mg/m^2 or DAS 72 mg/m^2powder for oral suspension (PFOS) QD. Primary objectives were major cytogenetic response (MCyR) for CML-CP R/I to IM and complete cytogenetic response (CCyR) for ND CML-CP (MCyR $>$30% and CCyR $>$55% considered of clinical interest). **Results:** 113 pediatric CML-CP pts were treated. Cumulative rate of MCyR $>$30% was reached as early as 3 mo (55%; [95% CI 36, 74]) for IM-R/I CML-CP. Cumulative rate of CCyR $>$55% was reached as early as 6 mo (64% [95% CI 53, 74] for ND CML-CP; 61% [95% CI 46, 74] for pts on tablets and 70% [95% CI 51, 84] for pts on PFOS). Estimated PFS by 48 mo was $>$75% for CML-CP R/I to IM and $>$90% for ND CML-CP. One CML-CP pt R/I to IM died 1 y after stopping DAS from gastrointestinal bleeding. AEs were consistent with those observed in adults, except no DAS-related pleural/pericardial effusion or pulmonary arterial hypertension (PAH) were reported here. **Conclusions:** In the largest prospective trial of pediatric pts with CML-CP, target responses were met early and increased over time with DAS treatment. The efficacy and safety of DAS were consistent with previous reports in adults, except no cases of pleural/pericardial effusion or PAH were observed. These results suggest DAS is safe and highly effective in the first- or second-line treatment of pediatric CML-CP. Clinical trial information: NCT00777036.

		ND CML-CP	
	CML-CP R/I to IM	Tablet	PFOS
Pts treated, n	29	51	33
Median duration of treatment, mo (range)	50 (2-90+)	52 (8-75+)	27 (<1-42+)
Responses by 24 mo, % (95% CI)			
MCyR	90 (73, 98)	96 (90, 99)	
		98 (90, 100)	94 (80, 99)
CCyR	83 (64, 94)	94 (87, 98)	
		96 (87, 100)	91 (76, 98)
Major molecular response	55 (36, 74)	70 (59, 80)	
		75 (60, 86)	64 (45, 80)

10512 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). *First Author: Deepa Bhojwani, Children's Hospital Los Angeles, Los Angeles, CA*

Background: Inotuzumab ozogamicin (InO), a CD22-targeting antibody linked to calicheamicin demonstrated exceptional activity in R/R ALL in adults. InO has been available to pediatric patients with R/R ALL via a compassionate access program. **Methods:** Participating international pediatric oncology centers received IRB approval to submit retrospective demographic, outcome and toxicity data on pediatric patients who received at least one dose of InO. **Results:** Thirty-four patients, age 2.3-21.4 yrs (median 11.7) received 1-4 cycles (3 weekly doses) of InO. Patients were heavily pretreated in 1^{st}-5^{th}relapse; 28 were refractory to their preceding regimen. Thirteen patients had prior hematopoietic stem cell transplant (HSCT), 27 received prior CD19 and 8 prior CD22-directed therapy. Pre-InO disease was M3 (> 25% blasts) in 26 patients, M2 (5-25%) in 3, and MRD only in 5 (1 with extramedullary disease). Of 29 patients with M2/M3 disease at baseline, 18 (62%) achieved a complete remission (CR), 13 of whom were MRD negative. Post-InO, 15 patients proceeded to HSCT and 5 to CAR T-cell therapy. Alterations in CD22 expression at subsequent relapse were noted in two patients with available blasts samples. No deaths were attributed to InO during therapy. The incidence of grade 3/4 infections was 38% and were of the expected types. Grade 1-4 hepatic toxicity was noted in 11/34 (32%) patients, primarily asymptomatic elevations in transaminases/bilirubin. There was no sinusoidal obstruction syndrome (SOS) during InO therapy but 8/15 patients who received HSCT post-InO developed SOS. One patient died from SOS, but the others recovered. The incidence of SOS was higher in patients who had undergone prior HSCT (6/8) versus no prior HSCT (2/7). SIRS (1), neurotoxicity (2) and hemorrhage (3) were infrequent. Three patients had musculoskeletal pain associated with edema. **Conclusions:** Single agent InO had a CR rate of 62% in heavily pretreated pediatric patients. Toxicities were similar to adults with hepatic and infectious toxicity being the most common. Overall InO was well tolerated, but the incidence of SOS was high in patients who underwent HSCT post-InO, particularly in those who had undergone a prior HSCT.

10513 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Efficacy and safety of defibrotide (DF) to treat hepatic veno-occlusive disease/ sinusoidal obstruction syndrome (VOD/SOS) after primary chemotherapy (CT): A post hoc analysis of final data. *First Author: Nancy A. Kernan, Pediatric Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: VOD/SOS, which may be unpredictable and potentially life-threatening, is typically considered a complication of hematopoietic stem cell transplantation (HSCT); VOD/SOS with multi-organ dysfunction (MOD) may be associated with >80% mortality. DF is approved to treat hepatic VOD/ SOS with renal or pulmonary dysfunction post-HSCT in the US and to treat severe hepatic VOD/SOS post-HSCT in the EU. However, VOD/SOS can occur after CT without HSCT. **Methods:** In an expanded-access protocol for patients (pts) with VOD/SOS post-HSCT or CT, with/without MOD (renal/pulmonary), DF 25 mg/kg/d (6.25 mg/kg q6h) was given a recommended ≥21 days. Post-CT subgroup survival was analyzed post hoc from the day DF was started (days 0–30 after start of CT) for 70 days (ie, up to 100 days, as follow-up was collected for 100 days post-CT). **Results:** Of 1154 VOD/SOS pts receiving DF, 137 (12%) developed VOD/SOS post-CT without HSCT. Among 82 pts (38 with MOD) treated by day 30 after start of CT, median age was 7.5 yrs (range, 0–68 years) and 66 (81%) were ≤16 yrs. Most common primary diseases were acute leukemias (65%). Kaplan-Meier estimated survival at day +70 was 74% overall (95% CI, 63–82%); 66% (49–79%) and 81% (66–90%) in pts with/ without MOD, respectively. In the pediatric pts, estimated survival at day +70 was 80% (68–88%); in adult pts, 50% (25–71%). Adverse events (AEs) were reported in 54/82 pts (66%); 22 (27%) had AEs assessed as possibly related to DF, most commonly (≥2%) pulmonary or mouth hemorrhage (4% each) and hematochezia, nausea, encephalopathy, epistaxis, or hypotension (2% each). Hemorrhagic AEs of any relatedness (≥2%) were pulmonary (6%), epistaxis or mouth (4%), and hematochezia (2%). Related AEs led to discontinuation in 6 pts and were associated with 1 death (pulmonary hemorrhage, hypotension). **Conclusions:** The 74% survival rate at day +70 in pts with VOD/SOS receiving DF within 30 days of starting CT (80% in pts ≤16 yrs) is clinically encouraging. Of note is the 66% survival rate in pts with MOD. The safety profile was consistent with that previously reported in the overall population of this protocol. Support: Jazz Pharmaceuticals Clinical trial information: NCT00628498.

10514 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Measuring mercaptopurine (6MP) adherence using red cell 6MP metabolite levels in children with acute lymphoblastic leukemia (ALL): A COG AALL03N1 study. *First Author: Anna Lynn Hoppmann, University of Alabama at Birmingham, Birmingham, AL*

Background: Non-adherence to 6MP (monitored with medication event monitoring system [MEMs]) is associated with an increased risk of relapse in children with ALL.(JAMA Oncol, 2015) Self-report over-estimates true medication intake, particularly in non-adherent patients.(Blood, 2017) However, monitoring adherence using MEMs is logistically difficult. We investigated whether red cell 6MP metabolite levels (thioguanine nucleotide [TGN] and methylated mercaptopurine [MMP]) taken together, could identify non-adherent patients. **Methods:** The analysis included children with ALL in maintenance. To minimize variability in TGN and MMP levels due to pharmacogenetics, we excluded *TPMT* heterozygotes and homozygote mutants. We also excluded Asians to remove variability due to *NUDT15*. TGN and MMP levels were drawn at 6 consecutive monthly time points for each patient and averaged. TGN and MMP levels (pmol/8 x 10^8red cells) were standardized, adjusted for 6MP dose intensity, and then analyzed using cluster analysis (Spath, H. [1980]). **Results:** The 373 patients eligible for analysis yielded 5 clusters. Cluster #1 (n = 119; mean MMP: 15,656; mean TGN: 158); Cluster #2 (n = 211; MMP: 6,042; TGN: 135); and 3 very small outlying clusters (total N = 43). Adjusting for age, sex, race/ethnicity, cytogenetics and NCI risk, we found that patients in Cluster #2 were 2.6 times as likely to be non-adherent (MEMs-based adherence < 95%) compared to Cluster #1 (95% CI 1.5-4.4; *P*= 0.0007). Mean MEMs-based adherence was significantly higher for patients in Cluster #1 (94.3%) when compared to those in Cluster #2 (87.8%, p = 0.0002). Using Fine-Gray proportional subdistribution hazards models for competing risks and adjusting for clinical and sociodemographic factors, we found that patients in Cluster #2 were at a 2.3-fold higher risk of relapse compared with those in Cluster #1 (95%CI, 1.0-6.4, p = 0.058). **Conclusions:** These findings illustrate the potential for using a combination of red cell TGN and MMP levels in identifying non-adherent patients. We propose to use these and clinical and demographic factors associated with non-adherence in creating an adherence calculator.

10515 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Four versus five chemotherapy courses in patients with low risk acute myeloid leukemia: A Children's Oncology Group report. *First Author: Kelly D. Getz, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: For pediatric patients with low risk (LR) acute myeloid leukemia (AML), the Children's Oncology Group (COG) trial AAML1031 used a 4-course chemotherapy backbone consisting of two induction courses of cytarabine/ daunorubicin/etoposide, a third course of cytarabine/etoposide and a fourth course of cytarabine/mitoxantrone. The prior COG trial, AAML0531, included the same four courses plus a fifth course of high dose cytarabine. Removal of course 5 from AAML1031 was based in part on prior studies that suggested no benefit from a fifth course. **Methods:** We compared overall survival (OS), disease free survival (DFS), and relapse risk (RR) for LR patients receiving four versus five chemotherapy courses in a pooled analysis of comparable patients treated on AAML0531 and AAML1031. LR was defined as the presence of inv (16)/t(16;16) or t(8;21) cytogenetic features, NPM1 or CEBPA mutations, or MRD < 0.1% post-Induction I in those with no high risk features. AAML0531 patients assigned to gemotuzumab were excluded. Follow-up for outcomes began at the start of course 4. Cox (OS and EFS) and risk (RR) regressions were used to estimate unadjusted hazard ratios (HR) comparing outcomes for patients who received only four versus five chemotherapy courses. Start of a fifth chemotherapy course was assessed as a time-varying exposure in all analyses to avoid exposure misclassification. **Results:** A total of 921 LR patients (225 from AAML0531, 696 from AAML1031) were included; 191 (21%) received a fifth course. There were no significant differences in distributions of sex, age, race, or ethnicity between patients treated with four or five courses. Median times to absolute neutrophil count and platelet count recovery after course 4 were also comparable. Patients who received only four courses had significantly lower OS (HR = 1.83, 95% CI: 1.22-2.74, p = 0.003), DSF (HR = 1.49, 95% CI: 1.13-1.97, p = 0.005), and higher RR (HR = 1.42, 95% CI: 1.08-1.88, p = 0.013) compared to those who received five courses. **Conclusions:** Removal of a fifth cytarabine-containing course appears to result in worse OS, DFS, and RR in pediatric patients with LR AML. Multivariable analyses to further refine the estimates are ongoing.

10516 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Temporal trends in late-onset morbidity and mortality after medulloblastoma diagnosed across three decades: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Ralph Salloum, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: Therapy for medulloblastoma and primitive neuroectodermal tumor has evolved from surgery and adjuvant radiotherapy to risk-adapted multimodal regimens. The impact of these changes in treatment on long-term outcomes remains unknown. **Methods:** Cumulative incidence of late mortality (> 5 years from diagnosis), subsequent malignant neoplasms (SMN), chronic health conditions and psychosocial functioning were evaluated among 5-year survivors in CCSS diagnosed between 1970 and 1999. Survivors were stratified according to treatment decade (1970s, 1980s, 1990s) and treatment exposure (surgery + craniospinal irradiation [CSI] ≥30 Gy, no chemotherapy; surgery + CSI ≥30 Gy + chemotherapy [high-risk therapy], surgery + CSI ˂30 Gy + chemotherapy [standard-risk therapy]). Rate ratios (RRs), odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for long-term outcomes among treatment eras and exposure groups using multivariable piecewise-exponential models. **Results:** Among 1,380 eligible survivors (median [range] age 29 [6-20] years; 21.4 [5-44] years from diagnosis), the 15-year cumulative incidence of all-cause (21.9% 1970s vs. 12.8% 1990s; p = 0.003) and recurrence-related (16.2% vs 9.6%, p = 0.03) late mortality decreased with no reduction in mortality attributable to late effects of therapy including SMN. Among 959 participants, the incidence of SMN did not decrease by era or by treatment group. However, survivors treated in the 1990s had an increased cumulative incidence of severe, life-threatening and fatal health conditions (16.9% 1970s vs 25.4% 1990s; p = 0.03), and were more likely to develop multiple severe or life-threatening health conditions, RR = 2.98 (95% CI, 1.10-8.07). Survivors of standard-risk therapy were less likely to use special education services than high-risk therapy patients, OR = 0.51 (95% CI, 0.33-0.78). **Conclusions:** Historical changes in therapy have improved 5-year survival, reduced risk of late mortality due to disease recurrence, and reduced special education utilization, at the cost of increased risk for multiple, severe and life-threatening chronic health conditions.

10517 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Subcortical brain volumes and neurocognitive function in survivors of childhood acute lymphoblastic leukemia (ALL) treated with chemotherapy-only. *First Author: Nicholas Steve Phillips, St. Jude Children's Research Hospital, Memphis, TN*

Background: Brain deep grey nuclei and glucocorticoid receptor rich hippocampal subregions may be sensitive to neurotoxic effects of chemotherapy-only protocols for childhood ALL and associated with neurocognitive problems in long-term survivors. **Methods:** Brain MRIs and neurocognitive tests were obtained on 176 survivors (49% male, mean [range] age at diagnosis 6.8 [1-18] years, 14.5 [8-27] years at evaluation). MRI's were also obtained on 82 healthy community controls (57% male, 13.8 [8-26] years at evaluation). General linear models were used to compare subcortical brain volumes between survivors and controls. Among survivors, gender stratified multivariable linear models were used to test associations between subcortical volumes, and serum concentration of dexamethasone (DEX) and high-dose methotrexate (HDMTX), adjusting for age at diagnosis, and intracranial volume (ICV). Volumes were also compared to neurocognitive tests. **Results:** Survivors had smaller volumes in bilateral thalami (p's < 0.05) and hippocampal subregions (p's < 0.001) compared to controls. After controlling for ICV, HDMTX exposure and younger age at diagnosis were associated with smaller bilateral thalami in male survivors (p's < 0.05). DEX was associated with a smaller right thalamus in males (p = 0.04). Smaller hippocampi in both males and females were associated with younger age at diagnosis (p's < 0.01). Smaller left thalamus was associated with worse verbal fluency scores in all survivors (p's < 0.05). Smaller bilateral thalami and hippocampal subregions in girls were associated with worse processing speed, inhibition and cognitive flexibility; poor memory span correlated with smaller left CA1 and right thalamus volumes (all p's < 0.05). Smaller bilateral thalami and right hippocampal subregions, in girls, correlated with slower processing speed (p's < 0.05). In males, smaller left fimbria volume was correlated with poor attention (p = 0.03). **Conclusions:** ALL survivors have significantly smaller thalamic and hippocampal volumes compared to healthy community controls. In survivors, smaller volumes correlate with worse cognitive performance.

10518 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Family history of cardiovascular disease and cardiovascular comorbidities risk in a pediatric cancer population. *First Author: Thomas Patrick Curtin, University of Utah School of Medicine, Salt Lake City, UT*

Background: Survival rates for childhood cancer patients have improved dramatically, but the growing survivor population suffers from increased treatment-related toxicity including high risk for cardiovascular disease (CVD). While the link between chemotherapy and radiation to cardiotoxicity is well established, few studies seek to determine if an underlying familial risk for cardiovascular disease contributes or predicts this risk. The Utah Population Database (UPDB) is a genealogical resource linked to statewide cancer diagnoses and electronic medical data in which family history is objectively determined. **Methods:** We calculated the risk of subsequent CVD (ICD-9 401-449) in relatives of 5602 pediatric cancer patients diagnosed at ages 0-19 in Utah from 1966-2013 with no congenital CVD-related anomalies (ICD-9 745-747, 758-759). We identified 964 patients with subsequent CVD diagnoses. Cox models provided recurrence-risk estimates in first-degree relatives of patients compared to relatives of 5:1 matched controls. **Results:** Pediatric cancer patients were at 5-fold risk of CVD compared to controls ($P< 10^{-15}$). In pediatric patients with subsequent CVD, first-degree relatives were at 30% increased CVD risk compared to relatives of cancer-free controls (HR = 1.31, 95%CI 1.16-1.47; $P< 10^{-5}$). In pediatric patients without CVD, only parents exhibited slight CVD risk (HR = 1.08, 95%CI 1.03-1.14; $P= 0.002$). In 685,000 individuals with a non-congenital CVD history, pediatric cancers among their first-degree relatives were associated with a similar increased risk of subsequent CVD, compared to pediatric cancers among relatives of controls with no CVD events (HR = 1.39, 95%CI 1.18-1.64, $P< 10^{-4}$). **Conclusions:** The UPDB is powerful for investigating comorbidities in cancer patients and their families without recall bias from self-reported family medical history. A family history of CVD may increase risk of CVD-related comorbidities among pediatric cancer patients by 30-40% beyond that observed in patients without a CVD family history. This finding suggests that in addition to a cancer family history, a CVD-related family history should be assessed in children diagnosed with cancer.

10519 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Complete dexrazoxane cardioprotection for cardiac function but incomplete female cardioprotection for cardiac structure in doxorubicin-treated osteosarcoma survivors: Hearts too small for the body. *First Author: Lisa M. Kopp, University of Arizona, Tucson, AZ*

Background: Dexrazoxane is protective for lower-dose doxorubicin (< 300 mg/m^2) cardiotoxicity in childhood cancer, but the effect of dexrazoxane (DXRZ) administered with higher-dose (HD) doxorubicin (DOXO) is unknown. **Methods:** We evaluated patients from Children's Oncology Group trials for localized (P9754) and metastatic (AOST0121) osteosarcoma (OS) who received HD DOXO (375-600 mg/m^2) preceded by DXRZ (10:1 ratio), methotrexate, and cisplatin; some also received ifosfamide alone or ifosfamide/etoposide ± trastuzumab. Cardiotoxicity was identified by echocardiography and by serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations. **Results:** 81 DXRZ -treated OS patients (age at enrollment = 13.7 years; range 3.8 - 23.7 years) had normal left ventricular (LV) systolic function as measured by LV fractional shortening and no heart failure. Female sex and longer follow-up since DOXO were associated with a significantly smaller LV dimension z-score normalized to BSA (μ = -1.20, 95%CI [-1.70, -0.70]). Similarly, in the one-third of patients treated $>$ 81 days after minimal expected treatment (groups equally partitioned by time), significantly thinner LV posterior wall thickness for BSA (μ = -0.57, [-1.05, -0.09]) was found. Interventricular septal wall thickness (μ = -0.84, [-1.2, -0.48]) and LV mass (μ = -0.73, [-1.06, -0.40]) were significantly smaller for BSA than normal for both sexes. For females, these became significantly more abnormal with increasing length of follow-up. Females also showed progressive increases in NT-proBNP. **Conclusions:** DXRZ is cardioprotective for HD DOXO in terms of LV function and heart failure. Females had progressive abnormalities of LV structure, leading to smaller hearts for body size. This was associated with increasing cardiac stress, as measured by NT-proBNP. DXRZ protection was incomplete for HD DOXO effects on LV structure, resulting in higher LV stress and risk for late LV dysfunction. DXRZ should continue to be used in this population, including for females who exhibit more cardiotoxicity than males at specific cumulative DOXO doses.

10520 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Risk of subsequent breast cancer after radiotherapy according to hormone-receptor status: A nested case-control study in the Childhood Cancer Survivor Study (CCSS). *First Author: Lindsay M. Morton, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Survivors of childhood cancer have a high absolute risk of subsequent breast cancer after chest-directed radiotherapy; however, it is not known if this risk differs by hormone-receptor status and radiation to the ovaries. **Methods:** We conducted a nested case-control study within the CCSS of 282 five-year survivors of childhood cancer with subsequent breast cancer and 1202 matched controls. Radiation dose to the location of the breast tumor (or corresponding location for controls) and mean dose to the ovaries were estimated from treatment records for each patient. Risk of radiation-related breast cancer was measured with the Excess Odds Ratio per Gray (EOR/Gy) and corresponding 95% confidence interval (CI), derived from conditional logistic regression. **Results:** The median age at subsequent breast cancer diagnosis was 39 years (range 21-58). Although 87% of cases and 70% of controls received radiotherapy, breast doses were higher in cases than controls (61% vs 24% breast dose $>$ 10Gy), whereas ovarian doses were lower (7% vs 13% ovary dose $>$ 5Gy). In the subset of cases (n = 159) with currently available estrogen receptor (ER) status (76% cases ER+, 24% cases ER-), there was a linear dose-response relation with radiation dose to the breast that was similar for ER+ (EOR/Gy = 0.51; 95%CI: 0.19-1.34) and ER- breast tumors (EOR/Gy = 0.41; 95%CI: 0.05-2.88). If the patient received an ovarian dose $>$ 5Gy, this dose-response was significantly reduced for ER+ tumors but not for ER- tumors. **Conclusions:** Preliminary analyses demonstrate that radiation exposure to the breast to treat childhood cancer results in an increased risk of both ER+ and ER- breast cancers. The novel finding that only the risk of ER+ breast cancer is lowered if the ovaries are also exposed is consistent with known differences by hormone receptor status in the biological mechanisms of breast carcinogenesis.

10521 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Biomarkers of brain injury and neurologic outcomes in children treated with chemotherapy for acute lymphoblastic leukemia (ALL). *First Author: Yin Ting Cheung, St. Jude Children's Research Hospital, Memphis, TN*

Background: Little is known about neurotoxic mechanisms associated with chemotherapy in children with ALL. Cerebrospinal fluid (CSF) biomarkers of brain injury may provide insight into this process. **Methods:** 235 patients (51% male; mean [SD] age diagnosed 6.8 [4.7] years) treated on a chemotherapy only protocol provided CSF samples following diagnosis and through consolidation. CSF was assayed for biomarkers of myelin degradation (myelin basic protein [MBP]), neuronal damage (nerve growth factor [NGF], total-Tau [T-Tau]) and astrogliosis (glial fibrillary acidic protein [GFAP]). Leukoencephalopathy was evaluated by brain MRI's during therapy. At $\geq$5 years post-diagnosis, 138 (70%) of the 198 still eligible survivors (without relapse and unrelated neurologic injury) completed neurocognitive testing and brain diffusion tensor imaging of white matter integrity at age 13.6 [4.6] years. Log-binomial and general linear models were used to examine whether biomarker changes from baseline through consolidation were related to serum methotrexate exposure, acute leukoencephalopathy, and long-term brain outcomes. **Results:** NGF and T-Tau increased from baseline to consolidation (P's $<$ 0.001), while MBP and GFAP were elevated at baseline and remained so through consolidation. The number of intrathecal injections (methotrexate, hydrocortisone, cytarabine) was positively correlated with NGF increase at consolidation (P= 0.005). Increases in GFAP (RR 1.2; 95% CI [1.0 – 1.4]), MBP (RR 1.1 [1.0 – 1.1]) and T-Tau (RR 1.8 [1.1 – 2.8]) were related to higher risk for acute leukoencephalopathy, and higher diffusivity in frontal lobe white matter at $\geq$5 years post-diagnosis (P's $<$ 0.05). Increase in T-Tau at consolidation was associated with worse long-term sustained attention (P= 0.03), and visual- (P= 0.04) and visual-motor (P= 0.02) processing speed. **Conclusions:** Glial injury, which is evident at diagnosis, may be related to leukemia and methotrexate exposure. Neuronal injury is associated with intrathecal chemotherapy and long-term neurocognitive and brain imaging outcomes. Monitoring CSF biomarkers may be useful in identifying individuals at risk for poor neurological outcomes.

10522 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Longitudinal analysis of quality of life outcomes in children during treatment for acute lymphoblastic leukemia: A report from the Children's Oncology Group (COG) AALL0932. *First Author: Daniel Zheng, Yale School of Medicine, New Haven, CT*

Background: 5-year event-free survival for average-risk acute lymphoblastic leukemia (AR-ALL) in children is ~95%. However, therapy involves multi-agent chemotherapy, frequent hospital visits (duration of therapy is 26 months for girls and 38 months for boys) and painful procedures that can adversely affect quality of life (QOL). **Methods:** AR-ALL patients enrolled on COG AALL0932 were offered participation if $\geq$4 years old at diagnosis with an English-speaking parent. At ~2, 8, 17, 26, and 38 (boys only) months after diagnosis, parents completed the PedsQL4.0 and the Family Assessment Device instruments for QOL (assessing physical and emotional functioning) and family functioning, respectively. The proportions of individuals scoring in the impaired range (i.e. 2 SD below population mean) were calculated at each timepoint. Patterns of impairment over time and potential predictors were examined. **Results:** 594 participants with AR-ALL (48% female, 68% white) were diagnosed at a median age of 5.6 (IQR: 4.6–7.1) years. At 2 months, a significant percentage of participants had impaired scores compared to population norms for physical (36.5 vs. 2.3; 95% CI 32.3-40.8) and emotional functioning (26.2 vs. 2.3; 95% CI 22.5-30.2). Although scores improved over time, elevations persisted at 26 months for physical (11.9 vs. 2.3; 95% CI 8.4-16.1) and emotional (9.8 vs. 2.3; 95% CI 2.0-6.7) functioning. In repeated measures analysis with multivariate modeling, emotional impairment at 2 months (OR 3.7; 95% CI 1.5-7.7) and abnormal family functioning (OR 1.5; 95% CI 1.1-2.1) significantly predicted emotional impairment. QOL outcomes were similar for girls at 26 months and boys at 38 months. **Conclusions:** Many children with AR-ALL experience severe impairment in both physical and emotional functioning that begins early in treatment and persists. Family functioning is a modifiable risk factor that may be targeted for early screening and intervention.

10523 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Patient-reported quality of life (QOL) following CTL019 in pediatric and young adult patients (pts) with relapsed/refractory (r/r) b-cell acute lymphoblastic leukemia (B-ALL). *First Author: Andrew Charles Dietz, Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA*

Background: The global ELIANA trial (NCT02435849) evaluates the efficacy and safety of CTL019, a single infusion of genetically modified autologous chimeric antigen receptor–expressing T cells targeting CD19+ cells in pediatric and young adult r/r B-ALL pts. Analyses show a complete response rate of 82% with or without complete blood count recovery $\leq$ 3 months. A serious adverse event rate of 71% was observed in $\leq$ 8 weeks of infusion, decreasing to 17% at $>$ 8 weeks (Grupp S, et al. *Blood*. 2016;128(22) [abstract 221].). This analysis further evaluates the clinical benefit of CTL019. QOL was assessed before and after CTL019 infusion. **Methods:** Infused pts were 3-23 y/o with CD19+ B-ALL who were chemo refractory, relapsed after allogeneic stem cell transplant (SCT), or otherwise ineligible for SCT. Pts $\geq$ 8 y completed the Pediatric Quality of Life Inventory (PedsQL) and EuroQol EQ-5D at baseline and following CTL019 infusion. Minimal clinically important differences are estimated to be 4.4 and 7 to 10 for PedsQL and EQ-5D, respectively. **Results:** 62 of 81 enrolled pts were infused; 56% had relapsed after SCT with median of 3 prior therapies. At interim analysis, 50 pts were treated $\geq$ 3 months prior to data cutoff and eligible for primary efficacy analysis. A total of 39 pts were $\geq$ 8 y. Mean PedsQL total and EQ-5D VAS scores, respectively, were 58.4 and 69.4 at baseline. Mean changes from baseline for the PedsQL total and EQ VAS scores, respectively, were 13.9 and 13.7 at month 3 and 12.8 and 10.9 at month 6, supporting clinically meaningful improvements in QOL. Similar trends were observed with each PedsQL subscale. With EQ-5D, the proportions of pts reporting problems with mobility, self-care, usual activities, anxiety/depression, or pain/discomfort were notably decreased at months 3 and 6 compared with baseline. **Conclusions:** Clinically meaningful improvements in QOL were observed at 3 and 6 months after CTL019 therapy in pediatric and young adult r/r B-ALL pts, including fewer problems in each EQ-5D domain. These results suggest improved QOL after this one-time immunocellular therapy beyond the period of acute toxicities. Clinical trial information: NCT02435849.

10524 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

A phase I/II study of atezolizumab in pediatric and young adult patients with refractory/relapsed solid tumors (iMATRIX-Atezolizumab). *First Author: Birgit Geoerger, Gustave Roussy, Villejuif, France*

Background: Atezolizumab targets programmed death-ligand 1 (PD-L1), leading to enhanced anticancer T-cell response. The iMATRIX-Atezolizumab study (phase I/II, multicenter, open-label; NCT02541604) assessed the safety, pharmacokinetics (PK) and preliminary activity of atezolizumab in pediatric/young adult patients with refractory/relapsed solid tumors. **Methods:** Patients aged < 30 years with refractory/relapsed non-central nervous system solid tumors received atezolizumab every 3 weeks until loss of clinical benefit (< 18 years old, 15mg/kg [maximum dose 1200mg]; ≥18 years old, 1200mg). Safety/PK were assessed across tumor types and initial response was assessed by tumor-type cohorts after approximately 10 patients in each cohort had been treated. **Results:** As of July 19 2016, 74 patients (median age 14 years; range 2–29) were enrolled: osteosarcoma, n = 12; Ewing sarcoma, n = 11; neuroblastoma, n = 11; rhabdomyosarcoma (RMS), n = 10; non-RMS soft tissue sarcoma, n = 10; Wilms tumor, n = 6; Hodgkin lymphoma (HL), n = 5; non-HL, n = 1; other tumor types, n = 8. PK data (n = 48) were similar to that in adults (geometric mean C_{min}, μg/mL [cycle 2, day 1, pre-dose]: 53.6 [2– < 6 years old]; 54.1 [6– < 12 years old]; 62.0 [12– < 18 years old]; 68.0 [adult]). Most tumors, except HL, had < 1% (score 0) tumor cell [TC]/tumor-infiltrating immune cell (IC) PD-L1 expression with overall TC/IC-positive expression rates (≥1%, score 1–3) of 7% and 10%, respectively. All available HL samples had ≥5% (score 2–3) TC/IC PD-L1 expression. 67/71 patients who received atezolizumab (median cycles 2; range 1–10) had ≥1 adverse event (AE; mainly immune-related grade 1–2); 17 patients (24%) had treatment-related grade 3–4 AEs. One AE (grade 3 transaminase increase) led to study drug discontinuation. Common AEs were pyrexia (37%), fatigue (34%) and constipation (32%). 2/5 patients with HL had a partial response (PR); the only patient with atypical rhabdoid tumor (RT) had an unconfirmed PR. **Conclusions:** The PK and safety profile of atezolizumab in pediatric and young adult patients is similar to that in adults. Preliminary antitumor activity was seen in HL and RT; new cohorts are planned in RT and atypical teratoid RT. Clinical trial information: NCT02541604.

10525 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Phase 1/2 KEYNOTE-051 study of pembrolizumab (pembro) in pediatric patients (pts) with advanced melanoma or a PD-L1$^+$ advanced, relapsed, or refractory solid tumor or lymphoma. *First Author: Birgit Geoerger, Gustave Roussy, Villejuif, France*

Background: In phase 1 of the KEYNOTE-051 study (NCT02332668), the 2 mg/kg Q3W approved adult dose of pembro was also determined to be the pediatric recommended phase 2 dose. In phase 2, presented herein, we further evaluated this dose in pediatric pts with advanced cancer. **Methods:** Children aged 6 mo to < 18 y with advanced melanoma or a PD-L1$^+$ advanced, relapsed or refractory solid tumor or lymphoma, measurable disease per RECIST v1.1, and performance score ≥50 using Lansky Play or Karnofsky scales received pembro 2 mg/kg Q3W for 35 cycles or until confirmed disease progression per immune-related RECIST by investigator review, intolerable toxicity, or pt/investigator decision to discontinue. Tumor imaging was performed every 8 wk for the first 6 mo, then every 12 wk thereafter. AEs were graded by NCI CTCAE v4.0. Key efficacy endpoints were ORR, disease control rate (DCR), and PFS per RECIST v1.1 by investigator and OS. **Results:** Of 369 pts prescreened, 364 were evaluable for PD-L1 expression; of these, 121 (33.2%) were PD-L1$^+$. 66 pts were enrolled; median follow-up was 2.5 mo (range, 0.2-18). As of the data cutoff (Nov 7, 2016), 23 (34.8%) pts were still on treatment. Median age was 13 y (range, 1-17), 77.3% had metastatic disease, and 34.8% had ≥3 prior lines of therapy for recurrent/metastatic disease. Primary diagnoses were non-CNS solid tumors (n = 45), CNS tumors (n = 16), and lymphoma (n = 5). 5 (7.6%) pts had grade 3-4 treatment-related AEs (TRAEs), most commonly neutropenia (n = 2). No treatment-related deaths occurred; 1 pt discontinued for a TRAE (grade 3 AST increased). 1 pt each with Hodgkin lymphoma, adrenocortical carcinoma, mesothelioma, and glioblastoma had partial response for an ORR of 6.1% (95% CI, 1.7-14.8); 7 (10.6%) pts had stable disease for a DCR of 16.7% (95% CI, 8.6-27.9). Median PFS and OS were 1.8 mo and 9.2 mo, respectively; 12-mo PFS was 10.2% and OS was 40.5%. Potential effects of pembro on the developing immune system (eg, T and B cells, vaccinated antibodies) will also be presented. **Conclusions:** Pembro showed low toxicity and warrants further study to determine activity in select pediatric tumors. Enrollment in KEYNOTE-051 is ongoing. Clinical trial information: NCT02332668.

10526 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

ADVL1412: Initial results of a phase I/II study of nivolumab and ipilimumab in pediatric patients with relapsed/refractory solid tumors—A COG study. *First Author: Kara L. Davis, Lucile Packland Childrens Hosptal Stanford University, Stanford, CA*

Background: Checkpoint inhibitors have produced impressive responses in cancer. We report results of a Phase 1 study of nivolumab (nivo) alone and in combination with ipilumumab (ipi) in children with relapsed/refractory solid tumors and activity of nivo in patients with osteosarcoma (OS) and Ewing sarcoma (EWS) treated with the RP2D. **Methods:** Children with relapsed/refractory solid tumors (excluding CNS tumors or metastases) were eligible for Phase I Cohorts A and C. Using a rolling 6 design, Cohort A tested nivo at the adult RP2D, 3mg/kg Q14d (cycle = 28d). Cohort C tested nivo + ipi at 2 dose levels (DLs): DL1 nivo 1mg/kg + ipi 1mg/kg and DL2 nivo 3mg/kg + ipi 1mg/kg Q21d x 4 then nivo alone Q14d. At the RP2Ds, 6 additional patients were enrolled in each cohort for pharmacokinetics (PK). Phase II expansion cohorts enrolled patients with measurable OS (Cohort B2, n = 10) or EWS (Cohort B4, n = 10) respectively to assess activity of the RP2D of single agent nivo. **Results:** Twelve evaluable patients enrolled in Cohort A, none had DLTs. The pediatric RP2D of nivo alone was identified as 3 mg/kg Q14d. Five evaluable patients enrolled in Cohort C:DL1 without DLT, then 12 patients enrolled in Cohort C:DL2 with one DLT within the 21d reporting period (Gr 2 creatinine increase), defining the RP2D of nivo 3mg/kg + ipi 1mg/kg at the schedule above. In 39 patients treated in cohorts A, B2, B4 and C, pleural effusions occurred in 7 with variable attributions to drug, leading to a protocol amendment mandating supportive care and corticosteroids for pleural effusions on study. Common toxicities included anemia, elevated liver enzymes, rash, fatigue, and nausea, generally Grade 1. In Cohort A, nivo C_{max}, $t_{1/2}$ and Cl_pvalues were 63.2±15.7 mg/mL, 10.7±1.8 d and 0.196±0.075 ml/h/kg, respectively. In the Phase II expansion cohorts, no objective responses were observed in OS or EWS. **Conclusions:** Nivo alone or with ipi at the doses tested is safe in pediatric patients with relapsed/refractory solid tumors. The pediatric RP2D of nivo is 3mg/kg alone or in combination with ipi 1mg/kg. Single agent nivo did not have antitumor activity in OS or EWS. Enrollment to other expansion cohorts with nivo or nivo/ipi is ongoing. Clinical trial information: NCT02304458.

10527 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Type, intensity, and duration of chemotherapy (CHT) and their correlation with prognosis of localized soft tissue Ewing tumors (STET): Experience of the Cooperative Weichteilsarkomstudiengruppe (CWS). *First Author: Ewa Koscielniak, Klinikum Stuttgart Olgahospital, Stuttgart, Germany*

Background: The optimal type and intensity of CHT in the treatment of STET is still a matter of debate. The CWS group has treated STET similar to rhabdomyosarcoma. We have analyzed the prognosis of STET in relation to the CHT regimens used in three consecutive CWS studies CWS-91, -96 and CWS-2002P. **Methods:** 243 pts with localized STET were included. Their median age was 12 (range 0.1-29) yrs. In the CWS-91 pts with primary tumor resection (IRSG I and II) were treated with VACA (vincristine (VCR), actinomycin D (Act D), cyclophosphamide (CYC), doxorubicin (DOX), for 10 or 20 weeks. All other CWS-91 pts (high risk group, HRG) received EVAIA (ifosfamide (IFO) instead of CYC plus VP16) for 37 weeks. In the CWS-96 and CWS-2002P all STET pts were allocated to the HRG. In CWS-96 therapy was randomized: VAIA (IFO, DOX, Act D, VCR) vs. CEVAIE (Epi-DOX instead of DOX, plus carboplatin and VP16), for 25 weeks. In CWS-2002P VAIA (25 weeks) plus maintenance CHT with CYC and vinblastine (VBL) for 26 weeks were used. The cumulative doses varied: IFO 24-72 g/m^2, CYC 4.8-7.35 g/m^2, DOX 120-360 mg/m^2, Act D 3-9 mg/m^2, VP16 1.8-5.4 g/m^2. Irradiation was stratified depending on results of the primary or secondary resection and response. **Results:** 5 yr event free (EFS) and overall survival (OS) were 64% and 73%. The median observation time of survivors was 9 yrs. 5yr EFS and OS by study were: CWS-91 64 % and 72 %, CWS-96 57% and 70 %, CWS-2002P 78 % and 86 % respectively (n.s.). 5 yr EFS and OS for VACA arm were 79% and 90%. 5 yr EFS and OS by CHT for HRG were: EVAIA 57% and 65%, VAIA 64% and 80%, CEVAIE 45% and 54%, VAIA with CYC/VBL 84% and 87%, respectively (p = 0 .003). 5yr EFS and OS for irradiated (n = 181) vs. not irradiated (n = 48) patients were 63 % and 72% vs. 63% and 79%, respectively. **Conclusions:** The outcomes between CHT arms differed significantly: CEVAIA correlated with the worst outcome while VAIA with CYC/VBL showed the best results. A small group of low risk patients have an excellent prognosis with substantially reduced CHT. Ewing tumors are biologically heterogeneous and more diversification in therapy stratification is warranted to avoid overtreatment.

10528 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Risk stratification including FOXO1 fusion status (FOXO1) in patients with rhabdomyosarcoma (RMS) treated on six recent frontline trials: A report from the Children's Oncology Group (COG). *First Author: Emily Hibbitts, Children's Oncology Group, Gainesville, FL*

Background: Clinical risk factors associated with outcome in children with either localized or metastatic RMS were identified by Meza et al. (2006) and Oberlin et al. (2008). We re-examined risk stratification by adding FOXO1 to traditional clinical prognostic factors in children with localized or metastatic RMS in a large cohort from COG frontline clinical trials. **Methods:** Data from six COG clinical trials (D9602, D9802, D9803, ARST0331, ARTS0431, ARST0531) accruing previously untreated patients with RMS from 1997 to 2013 yielded 1,853 eligible patients (two studies each for low, intermediate and high risk patients). Survival tree regression for event-free survival (EFS) and overall survival (OS) was conducted to determine prognostic impact of risk factors. Recursively, the factor most strongly associated with outcome was selected for branching and split using a goodness of fit measure. Factors included were age, FOXO1, group, histology, nodal status, number of metastatic sites, primary site, sex, tumor size, and presence of metastases in bone/bone marrow, soft tissue, effusions, lung, distant lymph nodes, and other sites. **Results:** 5-year overall EFS and OS was 0.67 (SE, 0.01) and 0.77 (SE, 0.01), respectively. Survival trees for EFS and OS found localized versus metastatic at the first split and included FOXO1 as a significant risk factor. **Conclusions:** FOXO1 improves risk stratification of patients with localized RMS, although histology and pattern of metastases are more predictive for patients with metastatic RMS. Our findings support incorporation of FOXO1 in risk stratified clinical trials.

Top prognostic factors identified based on EFS.

Branch 1		Branch 2		Branch 3	
	EFS ± SE		EFS ± SE		EFS ± SE
Localized (N=1624)	0.73 ± .01	Favorable site (N=746)	0.82 ± .02	FOXO1 – (N=706)	0.84 ± .02
				FOXO1 + (N=40)	0.57 ± .09
		Unfavorable site (N=878)	0.65 ± .02	FOXO1 – (N=605)	0.70 ± .02
				FOXO1 + (N=273)	0.52 ± .04
Metastatic (N=229)	0.26 ± .03	Embryonal (N=98)	0.47 ± .06	1 Metastatic site (N=60)	0.57 ± .07
				> 1 Metastatic site (N=38)	0.32 ± .09
		Alveolar (N=131)	0.11 ± .03	No bone metastases (N=46)	0.22 ± .06
				Bone metastases (N=85)	0.05 ± .02

10529 Poster Discussion Session; Unassigned in Poster Discussion Session, Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Genomic index in pediatric synovial sarcoma (SYNOBIO study): The European Pediatric Soft Tissue Sarcoma Group (EpSSG) experience. *First Author: Daniel Orbach, Institut Curie, Paris, France*

Background: A genomic index (GI) tool using array comparative genomic hybridization (aCGH) on tumor cells has recently been developed, and shown a high prognostic value in adult soft tissue sarcomas. GI correlates with genomic instability, and has emerged as independent prognostic factor associated with the risk of metastases developing in synovial sarcoma (SS). The aim, therefore, was to assess GI in pediatric patients with SS, to assess its value as a prognostic factor and its role in risk stratification. **Methods:** All pediatric/adolescent/young adults' (<25 years) with localized SS prospectively included in the European EpSSG-NRSTS05 protocol with a contributive aCGH were selected. Tumors had a central pathological review or harbored the specific fusion transcript (SYT-SSX). Definition of GI was A^2/C, where A is the total number of alterations (segmental gains and losses) and C is the number of involved chromosomes on aCGH results. GI_1 group corresponds to cases with no or few alterations (flat profile, GI≤1) and GI_2 group cases with many alterations (complex CGH profile; GI>1). **Results:** A total of 48 patient's samples were available. The median age of the cohort was 13 years (range: 4-24). Patients received surgery only (19%), with adjuvant therapy (17%) or perioperative therapy (64%). GI_1 group corresponded to 54.2%, and GI_2 to 45.8%. After a median follow up of 58 months (range: 0.1-107), 10 tumor events occurred and 5 patients died. Patients with high GI have more axial (P<0.01), invasive (P=0.04) and higher therapeutic risk groups' tumors (unresectable/axial tumors; P<0.015). Respectively for GI_1 vs. GI_2 groups, 5-year event free survival (EFS) rates were 91.8±5.6% vs. 58.9±11.2% (P<0.0084) and 5Y-Metastatic Free Survival 91.8±5.5% vs. 68.6±10.6% (P=0.055). In multivariate analysis, GI adjusted for IRS groups, site and tumor size remains prognostic for EFS (P<0.025). **Conclusions:** Although tumor events were rare for SS in NRSTS 2005, high GI selected patients with high risk tumor features and predicted a poorer outcome. GI may explain aggressive behavior of some pediatric SS. Founding sources: "Enfant-et-santé/SFCE," "Info sarcome," and "La ligue contre le cancer."

10530 Poster Session (Board #287), Sun, 8:00 AM-11:30 AM

Blinatumomab use in pediatric patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) from an open-label, multicenter, expanded access study. *First Author: Franco Locatelli, Bambino Gesù Children's Hospital, Rome; University of Pavia, Pavia, Italy*

Background: Blinatumomab (blin), a bispecific T-cell engaging antibody construct, has shown antileukemia activity and tolerability in pts with r/r ALL. We further evaluated safety and efficacy of blin in the first 40 pediatric pts with r/r ALL enrolled in an expanded access study (NCT02187354). **Methods:** Eligible pts (28 d to < 18 yrs) had ≥ 5% blasts and r/r ALL (refractory, ≥ 2 relapses or relapse after transplant [HCT]). Blin was dosed by continuous infusion (4 wks on/2 wks off) for up to 5 cycles (≥ 5 to < 25% blasts: 15 $\mu g/m^2$/d; ≥ 25% blasts: 5 $\mu g/m^2$/d on d1−7 in cycle 1, then 15 $\mu g/m^2$/d). The primary endpoint was incidence of treatment-emergent (TE) and treatment-related (TR) adverse events (AEs); key efficacy endpoints were complete response (CR) and minimal residual disease (MRD, by PCR or flow cytometry) in the first 2 cycles, relapse-free survival, overall survival and HCT rate. **Results:** Of the first40 treated pts (median age, 9 [range, 1−17] yrs), 24 (60%) had ≥ 2 relapses, 20 (50%) relapsed after HCT and 5 (13%) were primary refractory; 18 (45%) had ≥ 50% blasts and 21 (53%) had prior HCT. Safety and key efficacy outcomes are shown in the table, including 63% CR in the first 2 cycles. There were 8 relapses and 20 deaths after treatment. Regardless of causality, the most frequent TEAEs were pyrexia (78%), cytokine release syndrome (CRS; 23%) vomiting (23%) and anemia (20%); all 9 CRS events were grade (gr) 1 or 2 and 1 tumor lysis syndrome was gr 3. 10 (25%) pts interrupted treatment and 2 (5%) discontinued due to TRAEs; 13 (33%) pts had gr ≥ 3 TRAEs, including 2 of 3 neurologic events (depressed level of consciousness and headache; both gr 3); 2 fatal AEs were considered unrelated to blin. **Conclusions:**Here single-agent blin showed antileukemia activity in pediatric pts with high-risk r/r ALL including t(17;19) and AEs consistent with those previously reported for r/r ALL. Clinical trial information: NCT02187354.

	All Pts N=40
All TEAEs, n (%)	39 (98)
Gr 3	15 (38)
Gr 4	12 (30)
Fatal	2 (5)
CR[a], n (%)	25 (63)
< 50% blasts	15 (68)
≥ 50% blasts	10 (56)
t(17;19)	2 (100)
	Responders n=25
MRD response < 10^{-4}[a], n (%)	19 (76)
< 50% blasts	12 (80)
≥ 50% blasts	7 (70)
t(17;19)	2 (100)
HCT after CR, n (%)	10 (40)

[a]Of responders in first 2 cycles

10531 Poster Session (Board #288), Sun, 8:00 AM-11:30 AM

Cardiac effects of chimeric antigen receptor (CAR) T-cell therapy in children. *First Author: Danielle S. Burstein, Pediatric Cardiology, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Treatment with CAR T-cells targeting CD19 for pediatric leukemia has demonstrated significant efficacy with the principal toxicity being cytokine release syndrome (CRS). However, the cardiac effects related to CAR T-cell therapy have not been systematically evaluated. **Methods:** A retrospective chart review was performed on a large cohort who received CAR T-cell therapy from April 2012 through September 2016. Baseline oncologic and cardiac characteristics were recorded. Cardiomyopathy was defined as an ejection fraction < 55%, shortening fraction < 28%, or diastolic dysfunction. Primary outcome was cardiac event, defined as need for inotropic support or echocardiographic decline in function. Descriptive and univariate analyses were performed. **Results:** 93 patients were included [55% male, mean age 11.8 yrs (range 1.7-27.1)]; 98% had B cell ALL. Prior to treatment, 15% had cardiomyopathy and 1 patient had single ventricle Fontan palliation. Cardiac events occurred in 34 (36%) with mean onset 4.8 days (range 1-9) after CAR T-cell infusion, of whom 12 (35%) had abnormal systolic or diastolic function on echocardiogram and 6 (18%) required milrinone for cardiac support. 21 (22%) patients had CRS requiring tocilizumab and vasoactive infusions; there were no cardiac-related deaths. Factors associated with cardiac events included higher pre-treatment blast % on bone marrow biopsy [OR 10.45 (95% CI 3.87-28.22) for blast > 10%; p < 0.001] but not cardiomyopathy (p = 0.356), total body irradiation (p = 0.717) or anthracycline dose (p = 0.711). At discharge, 7 (7.5%) patients had worse cardiac function than at baseline, but only 2 (2%) had persistent cardiac dysfunction by 6 months post-infusion. Pre-treatment factors were not associated with persistent dysfunction. **Conclusions:** This is the first study to describe the cardiac effects of CAR T-cell therapy in children. CAR T-cell therapy appears to be safe, even in patients with cardiomyopathy. Although one-third experienced a cardiac event, persistent cardiac dysfunction is rare. Children with a pre-treatment blast > 10% were most at risk for cardiac events, a finding that may help identify patients who warrant close observation and early intervention with pressor support.

10532 Poster Session (Board #289), Sun, 8:00 AM-11:30 AM

Risk-adapted therapy utilizing upfront brentuximab vedotin (Bv) and rituximab (R) with reduced toxicity chemotherapy in children, adolescents, and young adults with Hodgkin lymphoma. *First Author: Jessica Hochberg, New York Medical College, Valhalla, NY*

Background: Cure rates for CAYA patients with Hodgkin Lymphoma remain high, however are limited by significant toxicity of chemoradiotherapy. Brentuximab Vedotin and Rituximab have shown efficacy in relapsed HL. We hypothesize that the addition of both to combination chemotherapy will be safe in newly diagnosed HL preserving current EFS with elimination of more toxic chemoradiotherapy. Objective: To evaluate the safety and overall response and EFS of Brentuximab and Rituximab in combination with risk adapted chemotherapy in CAYA with newly diagnosed HL. **Methods:** Age 1-30 yrs with newly diagnosed classical HL given 3 to 6 cycles of chemoimmunotherapy: Brentuximab vedotin with Doxorubicin, Vincristine, Prednisone and Darcarbazine (Bv-AVPD) for Low risk patients or Doxorubicin, Vinblastine, Darcarbazine and Rituximab (Bv-AVD-R) for Intermediate/High risk. Early response measured by PET/CT scan following 2 cycles. Slow responders received an additional 2 cycles of Bv-AVD-R for Intermediate Risk or Ifosfamide/Vinorelbine for High Risk patients. Radiation therapy was given ONLY to those patients not in CR. **Results:** Total = 19 patients. Median age = 15yr (range 4-23yr). Risk = 2 low, 13 intermediate, 4 high. Toxcity = 1 episode of GrIII mucositis, 1 episode of GrIII infusion reaction to Brentuximab. 17 patients have completed therapy. All 17 patients achieved a complete response to therapy for a CR = 100%. Eleven (58%) have achieved a rapid early response. No patient has required radiation therapy. For 17 patients who have completed therapy, the EFS and OS is 100% with a median follow up time of 915 days (30 months). **Conclusions:** The addition of Brentuximab vedotin and Rituximab to combination chemotherapy for newly diagnosed Hodgkin Lymphoma appears to be safe. Our early results show significant promise with a CR rate of 100% and 58% rapid early response. We have successfully deleted toxic alkylator, topoisomerase inhibitor, bleomycin and radiation from this treatment regimen. The EFS/OS to date is 100% with a median follow up time of 2.5 years. Further follow up and a larger cohort is needed to determine long term outcomes of this approach. Clinical trial information: NCT02398240.

10533 Poster Session (Board #290), Sun, 8:00 AM-11:30 AM

Intensified induction therapy with reduced total anthracycline exposure in pediatric low-risk acute myeloid leukemia. *First Author: Katherine Ashley Minson, Department of Pediatrics, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta and Emory University, Atlanta, GA*

Background: Despite advances in risk stratification and therapy, the post-induction disease free survival (DFS) and overall survival (OS) for children with low-risk acute myeloid leukemia (LR-AML) remain low with DFS and OS of 50% and 68%, respectively, on the standard arm of the recent Children's Oncology Group (COG) trial, AAML1031. Additionally, current therapy for pediatric LR-AML contains anthracycline doses exceeding thresholds known to increase the risk of adverse cardiac effects. In an effort to decrease exposure to cardiotoxic therapy, the Aflac Cancer and Blood Disorders Center adopted an institutional practice to treat LR-AML patients with a regimen of intensified induction therapy with decreased anthracycline exposure (Aflac-AML consisting of ADE10, Mitox/HiDAC, HiDAC/VP, Capizzi II). The aim of this study is to describe the associated toxicities and outcomes of this regimen in pediatric LR-AML. **Methods:** We retrospectively reviewed medical records of patients diagnosed with de novo LR-AML and treated per the Aflac-AML regimen from 2011-2014. Charts were reviewed for cardiac outcomes, ICU admissions, and the rate of infectious toxicities. DFS and OS were determined using Kaplan-Meier survival analysis. **Results:** We identified 11 LR-AML patients treated with Aflac-AML therapy. Patients received a planned 317 mg/m^2 cumulative anthracycline dose vs 442 mg/m^{2}for those treated on AAML1031. There was no decrease in LVEF with a mean change of +2.17% for Aflac-AML patients from the time of diagnosis to therapy completion (p = 0.23). The primary infectious toxicities observed were febrile neutropenia and bacterial infections with a median of 36.4±6% documented bacterial infections per cycle. Fungal and viral infections were rare as were ICU admissions – median 4.5±4% per cycle – and there were no toxic mortalities. The 3-year DFS and OS from end of induction I for Aflac-AML patients were 72.7% and 90.9%, respectively. **Conclusions:** The Aflac-AML regimen resulted in short-term toxicities and outcomes comparable to current chemotherapy regimens for pediatric LR-AML but with reduced anthracycline exposure. These data support use of this regimen for pediatric LR-AML patients.

10534 Poster Session (Board #291), Sun, 8:00 AM-11:30 AM

Early response rates and Curie scores at end of induction: An update from a phase II study of an anti-GD2 monoclonal antibody (mAb) with chemotherapy (CT) in newly diagnosed patients (pts) with high-risk (HR) neuroblastoma (NB). *First Author: Wayne Lee Furman, St. Jude Children's Research Hospital, Memphis, TN*

Background: We are conducting a Phase II trial of the anti-GD2 mAb hu14.18K322A given concomitantly *with* CT in newly diagnosed pts with HR NB. Our primary objective is to compare the response rate (RR; defined as ≥ PR) after two courses of CT with cyclophosphamide (CTX)/topotecan (TPT) and hu14.18K322A with GM-CSF and IL-2 to the RR reported by Park et al. (JCO 29:4351, 2011), using identical CT with GCSF only, in a two-stage group sequential design. Semiquantitative MIBG scoring (Curie; CS) has been shown to be a prognostic indicator of outcome in pts with HR NB (Yanik et al, J Nucl Med, 2013), particularly, those with CS > 2 at end of induction (EoI) CT have inferior outcomes. Here we update the RR and report the CS at EoI CT. **Methods:** Pts received induction CT (6 cycles) as described by Park et al, with the addition of hu14.18K332A (on d 2-5; 40mg/m^2/d x 4d), daily sc GM-CSF and sc IL-2 (1 x 10^6 IU/m^2/dose) qod x 6. ^{123}I-MIBG scans and scoring (CS) were obtained on all pts at diagnosis, after second course of CT and at EoI. **Results:** 42 evaluable pts completed the first two courses of CT (24 male, median age 2.9 yrs (range 6 m -15.2 yrs), 36 INSS 4, 19 *MYCN*amplified); 40/42 evaluable pts had measurable reductions in primary tumor volume after two courses of CT (median 79%, average 69%, range +5 – 100%). Responses (≥ PR) after two courses were seen in 32/42 (76.2%; 95% CI 61.3 – 87.9%); No mAb dose-reductions were made but 20/43 (47%) pts had infusion times extended. The development of human anti-human antibody reactivity (HAHA) to hu14.18K322A in the first 22 pts is minimal. Of the 36 INSS 4 pts, 1 withdrew prior to EoI and 2 are too early. The median CS at diagnosis for the 33 stage 4 pts who have completed induction CT was 18 (range 1 – 28). At EoI the median CS was 0 (range 0 -23); 29/33 INSS 4 pts had EoI CS ≤ 2. **Conclusions:** The addition of hu14.18K322A to two courses of CTX/TPT significantly improves the RR compared to two courses of CTX/TPT alone (32/42 vs 12/30 as reported by Park et al,; P = 0.000004). The improved median CS of the stage 4 patients from 18 at diagnosis to 0 at EoI suggest the improvement in early RR may translate into improved EFS as well. Clinical trial information: NCT01857934.

10535 Poster Session (Board #292), Sun, 8:00 AM-11:30 AM

Targeting the cell cycle for cancer therapy in rhabdomyosarcoma. *First Author: Elizabeth Stewart, St. Jude Children's Research Hospital, Memphis, TN*

Background: Rhabdomyosarcoma (RMS) is an aggressive malignancy of childhood with a poor prognosis in patients with metastatic or recurrent disease. Inhibitors of Wee1 kinase and heat shock protein 90 (HSP90) have in vitro activity in RMS and have emerged as potential novel treatment strategies. We performed a comprehensive preclinical phase III study to compare the Wee1 inhibitor AZD1775 and HSP90 inhibitor ganetespib (GANET) in combination with irinotecan (IRN) and vincristine (VCR). **Methods:** Orthotopic xenografts (O-PDXs) were created by injecting luciferase labeled RMS cells into the hind-leg muscle of CD-1 nude mice. Pharmacokinetic studies on RMS O-PDXs were performed to determine matched human AUC-guided dosing. A total of 540 O-PDXs derived from 4 high risk RMS patients, 2 alveolar and 2 embryonal, were randomly enrolled into 14 treatment groups. Six courses of blinded placebo-controlled therapy were given on a clinically relevant schedule. Mice were classified as having progressive disease if tumor approached 20% body weight at any time in the study. For mice completing all 6 courses, bioluminescence was used to determine complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). **Results:** The addition of AZD1775 to IRN and VCR demonstrated the most significant response for all 4 O-PDX lines tested; 70% of mice achieved a CR or PR. GANET combined with IRN and VCR had a 54% response (CR + PR) which was not significantly better than IRN plus VCR for most O-PDXs tested. Overall response data for select treatment groups is shown in the table below. **Conclusions:** Comprehensive preclinical testing using multiple O-PDX models of RMS that represent the clinical spectrum of disease is feasible. Comparison of novel treatment regimens to standard of care at clinically relevant doses is warranted as justification for future clinical trials. Observation to assess durable response following completion of therapy is ongoing to determine if AZD1775 remains a promising treatment strategy.

Treatment Group	CR%	PR%	SD%	PD%	CR+PR%	CR+PR+SD%
Control	0	0	0	100	0	0
GANET	0	0	0	100	0	0
AZD1775	0	0	0	100	0	0
IRN + VCR	22	14	8	56	36	44
GANET + IRN	14	17	17	53	31	47
AZD1775 + IRN	19	22	11	47	42	53
GANET + IRN + VCR	29	26	3	43	54	57
AZD1775 + IRN + VCR	43	27	19	11	70	89

10536 Poster Session (Board #293), Sun, 8:00 AM-11:30 AM

Clinical outcomes of adolescents and young adults (AYA) with advanced solid tumors participating in phase I trials. *First Author: Raghav Sundar, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: AYA cancer patients are relatively under-represented in clinical trials, with no published data regarding their outcomes in phase I studies. Trials utilizing novel therapeutic agents are often considered in these patients, due to their tendency to have good organ reserve, and ability to tolerate additional lines of therapy. This study describes the experience of AYA patients with advanced solid tumors treated in a specialized drug development unit. **Methods:** Patient characteristics and clinical outcomes of AYA patients (defined as age 15 to 39 years at time of initial cancer diagnosis) treated at the Drug Development Unit, Royal Marsden Hospital, United Kingdom, between 2002 and 2016, were captured and analyzed from case and trial records. **Results:** From a database of 2631 patients treated on phase I trials, 219 AYA patients (8%) were identified. Major tumor types included gynaecological cancer (24%), sarcoma (18%), gastrointestinal (16%) and breast cancer (11%). Patients had a median of 3 previous lines of systemic chemotherapy (range 0 – 6), and 19% participated in 2 or more phase I studies. Twenty (9%) had a known hereditary cancer syndrome (most commonly BRCA), 27% had a family history (FH) of cancer, 15% no FH and 49% no FH documented. Molecular characterization of tumors (n = 45) identified mutations most commonly in *p53* (33%), *PI3KCA* (18%) and *KRAS* (9%). Major trial categories included DNA damage repair (16%), PI3K (16%) and anti-angiogenesis (15%) agents. Grade 3/4 toxicities were experienced in 25% of patients (10% hematological). Of the 214 evaluable patients, objective response rate was 12%, with clinical benefit rate at 6 months of 22%. Median progression free survival was 2.3 months (95% CI: 1.9 to 2.8), median OS was 7.6 months (95% CI: 6.3 to 9.5), and 2-year OS was 11%. Of patients with responses, 35% were matched to phase I trials based on germline or somatic genetic aberrations. **Conclusions:** A sub-group of AYA patients with advanced solid tumors derive considerable benefit from participating in trials involving novel therapeutics. Future research must focus on predictive biomarkers and molecular profiling to identify those that would benefit from novel therapies.

10537 Poster Session (Board #294), Sun, 8:00 AM-11:30 AM

ADVL1522: A phase 2 study of IMGN901 (lorvotuzumab mertansine; IND# 126953, NSC# 783609) in children with relapsed or refractory Wilms tumor, rhabdomyosarcoma, neuroblastoma, pleuropulmonary blastoma, malignant peripheral nerve sheath tumor (MPNST), and synovial sarcoma: A Children's Oncology Group study. *First Author: James I. Geller, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: Lorvotuzumab mertansine (IMGN901; LM) is an antibody-drug conjugate, linking anti-mitotic agent (DM1) to an anti-CD56 antibody. Preclinical data show effects in Wilms tumor (WT), rhabdomyosarcoma (RMS), and neuroblastoma (NBL). Synovial sarcoma (SS), MPNST and pleuropulmonary blastoma (PPB) also express CD56. A phase 2 trial assessing the efficacy and tolerability of LM administered at the adult recommended phase 2 dose (RP2D) was conducted in children with relapsed tumors. **Methods:** LM (110 mg/m^2/dose) was administered IV on days (d) 1 and 8 of 21 d cycles, with dexamethasone pre-medication. The tolerability of LM was assessed in 6 patients prior to trial activation group-wide. Dose limiting toxicity (DLT) was assessed using CTCAE. Response was assessed by RECIST. Pharmacokinetics (PK) were obtained during cycle 1. Peripheral blood CD56-positive cells were measured d1 and d8 pre-dose. Tumor CD56 expression by immunohistochemistry in archival tissue was scored (0-3+). **Results:** Sixty-two patients were enrolled. The median (range) age was 14.3 y (2.8–29.9); 35 were male. Diagnoses included WT (17), RMS (17), NBL (12), SS (10), MPNST (5) and PPB (1). One patient was ineligible due to lack of measurable disease. Of 61 eligible patients, 47 were evaluable for toxicity, 50 for response, 50 for tumor CD56 expression; and 18 consented to optional PK. Five patients experienced 9 DLTs: hyperglycemia (1), colonic fistula (1) with perforation (1), nausea (1) with vomiting (1), increased ALT (2 in cycle 1; 1 in cycle 2 with increased AST (1)). Non-dose limiting toxicities (Grade $\geq$3) attributed to LM included lymphopenia, anemia, vomiting, dehydration, hypokalemia, hyperuricemia, hypophosphatemia. Mean DM1 C_{max}, $t_{1/2}$ and $AUC_{0-\infty}$values were 922 ng/ml, 33 h and 27400 ng/ml*h, respectively. Tumor CD56 expression was 0 (8%), 1+(4%), 2+(12%), 3+(76%). LM and CD56 antibody PK, and response, will be reported. **Conclusions:** LM (110 mg/m^2) is tolerated in children at the adult RP2D. Clinical trial information: NCT 02452554.

10538 Poster Session (Board #295), Sun, 8:00 AM-11:30 AM

Mortality in young adults with Ewing sarcoma treated at specialized cancer centers in California. *First Author: Elysia Marie Alvarez, Stanford University Medical Center, Palo Alto, CA*

Background: Ewing sarcoma is a rare malignancy of the soft tissue or bone that is most frequently seen in children and adolescents. One study suggested that care at specialized cancer centers (SCC) may mitigate survival disparities associated with public insurance in patients with sarcoma, but no large population-based studies have considered how location of care affects survival outcomes. **Methods:** We performed a retrospective, population-based cohort analysis of patients hospitalized within one year of diagnosis with primary Ewing sarcoma between 2000–2013 using the California Cancer Registry linked with state hospitalization data. Patients were divided into two groups based on whether they received inpatient treatment at a SCC [Children's Oncology Group (if age $\leq$25) and/or National Cancer Institute-designated center] or not. We excluded 12 patients whose location of cancer treatment could not be determined. Multivariable Cox proportional hazards regression identified factors associated with mortality. Results are presented as adjusted hazard ratios (HR) and 95% confidence intervals (CI). **Results:** Of the 470 patients with newly diagnosed Ewing sarcoma, 40% were female, 52% were non-Hispanic white, and 53% had private health insurance. Sixty-one percent received their inpatient care at a SCC. Multivariable analysis across all ages demonstrated that higher mortality was associated with increasing age, metastatic disease, and large tumors, but mortality was not impacted by treatment at an SCC (HR 0.77, CI: 0.55-1.08; p = 0.134). However, when analyses were stratified by age, treatment at a SCC was associated with lower mortality among patients ages 19–39 years, but not among younger or older patients, and this association was only apparent within 2 years of diagnosis (HR = 0.43, CI: 0.23-0.79; p = 0.007). **Conclusions:** Our results suggest that treatment for Ewing sarcoma at a SCC significantly improves survival in young adults adjusted for other factors known to be associated with poor prognosis (metastatic disease, larger tumor size and older age). The lower mortality in this age group may be due to access to clinical trials and other specialized services specific to young adults available at SCCs.

10539 Poster Session (Board #296), Sun, 8:00 AM-11:30 AM

Pilot study of a comprehensive precision medicine platform for children with high-risk cancer. *First Author: Loretta Lau, Sydney Children's Hospital, Sydney, Australia*

Background: Genomic analyses can identify actionable mutations in a subset of childhood cancers. However it has been challenging to translate actionable mutations into substantial benefits for adult cancers despite high mutation frequency. **Methods:** To test whether we could enhance identification of personalised therapies for high risk (HR) childhood cancers we conducted a pilot study (TARGET) evaluating a novel, comprehensive precision medicine platform incorporating molecular profiling, *in vitro* and *in vivo* drug testing. **Results:** We evaluated the first 29 patients with HR cancer (expected survival $<$ 30%) enrolled prospectively over 15 months. Samples were collected from 15 CNS tumors, 10 solid tumors and 4 leukemias. All samples underwent targeted DNA sequencing. Pathogenic or likely pathogenic mutations were found in 59% (17/29) of tumors. 41% (12/29) had potentially actionable mutations. RNA-sequencing was performed on 27 samples. Previously described fusions were identified in 19% (5/27; 1 targetable, 1 clinical relevant and 3 diagnostic fusions). 37% (10/27) of samples also had actionable aberrations related to copy number changes or RNA expression. *In vitro* culture and establishment of patient-derived xenograft (PDX) were attempted in 19 and 21 fresh samples, respectively. The success rate of establishing a primary culture was 42% (8/19) and PDX engraftment rate was 67% (14/21). At least 1 drug hit was identified in 5 (56%) of the 9 samples screened using a high throughput drug screen of up to 165 compounds. Drug testing has been completed in 4 PDXs and was informative in all 4 cases allowing prioritisation of treatment recommendations. Genomic analysis in combination with RNA-seq, *in vitro* drug screening and PDX drug testing enriched the analysis and increased the ability to make personalised treatment recommendations from 41% (targeted panel alone) to 66%. **Conclusions:** This pilot study demonstrates that this novel, comprehensive platform is feasible and has the potential to improve outcome for HR childhood cancers. A multicentre study testing the implementation of the platform on a national level (PRISM trial) will open for Australian children with HR cancer under the Zero Childhood Cancer Program in 2017.

10540 Poster Session (Board #297), Sun, 8:00 AM-11:30 AM

Outcomes of children with hereditary medullary thyroid carcinoma (MTC) treated with vandetanib. *First Author: Ira Lignugaris Kraft, Center for Cancer Research, Division of Cancer Treatment and Diagnosis, Bethesda, MD*

Background: Vandetanib is well tolerated and active in children with advanced or metastatic hereditary MTC (NCT00514046) [data cutoff 7/2011; Clin Cancer Res. 2013 Aug 1;19(15):4239-48]. We report outcomes as of 1/2017. **Methods:** We monitored toxicities, RECISTv1.0, carcinoembryonic antigen (CEA), and calcitonin (CT) response. Patients (pts) removed from the vandetanib trial were followed on a natural history study (NCT01660984). **Results:** Of 17 pts (8 male, age 13 years (9-17)*) enrolled, 1 was lost to follow-up. Of the 16 pts analyzed, 15 had a *RET* p.M918T germline mutation. The duration of vandetanib therapy was 5.6 years (0.1-9.2+) with treatment ongoing in 8 pts. Best response was partial response (PR) in 10, stable disease (SD) in 5, and progressive disease (PD) in 1 pt. Time to achieve PR (n = 10) was 0.6 years (0.4-2.4). Time to best response (n = 16) was 1.5 years (0.1-4.1). Duration of response was 5.1 years (1.3-8.6+) in pts with PR and 4.8 years (0.6-7.3+) in pts with SD. Seven of 8 pts with PD subsequently received sunitinib, sorafenib, and/or cabozantinib. Disease progression occurred as increase in target (n = 2), non-target/new lesions (n = 5), or CT/CEA (n = 1). Six pts died from disease 2.1 years (0.4-4.3) after stopping vandetanib. Progression free survival was 6.2 years (95% CI 3.0-na) and overall survival was 7.9 years (95% CI 5.9-na).Pts had no difference in enrollment age, baseline CT/CEA, or tumor size per response categories (n = 16). Rate of CEA/CT decrease during initial 4 months of treatment was not associated with PR/SD compared to PD (n = 16). While on vandetanib, 6 pts with PD had CEA or CT doubling time (DT) of $<$ 2 years within 1 year prior to PD. All pts with ongoing PR/SD had CEA and CT DT $>$ 2 years while on vandetanib. No pts came off treatment for toxicity. Dose reductions occurred in 8 pts for grade (gr) 2 weight loss (n = 2), palpitations (n = 1), arrhythmia (n = 1), elevated creatinine (n = 1), diarrhea (n = 2), and gr 3 constipation (n = 1). **Conclusions:** Many children with hereditary MTC sustained PR/SD on vandetanib. However, half ultimately developed PD and died from disease despite treatment with other targeted therapies. CEA/CT DT $<$ 2 years within 1 year of progression on vandetanib may be associated with PD. *Median (range)

10541 Poster Session (Board #298), Sun, 8:00 AM-11:30 AM

Role of radiotherapy to primary/metastatic sites in pediatric patients with metastatic rhabdomyosarcoma in the BERNIE study. *First Author: Alison Cameron, Bristol Haematology and Oncology Centre, Bristol, United Kingdom*

Background: Local control is a key part of treatment of local/locoregional rhabdomyosarcoma (RMS) and often involves radiotherapy (RT) with/without surgery. The role of RT in metastatic RMS is uncertain, with little published evidence to guide clinicians. We analyzed data from the BERNIE trial to assess the benefit of RT for patients (pts) with metastatic RMS. **Methods:** In the BERNIE study (NCT00643565) pts aged $\geq$6 months to $<$18yrs with metastatic RMS and non-RMS soft tissue sarcoma were randomized to receive chemotherapy (CT) with/without bevacizumab (BEV), surgery, and/or RT (at cycle 6–9) then maintenance CT. RT was recommended for all sites of metastases if feasible (investigator discretion allowed, resulting in variability in actual RT given). Pts were categorized into those receiving: RT all sites, partial RT, no RT. Event-free survival (EFS) and overall survival (OS) were calculated using Cox proportional hazards models and a landmark approach: only pts who were event free at day 221 (i.e. end of cycle 9 + 1 month) were included (EFS, n=85; OS, n=97). Variables adjusted were: treatment (as randomized), disease type (alveolar/embryonal/other), risk group, age $>$10yrs, metastatic lesion count (1, 2–3, 4+). The analysis was non-randomized, exploratory and post hoc. **Results:** Of 102 pts with RMS, 22 received no RT, 49 partial RT, and 31 RT to all sites. Baseline characteristics were mostly balanced, and comparable proportions of pts received BEV. Better OS was observed in the RT group (Table) (comparable with unadjusted results). A non-significant EFS improvement was observed for the RT groups. **Conclusions:** Partial RT and RT to all sites of disease in metastatic RMS was associated with significant OS benefits, albeit in small pt numbers. This should be confirmed in a prospective randomized trial. Clinical trial information: NCT00643565.

Effect of receiving RT for RMS on EFS and OS (adjusted data).

	Hazard ratio*	p*	% Pts event free/surviving at 3yrs (95% confidence interval)
No RT (n=22)			
EFS	-	-	9 (2–56)
OS	-	-	23 (10–56)
Any RT (n=80)			
EFS	0.52	0.0541	47 (35–63)
OS	0.25	0.0002	64 (53–77)
Partial RT (n=49)			
EFS	0.51	0.0621	42 (28–64)
OS	0.31	0.0020	53 (39–72)
RT all sites (n=31)			
EFS	0.54	0.1841	58 (41–82)
OS	0.11	0.0020	84 (71–100)

*Comparison vs no RT

10542 Poster Session (Board #299), Sun, 8:00 AM-11:30 AM

Phase I study of talazoparib and irinotecan in children and young adults with recurrent/refractory solid tumors. *First Author: Sara Michele Federico, St. Jude Children's Research Hospital, Memphis, TN*

Background: Poly (ADP-ribose) Polymerase inhibitors (PARPi) target tumors with deficiencies in DNA repair mechanisms. Talazoparib (TAL), a potent PARP inhibitor, demonstrated significant efficacy in a Ewing sarcoma model when combined with DNA-damaging irinotecan (IRN). We performed a phase I trial to determine the maximum tolerated doses (MTDs) of TAL and IRN in pediatric patients with solid tumors. **Methods:** Cohorts of 3-6 eligible patients (pts) with recurrent/refractory solid tumors received escalating doses of oral (PO) TAL and intravenous (IV) IRN in a 3+3 design (Table 1). Each course was 21 days. Serum for TAL and IRN pharmacokinetics (PK) were obtained. Toxicities were assessed using CTCAE v.4 and responses were evaluated by RECIST v.1.1. **Results:** Twenty-four pts (9 male; median age, 11 years; 18 recurrent) received a median of 2 courses (range, 1-18). Fifteen pts had prior exposure to IRN. Table 1 summarizes the dose-limiting toxicities (DLTs) in course 1. The most common grade 3 or higher non-hematologic and hematologic toxicities in 82 evaluable courses were febrile neutropenia (5), elevated gamma-glutamyltransferase (GGT, 4), neutropenia (22) and lymphopenia (17). Two of 22 evaluable patients had a response (CR Ewing sarcoma, 18 courses; PR synovial sarcoma, 10 courses) and 9 had disease stabilization, median 4 courses (range, 4-10). Results of PK tests will be presented. **Conclusions:** The recommended phase II doses are TAL 600mcg/m^2 (max 1000mcg/dose) days 1-6 and IRN 40mg/m^2/day days 2-6. This regimen is feasible with evidence of anti-tumor activity and warrants further investigation. Clinical trial information: NCT02392793.

Dose level	TAL mcg/m^2/dose, PO	TAL Schedule Days (D)	Maximum TAL (mcg/dose)	IRN mg/m^2/dose, IV daily	# of pts	DLT course 1 (# of pts)
1	400	D 1-6: daily	800	20	6	Thrombocytopenia (1), GGT (1)
2	600	D 1: twice a day D 2-6: daily	D 1: 500mcg/dose D 2-6: 1000mcg/dose	20	3	0
3	600	D 1: twice a day D 2-6: daily	D 1: 500mcg/dose D 2-6: 1000mcg/dose	30	6	Neutropenia (1)
4	600	D 1: twice a day D 2-6: daily	D 1: 500mcg/dose D 2-6: 1000mcg/dose	40	6	Neutropenia (1)
5	600	D 1: twice a day D 2-6: daily	D 1: 500mcg/dose D 2-6: 1000mcg/dose	50	3	Thrombocytopenia (2), neutropenia (2), GGT (1), colitis (1)

10543 Poster Session (Board #300), Sun, 8:00 AM-11:30 AM

A phase I trial of pomalidomide for children with recurrent, progressive/refractory central nervous system (CNS) tumors: A Pediatric Brain Tumor Consortium (PBTC) study. *First Author: Jason R. Fangusaro, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL*

Background: CNS malignancies are the most common solid tumors among children. Novel therapies are needed to help improve the survival outcomes in children with recurrent disease. Pomalidomide is an immunomodulatory agent thought to also function through a combination of anti-angiogenic, anti-inflammatory and cytotoixic activity making it a good candidate to explore in pediatric CNS tumors. **Methods:** A Phase I trial of pomalidomide was conducted among children $\geq$ 3 to $<$ 21 years old with recurrent, progressive/refractory CNS tumors using the "rolling 6" dose escalation design. The primary objective was to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) when given orally once daily for 21 consecutive days of a 28-day course. Once the MTD was established, 12 additional patients were enrolled on expansion cohorts based on age and steroid use. **Results:** 29 children were enrolled and 25 were evaluable for dose limiting toxicity (DLT) evaluation. The MTD was 2.6 mg/m^2 (Dose level 2). DLTs observed at dose level 3 (3.4 mg/m^2) included diarrhea (n = 1), thrombocytopenia (n = 1) and lung infection (n = 1), all grade 3. The most common toxicities were grade 1 lymphopenia (55%), leukopenia (62%) and thrombocytopenia (38%). There were no obvious differences in tolerability based on age or steroid use. Pharmacokinetics were similar to those observed in adults and increased in a dose-dependent manner. At the RP2D of 2.6 mg/m^2, the C_{max} was 97.4 ng/mL and the $t^1/_2$ was 4.1 hours. The median number of treatment cycles was 1.6 (0.2-12.3). Two patients, one with an oligodendroglioma and one with anaplastic pleomorphic xanthoastrocytoma, had long term stable disease for 9 and 18+ cycles. No objective responses were observed. Twelve month progression-free and overall-survivals were 5.2+/-3.6% and 12.8+/-8.5%, respectively. Immunologic correlate analyses are ongoing. **Conclusions:** The RP2D of pomalidomide is 2.6 mg/m^2 in children with recurrent brain tumors. Further prospective evaluation of this agent alone or in combination will be necessary to better understand its efficacy in specific pediatric CNS tumor populations. Clinical trial information: NCT02415153.

10544 Poster Session (Board #301), Sun, 8:00 AM-11:30 AM

Single-agent dose-finding cohort of a phase 1/2 study of lenvatinib (LEN) in children and adolescents with refractory or relapsed solid tumors. *First Author: Nathalie Gaspar, Institut Gustave Roussy, Villejuif, France*

Background: LEN is an inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT. LEN is approved in adults for radioiodine-refractory differentiated thyroid cancer (DTC) and in combination with everolimus in patients (pts) with advanced renal cell carcinoma. We show results from the single-agent LEN dose-finding part of a phase 1/2 study in children and adolescents with solid tumors. **Methods:** Pts had any relapsed or refractory solid tumor, evaluable or measurable disease, were aged 2 to ≤18 years, had < 2 prior VEGF-targeted therapies, and adequate organ function. A starting dose of LEN 11 mg/m^{2}was escalated with a time-to-event continual reassessment method. The primary endpoint was to determine the LEN recommended dose (RD). Secondary objectives included best overall response (BOR), objective response rate, safety, and pharmacokinetics (PK). **Results:** 23 pts enrolled (11 mg/m^2: n = 5, 14 mg/m^2: n = 11, 17 mg/m^2: n = 7). The most common tumors were rhabdomyosarcoma (n = 5), Ewing sarcoma (n = 4), and neuroblastoma (n = 3). 3 Dose-limiting toxicities occurred in cycle 1 at 14 mg/m^2 (increased alanine aminotransferase: 1; hypertension: 2). All pts had any-grade treatment-emergent adverse events (TEAEs; grade 3/4: 65%). Most common any-grade TEAEs were vomiting (52%), abdominal pain (48%), decreased appetite (48%), diarrhea (44%), and hypothyroidism (44%). 1 Pt discontinued LEN due to a LEN-related TEAE (hypertension). BOR was stable disease (n = 10). Effect of age on oral clearance and central volume of distribution was not significant. Exposure was similar to that in adults. LEN 14 mg/m^2/day was therefore identified as the RD. Updated cohort 1 data will be shown. **Conclusions:** The LEN RD in children and adolescents was similar to the adult dose and showed a reasonable safety profile. PK in these pts did not differ significantly from that in adults. The phase 1b dose-finding study of LEN in combination with chemotherapy in osteosarcoma (OS) and phase 2 LEN monotherapy (RD 14 mg/m^2) parts in DTC and OS are ongoing. Clinical trial information: NCT02432274.

10545 Poster Session (Board #302), Sun, 8:00 AM-11:30 AM

A curative approach to central nervous system metastases of neuroblastoma. *First Author: Kim Kramer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Neuroblastoma metastatic to the central nervous system (CNS NB) is associated with significant mortality (median survival < 6 months, < 10% survival at 36 months). Intraventricular compartmental radioimmunotherapy (cRIT) with radio-iodinated murine IgG1 monoclonal antibody ^{131}I-8H9 targeting tumor cell-surface glycoprotein B7-H3 offers a therapeutic strategy. We analyzed overall survival of patients with CNS NB treated with intraventricular ^{131}I-8H9 cRIT at Memorial Sloan Kettering Cancer Center (MSK) since 2003. **Methods:** After radiographic and/or pathologic confirmation of CNS NB, and assessment of adequate CSF flow, cRIT eligible patients underwent treatment on an IRB-approved protocol with either temozolomide/irinotecan-based CNS salvage regimen incorporating craniospinal radiation therapy, ^{131}I-8H9 cRIT plus systemic immunotherapy (group 1), or non-regimen therapies with ^{131}I-8H9 cRIT (group 2). cRIT administration involved a 2mCi tracer of ^{124}I- or ^{131}I-8H9 with nuclear imaging and CSF sampling for dosimetry followed by 1 or 2 therapeutic injections up to 70 mCi ^{131}I-8H9. Disease surveillance included serial MR brain/spine, MIBG, CT, and bone marrow evaluation. Data are presented as overall survival after detection of CNS metastasis. **Results:** 105 patients with CNS NB were evaluated;80 patients (76%) were treated (57 group 1, 23 group 2). Of the 25 patients who were not eligible for cRIT, survival averaged 8.6 months. Of 19 patients with radiographic evidence of disease at the time of cRIT, 7 (36%) demonstrated post cRIT radiographic improvement. At analysis, 45/80 (56%) patients were alive 4.8–152 months (median 58 months) after CNS metastasis, including 36 (45%) at 36 months and 23 (29%) > 60 months. Subgroup analyses of ^{131}I-8H9–treated patients identified age at NB diagnosis (≤18 months), relapse restricted to CNS and group 1 status as factors positively correlated with survival. **Conclusions:** 76% of patients with CNS NB treated at MSK received ^{131}I-8H9 cRIT, and approximately half completed multimodality CNS salvage regimen with ^{131}I-8H9 cRIT. Despite advanced CNS involvement, over 50% of patients treated with ^{131}I-8H9 cRIT are still alive and nearly 50% have survived at least 36 months. Clinical trial information: NCT00089245.

10546 Poster Session (Board #303), Sun, 8:00 AM-11:30 AM

Phase I study of pexidartinib (PLX3397) in children with refractory leukemias and solid tumors including neurofibromatosis type I (NF1) related plexiform neurofibromas (PN). *First Author: Lauren Hittson, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Refractory tumors remain a significant treatment challenge, and novel approaches targeting the tumor microenvironment may hold promise. Pexidartinib, an oral inhibitor of tyrosine kinases including CSF1R, KIT and FLT3, has activity in adults with tenosynovial giant cell tumor. **Methods:** We are conducting a phase 1 trial (NCT02390752) to determine the maximum tolerated dose (MTD) and plasma pharmacokinetics (PK) of pexidartinib in patients (pts) 3-21 years old with refractory leukemias and solid tumors including NF1 PN. The MTD is based on cycle (C) 1 toxicities. Pexidartinib is given once daily continuously (1C = 28 days) at DL 1: 400 mg/m2/dose, 2: 600mg/m2/dose, or 3: 800 mg/ m^2/dose. Response is assessed after C1 and then every other C, and for NF1 PN with volumetric MRI analysis after every 4 C. **Results:** Fourteen pts (8 M:6 F, median age 16 years, (range 4-21) with CNS tumors (n = 2), sarcomas (n = 7), peritoneal mesothelioma (n = 1), leukemia (n = 1), NF1 PN (n = 3) have enrolled at DL1 (n = 4), DL2 (n = 4) and DL3 (n = 6). No dose-limiting toxicities have been observed and 11 pts are evaluable for MTD determination (received ≥ 85% of pexidartinib doses in C1). Common non-DLT toxicities are fatigue, decrease in WBC, increase in creatinine kinase and serum amylase, headache, anorexia, vomiting, diarrhea, and hair hypopigmentation. Mean (SD) pexidartinib C1 day 1 PK parameters at [DL1 (n = 4), DL2 (n = 4), and DL3 (n = 4)] were: C_{max} DL1 2,813 ng/mL (1,483), DL2 6,065 ng/mL (1,308), DL3 10,323 ng/mL (2,129); $AUC_{0\text{-}24h}$ DL1 44,492 ng·h/mL (12,904), DL2 76,569 ng·h/mL (25,790), DL3 132,903ng·h/mL (40,482). The mean (SD) accumulation ratio (C1 D15 $AUC_{0\text{-}24h}$: C1 D1 $AUC_{0\text{-}24h}$) was 3.9 (0.7) for DL1, 2.4 (0.3) for DL2, and 1.4 (0.6) for DL3. Pts received a median of 1 C (range (1-21+). Pts with NF1 PN received 1, 4, and 6 C of pexidartinib and had stable disease. One pt with peritoneal mesothelioma is receiving C 21. **Conclusions:** In children, pexidartinib was tolerated at all dose levels, and the recommended phase II dose (RP2D) is 800 mg/m^2/dose once daily. This dose exceeds the adult RP2D of 1000 mg/day. Enrollment on the expansion cohort is ongoing. Clinical trial information: NCT02390752.

10547 Poster Session (Board #304), Sun, 8:00 AM-11:30 AM

Pazopanib therapy for adolescent and young adult desmoid tumors. *First Author: Laura Agresta, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: There is a lack of reliably effective medical therapies for desmoid tumors (DT). Surgical resection may be morbid, and even a complete resection does not preclude recurrence. Radiotherapy is associated with potentially severe late-effects, a risk that may be particularly detrimental in young patients. In a previous review of our single institution DT experience, we found that objective treatment responses to medical therapies were rare.However,we have recently observed promising effect from therapy with the tyrosine kinase inhibitor pazopanib in adolescent and young adult (AYA) patients with DT. **Methods:** Retrospective single institution chart review evaluating all pazopanib treatment in AYA patients with DT. **Results:** Five AYA patients, ages 15-21 years, with previously treated DT received pazopanib. Four patients with sporadic DT were documented by next generation sequencing to have mutations of *CTNNB1*, and 1 patient with intra-abdominal tumors following colectomy was known to carry a large germline interstitial chromosomal deletion (5q21.2q23.1) including the *APC* locus. The median duration of pazopanib treatment was 6 months at the time of analysis (range: 5-21), with treatment ongoing for 4 patients. None of the patients demonstrated progressive disease while on treatment. Best responses by Response Evaluation Criteria in Solid Tumors 1.1 (RECIST) were partial response in 3 of 5 and stable disease in 2 of 5 cases. One response was nearly complete. In one case of stable disease, tumor necrosis was evident on magnetic resonance imaging after 2 months on pazopanib. Four patients reported pain relief while on pazopanib, including one patient with stable disease. Pazopanib was discontinued in 1 patient after 18 months due to recurrent facial edema. Other grade 1-2 adverse effects responded to dose reduction. The only grade 3 adverse effect was increasing weakness in a patient with pre-existing myopathy; this patient tolerated pazopanib at a reduced dose. **Conclusions:** This is the first report of objective responses to pazopanib by RECIST criteria in AYA patients with DT. Given these benefits and relatively mild toxicity, we conclude that pazopanib therapy should be considered in this patient population.

10548 Poster Session (Board #305), Sun, 8:00 AM-11:30 AM

Effect of PD1/PD-L1 checkpoint blockade on efficacy of anti-GD2 antibody ch14.18/CHO in neuroblastoma. *First Author: Holger N. Lode, University Medicine Greifswald, Greifswald, Germany*

Background: Immunotherapy (IT) with anti-GD_2 antibody (Ab) ch14.18/CHO is effective for treatment of high-risk neuroblastoma (NB) patients mainly due to induction of GD_2-specific Ab-dependent cellular cytotoxicity (ADCC). Methods to further enhance the effect are important and currently explored in prospective clinical trials randomizing ch14.18/CHO ± scIL-2. Programmed death-1 (PD-1) is an inhibitory receptor expressed by activated T- and NK-cells, and cancer cells express PD-1 ligand. Here, we report for the first time effect and mechanism of PD-1/PD-L1 blockade in the context of ch14.18/CHO-based IT in preclinical models. **Methods:** Expression of PD-L1 and PD-1 on NB cells and leukocytes was analyzed by RT-PCR and flow cytometry in the presence of ch14.18/CHO or IL-2. Mechanism of PD-L1 induction was analyzed with anti-CD11b Ab. The effect of PD-1/PD-L1 blockade on ch14.18/CHO-mediated anti-NB immune response was evaluated using anti-PD-1 Ab both in vitro (Nivolumab) and in the syngeneic GD_2^+ NB NXS2 mouse model (anti-mouse PD-1). Mice (n = 10) were treated with ch14.18/CHO (5x300 μg, i.p.) in combination with anti-PD-1 (8x250 μg, i.p.), and compared to controls. **Results:** Culture of LA-N-1 (low PD-L1 baseline expression) in the presence of leukocytes and subtherapeutic ch14.18/CHO concentrations for 24h induced strong upregulation of PD-L1 resulting in complete inhibition of ADCC mediated by ch14.18/CHO. Co-incubation with anti-CD11b Ab abrogated this PD-L1 upregulation. Importantly, blockade with Nivolumab reversed the PD-L1-dependent inhibition of ADCC. Mice treated with ch14.18/CHO in combination with PD-1 blockade showed a strong reduction of tumor growth and prolonged survival as well as the highest level of NB cell lysis mediated by serum and leukocytes compared to controls. **Conclusions:** Ch14.18/CHO-mediated effects upregulate the inhibitory checkpoint PD-1/PD-L1 and combination of ch14.18/CHO with PD-1/PD-L1 blockade results in synergistic treatment effects in mice. This concept will be evaluated in a clinical trial.

10549 Poster Session (Board #306), Sun, 8:00 AM-11:30 AM

Long-term outcomes after irradiation (RT) for pediatric low-grade glioma. *First Author: Derek S. Tsang, St. Jude Children's Research Hospital, Memphis, TN*

Background: Treatment for pediatric low-grade glioma (LGG) is variable, depending on age and tumor location. Systemic therapy (ST) is often used to delay RT, but ST does not result in durable local control. The goal of this study was to evaluate event-free survival (EFS) and toxicities for pediatric LGG treated with RT over a 30-year period. **Methods:** All patients age ≤21 with intracranial pediatric LGG (WHO grade I-II) treated with RT at a single institution since May 1986 were included in this retrospective review. Patients with metastatic disease (M+) received craniospinal irradiation (CSI); otherwise, RT was conformal. EFS and overall survival (OS) were measured from the first day of RT. Events included death, progression, or secondary high-grade glioma. **Results:** 221 patients were eligible. Median follow-up was 11.3 yrs (range, 0.1-30.5). Median RT dose was 54 Gy. 10-yr EFS and OS were 67.9% (95% CI 60.4-74.3) and 91.1% (95% CI 85.8-94.5) for non-metastatic patients, respectively. For 12 M+ patients treated with CSI, 10-yr EFS and OS were 58.9% (95% CI 23.4-82.5) and 70.0% (32.9-89.2), respectively. 28.6% developed pseudoprogression (PP) with median time to onset and resolution of 6.1 months (IQR 3.6-14.6) and 6.4 months (IQR 3.5-11.7), respectively. Patients with PP had improved 10-yr EFS (83.4% vs. 61.0%, HR 0.40, p = .006). Patients with grade II tumors and who received pre-RT ST had lower EFS (Table). Sex, NF-1, tumor location, extent of surgery and CSI were not independently associated with EFS. 10-yr cumulative incidence of grade ≥2 vasculopathy was 7.5% (95% CI 4.9-11.4). There were 12 cases of secondary high-grade glioma, with a 20-yr cumulative incidence of 5.5% (95% CI 2.6-11.4). **Conclusions:** Irradiation provides long-term control of pediatric LGG in a majority of patients. Receipt of pre-RT systemic therapy was associated with reduced EFS; this association requires further investigation.

	n	10-yr EFS (95% CI)	Adjusted HR (95% CI)	p
Pre-RT systemic therapy				
No	141	73.7% (64.8-80.7)	Ref	
Yes	80	55.9% (43.0-67.0)	2.3 (1.4-3.7)	.0007
WHO grade				
I	146	68.2% (59.0-75.8)	Ref	
II	30	43.4% (22.4-62.8)	1.7 (1.0-3.1)	.07
OPG, no pathology	18	82.4% (54.7-93.9)	0.3 (0.1-1.1)	.07
Low-grade, NOS	27	76.1% (54.2-88.6)	0.8 (0.4-1.6)	.5

10550 Poster Session (Board #307), Sun, 8:00 AM-11:30 AM

Anti-GD2 immunotherapy in adults with high-risk neuroblastoma (HR-NB): The Memorial Sloan Kettering Cancer Center (MSKCC) experience. *First Author: Maya Suzuki, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The diagnosis of NB in adulthood is rare and little is known about its biology and clinical course. There is no established therapy for adult NB. Anti-GD2 immunotherapy is now standard in children with HR-NB but its use has not been reported in adults. **Methods:** After obtaining IRB waiver, records of all patients with adult-onset (≥18 years) NB seen at MSKCC between 1983 and 2015 were reviewed. Overall survival (OS) was tested by log-rank test. Cox-regression was used for multivariate analysis. **Results:** The subjects were 42 adults (median: 25; range18-71 years); 23 male and 19 female. Five, 1, 1 and 35 patients had INSS stage 1, 2, 3 and 4 disease, respectively. Genetic abnormalities included somatic *ATRX* (59%) and *ALK* mutations (43%) but not *MYCN*-amplification. 16 patients remain alive at a median follow-up of 5.3 years. OS for non-stage 4 patients was superior to stage 4 (median survival 14.6 vs 5.3 years; $p < 0.05$). However 5/7 patients with < stage 4 NB progressed to stage 4. Among 35 stage 4 patients, 4 achieved complete remission (CR) after induction chemotherapy and surgery, 11 underwent autologous stem cell transplant (ASCT) and 15 received multiple cycles of anti-GD2 antibodies 3F8 or hu3F8 without complications. In univariate analysis, patients ≤ 29 years old (n = 24) at diagnosis, those achieving CR, and those receiving anti-GD2 antibodies had superior OS ($p < 0.05$ for each). ASCT was not beneficial (p = 0.3 for ASCT vs no ASCT). For stage 4 patients, anti-GD2 immunotherapy was associated with favorable OS in multivariate analysis (95% CI of anti-GD2 antibody: 1.270 to 7.990). **Conclusions:** Adult-onset stage 4 NB demonstrates a high incidence of somatic mutations and is only partially chemosensitive. However, 3F8/hu3F8-based anti-GD2 immunotherapy appears to improve long-term survival and is well tolerated.

10551 Poster Session (Board #308), Sun, 8:00 AM-11:30 AM

Management of uni- or bilateral retinoblastoma with radiologic optic nerve invasion at diagnosis. *First Author: Marie-Louise Choucair, Institut Curie, Paris, France*

Background: To evaluate treatment and outcome of patients with uni- or bilateral retinoblastoma (RB) with radiologic optic nerve invasion (RONI) at diagnosis. **Methods:** Retrospective clinical, radiological and histological review of patients with uni- or bilateral RB with RONI at diagnosis treated in the Institut Curie. **Results:** Between 1997 and 2014, 936 patients with RB were treated in the Institut Curie. Eleven patients had detectable RONI confirmed by Computed Tomography and/or Magnetic Resonance Imaging. RB was unilateral in 10/11 patients, bilateral in 1. Median age at diagnosis was 29 months (range 12-96). The patient with the bilateral RB had a unilateral RONI. Nine patients had ON enhancement and 3 had meningeal sheath enhancement. Nine received neoadjuvant chemotherapy (CT) and 2 had a primary enucleation. Partial response to neoadjuvant CT was obtained for all the patients. Enucleation was performed in 10/11 patients, by anterior approach in 3 patients, by anterior and subfrontal approach in 7 patients. Three patients had positive ON margin and among them, 2 were primary enucleated. All enucleated patients received adjuvant treatment (conventional CT: 10, High Dose CT: 7 and radiotherapy: 5). Three patients died of meningeal progression (2 during treatment and 1 during the first year after treatment). The patient with the bilateral RB was lost to follow up just after a meningeal progression during treatment. Seven are still alive (median follow up: 8 years, range : 1.5-17.5). **Conclusions:** Neoadjuvant CT has an important place in the management of unilateral RB with RONI at diagnosis. Pretreatment accurate staging by orbital and brain MRI is mandatory, as well as preoperative reassessment. Surgery should be performed by experienced ophthalmologists and if necessary neurosurgical team in order to obtain the best conditions for a tumor-free resection margin in patients with RONI.

10552 Poster Session (Board #309), Sun, 8:00 AM-11:30 AM

Noninvasive molecular profiling of high-risk relapsed neuroblastoma by plasma cell-free DNA analysis. *First Author: Prachi Kothari, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Neuroblastoma (NB) is the most common extracranial solid tumor in children. 5-year survival rates for high-risk NB are < 50% despite intense multimodality treatment. Recent studies revealed that as opposed to diagnostic samples, relapsed NB tumors have a significantly higher mutational burden as a result of clonal evolution. This poses a challenge for the development of personalized therapies and warrants molecular profiling at relapse. However, tumor samples are not always accessible at relapse. Our study evaluates the feasibility of using cell-free DNA (cfDNA) to noninvasively characterize tumor profiles at relapse to identify targetable genetic variants. **Methods:** Tumor specimens, plasma and matched control samples from 10 patients with high-risk stage 4 NB were collected during multimodality treatment. Samples were analyzed using the MSK-IMPACT platform, a targeted deep sequencing assay to interrogate the exons and selected introns of 410 actionable genes. Tumor samples were collected from surgeries performed either at diagnosis, disease progression, or relapse. Plasma samples were collected at a time of disease progression, at an average 395 days (range of 47-1597 days) from tumor collection. Matched control samples were used to filter germline variants. **Results:** We detected somatic mutations and copy number alterations in tumor tissues and cfDNA of 10/10 and 6/10 patients, respectively. These included recurrent NB drivers such as MYCN amplification and ATRX mutations. In 4 patients, cfDNA also revealed somatic variants that were not detected in the original tumor specimens, including potentially targetable mutations in NRAS, MLL2, CIC and IDH2 that were recently reported to be enriched in the relapse setting, as well as ARID1B mutation that is associated with poor prognosis. **Conclusions:** This study suggests that it is feasible to noninvasively profile the dynamic genetic heterogeneity of NB by plasma cfDNA analysis. Such analysis can potentially supplement tumor profiling especially in the relapse setting to guide treatment plans. Our findings call for incorporation of cfDNA analysis in clinical trials to further evaluate its utility for clinical management of NB patients.

10553 Poster Session (Board #310), Sun, 8:00 AM-11:30 AM

Effects of the multikinase inhibitor regorafenib in neuroblastoma. *First Author: Peter E. Zage, Texas Children's Hospital, Pearland, TX*

Background: Neuroblastoma (NB) is the most common extracranial solid pediatric tumor, and children with high-risk NB have poor survival rates and need novel treatment strategies. Regorafenib, a multi-receptor tyrosine kinase (RTK) inhibitor approved for treating adult solid tumors such as advanced metastatic colorectal cancer and gastrointestinal stromal tumors, inhibits many RTKs, including PDGFR-β, VEGFR1-3, RET, c-Kit and FGFR family members. Based on the potential roles for these targets in neuroblastoma pathogenesis, we explored the therapeutic potential of Regorafenib alone and in combination with 13-cis-retinoic acid against neuroblastoma cells. **Methods:** We treated NB cell lines with increasing concentrations of Regorafenib and measured cell viability using MTT assays. We further measured the occupied percent confluence over time using continuous live cell imaging. We performed Western blots for caspase cleavage to measure apoptosis and flow cytometry to determine cell cycle expression. We performed Reverse Phase Protein Array (RPPA) analysis of neuroblastoma cells before and after treatment with regorafenib combined with 13-*cis*-retinoic acid. **Results:** IC_{50}values for the tested cell lines ranged between 2.5mcM and 12.5mcM after 72 hours of exposure to Regorafenib, and decreased viability was due to a combination of apoptosis and cell cycle arrest. RPPA analysis identified alterations in multiple proteins and pathways after Regorafenib with retinoic acid treatment, including the PI3K/Akt/mTOR and Jak/Stat pathways. Phosphorylation of Erk1/2, S6, Akt, and c-Jun were decreased, while protein expression of GATA3 was increased in a dose-dependent manner. **Conclusions:** Regorafenib treatment results in reduced neuroblastoma cell viability and increased apoptosis via effects on several signaling pathways. Effects on intracellular signaling pathways associated with responses to the combination of regorafenib plus retinoic acid represent opportunities to develop novel combination therapies, representing potential new therapeutic strategies for children with neuroblastoma.

10554 Poster Session (Board #311), Sun, 8:00 AM-11:30 AM

Long-term growth and development in 268 bevacizumab (BEV)-treated and 135 control pediatric/adolescent patients (pts): An integrated analysis. *First Author: Hermann L. Müller, Klinikum Oldenburg AöR, Medical Campus University Oldenburg, Oldenburg, Germany*

Background: BEV has an established safety profile in adults, but long-term data in children are limited. This analysis examined the effects of BEV on growth/development in pediatric/adolescent pts. **Methods:** Data (height, weight, body mass index [BMI], bone age data) were pooled (5 trials): NCT00643565 (Ph2/soft tissue sarcoma); NCT01390948 (Ph2/high-grade glioma); NCT00085111 (Ph1/refractory solid tumors); NCT00667342 (Ph2/osteosarcoma); NCT00381797 (Ph2/glioma, medulloblastoma, ependymoma). Pts (<18 yrs old) received ≥1 dose of BEV + chemotherapy (CT) (n=268) or CT alone (n=135). Analyses were exploratory/descriptive. Reference growth data: WHO (<2 yrs); Centres for Disease Control (≥2 yrs). **Results:** Across the trials, mean number of BEV administrations per pt ranged 5.6–19.9 (dose 5–15mg/kg every 2/3 weeks). Median follow-up time, months (range): BEV+CT, 37.9 (2.4–64.2); CT, 22.9 (2.8–69.2). At baseline, median height, weight, and BMI were close to that of the reference population (mean standard deviation scores [SDS] close to 0). Over 60 months, a slight decline was observed in the mean SDS for height and weight in both arms in this cohort with different tumors/treatments (Table), but remained within normal range of healthy children. Trends were similar for BMI. No delay in growth velocity or bone age in BEV-treated pts vs CT only was observed up to 3 yrs, regardless of age/gender. A subgroup analysis of pts in the growth hormone-dependent development phase was consistent with the overall results. **Conclusions:** In this analysis, BEV inclusion in the treatment regimen did not have a negative impact on pediatric growth/development beyond that of CT alone.

Mean SDS vs time.

		Height SDS		Weight SDS	
Months		**BEV+CT**	**CT**	**BEV+CT**	**CT**
Baseline	n	*268*	*134*	*268*	*135*
	Mean	0.2	0.15	0.33	0.18
6	n	*204*	*111*	*203*	*116*
	Mean	0.01	-0.01	0.1	-0.05
12	n	*135*	*73*	*132*	*76*
	Mean	-0.9	-0.06	0.02	-0.06
18	n	*70*	*28*	*61*	*29*
	Mean	-0.19	-0.49	-0.12	-0.34
24	n	*48*	*24*	*37*	*23*
	Mean	-0.33	-0.60	-0.17	-0.40
30	n	*39*	*16*	*18*	*16*
	Mean	-0.37	-0.77	-0.40	-0.63
36	n	*37*	*10*	*16*	*9*
	Mean	-0.50	-0.52	-0.64	-0.64
42	n	*32*	*8*	*9*	*7*
	Mean	-0.56	-0.61	-0.69	-0.73
48	n	*27*	*9*	*9*	*9*
	Mean	-0.58	-0.75	-0.60	-0.40
54	n	*20*	*5*	*4*	*5*
	Mean	-0.58	-0.91	-0.95	-0.80
60	n	*16*	*3*	*3*	*3*
	Mean	-0.46	-1.22	-0.52	-0.61

10555 Poster Session (Board #312), Sun, 8:00 AM-11:30 AM

Neuroblastoma metastatic to the central nervous system: Survival analyses from the German Childhood Cancer Registry and the literature. *First Author: Frank Berthold, University of Cologne, Cologne, Germany*

Background: Therapeutic innovation has resulted in an overall decline in childhood neuroblastoma (NB) mortality; however, metastatic NB to the central nervous system (CNS NB), which has emerged as a sanctuary site for NB metastases, remains difficult to treat and is typically fatal. The objective of this study was to describe the natural course of CNS NB. **Methods:** Data were sourced from a custom query of the German Childhood Cancer Registry (GCCR) and from the literature. Survival statistics were prepared from a diverse, thus generalizable, pool of CNS NB patients. Data are presented as secondary event-free and overall survival (EFS and OS) after diagnosis of first CNS recurrence from initial high-risk NB. **Results:** The GCCR query identified 85 patients with CNS NB diagnosed from 1990–2010, including 57 with isolated CNS disease. The median (95% confidence) EFS and OS times were 2.6 (1.5–3.8) and 4.7 (2.1–7.2) months, respectively, for all CNS NB patients, and 2.8 (1.4–4.1) and 6.8 (2.1–11.5) months, respectively, for isolated CNS NB patients. Secondary OS at 12, 18, and 36 months was 29.4%, 18.8%, and 8.2%, respectively, for all CNS NB patients, and 35.1%, 22.8%, and 12.3%, respectively, for isolated CNS NB patients. Thirteen publications were selected with 83 patients treated from 1979–2013. In addition to an inclusive analysis, a restricted analysis was performed, excluding patients who did not receive therapy with curative intent, to assess survival after therapeutic intervention. Median OS (95% confidence) was 5.6 (3.0–8.0) and 8.7 (5.8–11.0) months in the inclusive and restricted analyses, respectively. The proportion of patients surviving 12, 18, and 36 months at reporting were 24%, 12%, and 3.6%, respectively, for the inclusive population, and 33%, 17%, and 5%, respectively, for the restricted population. **Conclusions:** An assessment of the natural course of CNS NB from two sources arrived at similar conclusions with respect to overall and long-term survival. In general, median secondary OS is < 6 months and < 10% of patients survive 36 months. The findings were consistent across geographic regions and have not changed appreciably in 4 decades.

10556 Poster Session (Board #313), Sun, 8:00 AM-11:30 AM

A biomarker-guided approach to combining PARP inhibitors with radiotherapy in pediatric solid tumors. *First Author: Anang Shelat, St. Jude Children's Research Hospital, Memphis, TN*

Background: Ewing sarcoma (EWS) expresses high levels of Schlafen-11 (SLFN11). SLFN11 disrupts checkpoint maintenance and may serve as a biomarker to assess sensitivity to Poly (ADP-ribose) polymerase 1 and 2 inhibitors (PARPi). The goal of this study is to evaluate SLFN11 protein expression in a panel of pediatric solid tumors and correlate levels of protein with sensitivity to PARP inhibition combined with ionizing radiation (IR), a component of therapy for many pediatric solid tumors and a potent inducer of DNA damage. **Methods:** SLFN11 mRNA and protein levels were assessed by quantitative RT-PCR, and immunohistochemistry, Western blot, and immunofluorescence microscopy, respectively. PARPi included: talazoparib (TAL), niraparib (NIR), veliparib (VEL), and olaparib (OLA). Approximately 30 minutes after addition of systemic therapy, graded doses of radiation were delivered and viability across a panel of pediatric solid tumor cell lines was measured using the ATP-based Cell TiterGlo assay and confirmed with the colony formation assay. **Results:** We found that SLFN11 mRNA and protein is expressed at high levels in EWS, and SLFN11 is also variably present in a subset of other pediatric solid tumor lines, including desmoplastic small round cell tumor, osteosarcoma, and rhabdomyosarcoma. In all tumor cells with detectable SLFN11 expression, viability was reduced by greater than 90% when exposed to 2Gy IR and 1-10nM TAL, whereas cells with undetectable levels of SLFN11 were 5-10 times less sensitive. Intriguingly, variation in the potentiation between specific PARPi and IR correlated with the ability to form drug-induced PARP-DNA adducts, with the strong PARP trapper TAL showing ~10-fold higher potency compared to the moderate trapper NIR, and ~300-fold more potency relative to the weak trapper VEL. Consistent with our PARPi findings, the toposiomerase 1 inhibitor irinotecan, which also forms DNA adducts, potentiated with IR similarly to TAL at concentrations $<$ 10nM in tumor cells expressing detectable levels of SLFN11. **Conclusions:** SLFN11 is present in select pediatric solid tumors and may induce a DNA repair defect that is best exploited by combining low-doses of TAL and irinotecan with IR.

10557 Poster Session (Board #314), Sun, 8:00 AM-11:30 AM

Risk factors associated with metastatic site failure in patients with high-risk neuroblastoma. *First Author: John Thomas Lucas, St. Jude Children's Research Hospital, Memphis, TN*

Background: This retrospective study sought to identify predictors of metastatic site failure (MSF) in patients with high-risk (HR) neuroblastoma (NB). **Methods:** Seventy-six patients with HR NB treated on prospective trials at from 1997 to 2014 were eligible for inclusion. All patients were treated with induction chemotherapy (chemo) with surgery followed by myeloablative chemo & stem cell rescue. Primary & metastatic site (MS) RT were applied according to institutional protocol. CT & I-123 MIBG scans were used to assess Curie scores at diagnosis, post-induction, post-transplant & failure. Overall (OS), & progression-free survival (PFS) were described using the Kaplan-Meier estimator. Cox proportional hazards frailty (cphfR) & CPH regression (CPHr) were used to identify covariates predictive of MSF & new site MSF. **Results:** Forty-two (55%) patients had documented MSFs. Consolidative MS RT was applied to 30 MSs in 10 patients. Original site MSF occurred in 146 of 383 (38%) & 18 of 30 (60%) non-irradiated & radiated MSs respectively. Original site MSF occurred in post-induction MIBG avid lesions in 68 of 81 (84%) & 12 of 14 (85%) non-irradiated & radiated MSs respectively. The median OS & PFS were 61 mo (95% CI 42.6-NR) & 24.1 mo (95% CI 16.5-38.7). Univariate cphfR identified an increased hazard for original MSF when MIBG avid following induction chemo (HR 4.9, 95%CI 1.1-20.9, p = 0.03) & transplant (HR 7.3 95%CI 1.8-30.2, p = 0.006) relative to lesions that cleared after induction. Notably, MS RT nor site location did not modify the hazard for MSF. Multivariate CPHr identified inability to undergo transplant (HR 32.4 95%CI 9.3-96.8, p $<$ 0.001) &/or maintenance chemo (HR 5.2, 95%CI 1.7-16.2, p = 0.005) & the presence of lung metastases (HR 4.4 95%CI 1.7-11.1, p = 0.002) at diagnosis as predictors of new site MSF. The new MSF free survival at 3 years was 25% vs. 87% in patients with high-risk factors relative to those without the risk factors suggesting limited benefit of consolidative MS RT in this population. **Conclusions:** Metastatic lesions that remained MIBG avid following induction chemo & post-transplant had an increased hazard for MSF. Consolidative site RT likely has limited benefit in patients with HR features.

10558 Poster Session (Board #315), Sun, 8:00 AM-11:30 AM

Diabetes risk in childhood cancer survivors: A population-based study. *First Author: Iliana Carolina Lega, Women's College Research Institute, University of Toronto, Toronto, ON, Canada*

Background: Cure rates for childhood cancer have improved significantly over the last three decades. Diabetes has emerged as a delayed side-effect of treatment for childhood cancer. Methodologic limitations may have led to underestimation of the risk for diabetes in previous studies. Understanding the extent of diabetes risk and identifying risk factors for diabetes is imperative for improving screening and prevention strategies in this population. **Methods:** We used the Ontario population-based cancer registry and administrative health databases to evaluate the risk of diabetes in adult survivors of childhood cancer. Diabetes was measured using a validated algorithm. Survivors were compared to age and sex-matched controls from the general population using a multivariable, cause-specific hazard regression model where death and development of another cancer was treated as a competing risk. **Results:** We identified 10,438 1-year survivors of childhood cancer diagnosed prior to age 21 years between January 1st, 1990 and December 31st, 2010. Mean age at cancer diagnosis was 10.7 years (standard deviation [SD] 6.8) and the mean follow up was 11.2 years (SD 6.9). In multivariable models adjusted for rurality and income status, cancer survivors had a 55% increased rate of developing diabetes compared to matched controls (HR 1.55, 95% CI 1.31-1.83). Individuals treated for cancer between age 6-10 years (HR 4.01, 2.33-6.91) had the highest increased rate for diabetes among age categories. Leukemia (HR 2.39, 1.74-3.27) and lymphoma (HR 1.61, 1.12-2.31) was also associated with an increased risk for diabetes compared to the general population. **Conclusions:** Our study provides evidence of an increased risk for diabetes in adult survivors of childhood cancer. The increased risk is highest among those treated at younger ages, and after treatment for leukemia and lymphoma. Future research is warranted to identify optimal ways for diabetes screening and prevention in this population. Given the burden of cardiovascular disease in survivors, identifying and treating diabetes early may help improve overall morbidity and mortality.

10559 Poster Session (Board #316), Sun, 8:00 AM-11:30 AM

Solid organ transplant after treatment for childhood cancer: A report from the Childhood Cancer Survivor Study. *First Author: Andrew Charles Dietz, Children's Hospital Los Angeles, Los Angeles, CA*

Background: Childhood cancer therapy is associated with late onset, organ-specific impairment. However, the prevalence of and outcomes after solid organ transplant (SOT) in childhood cancer survivors (CCS) are unknown. **Methods:** Data on U.S-based participants in the Childhood Cancer Survivor Study were linked with the Organ Procurement and Transplantation Network. Cumulative incidence of transplant (CIT) 35 years after cancer diagnosis, multivariable Cox regression models for hazard ratios (HR), Kaplan-Meier (KM) survival and corresponding 95% confidence intervals (CI) were estimated. **Results:** Among 13,318 survivors, median follow-up age 39 years (interquartile range, IQR 33-46), and median time since cancer diagnosis 31 years (IQR 28-36 years), 100 CCS had SOT after study entry with characteristics and outcomes provided (table). **Conclusions:** Organ-specific radiation and chemotherapy exposure increase the risk for SOT after childhood cancer. Five-year survival rates after renal and cardiac SOT are favorable.

	Kidney	Heart	Liver	Lung
Number of SOT	50†	37	9	7
Wait List Only	21	25	15	6
CIT (95% CI)	0.39% (0.27-0.51)	0.30% (0.20-0.40)	0.07% (0.02-0.12)	0.05% (0.01-0.08)
Wait List or SOT	0.54% (0.40-0.67)	0.49% (0.36-0.62)	0.19% (0.10-0.27)	0.10% (0.04-0.16)
Median (IQR) Age in years at Cancer Diagnosis	2 ($<$ 1-9)	6 (3-11)	6 (4-9)	12 ($<$ 1-16)
Median (IQR) Age in years at SOT	25 (20-35)	28 (21-32)	37 (25-38)	30 (27-37)
Risk Factors for SOT or Wait List (HR, 95% CI)*	Nephrectomy (4.1, 2.2-7.6) Ifosfamide (22.7, 6.8-75.5) Total Body Irradiation (7.0, 2.3-21.3) Kidney Radiation $>$ 10-20 Gy (2.3, 1.1-4.7) $>$ 20 Gy (4.6, 1.1-19.5)	Anthracylines $>$ 0-150 mg/m^2 (8.4, 2.2-32.6) 151-300 mg/m^2 (5.0, 1.3-19.5), 301-450 mg/m^2 (26.5, 9.9-71.0) $>$ 450 mg/m^2 (94.2, 35.3-251.2) Heart Radiation $>$ 20-30 Gy (6.1, 1.8-20.6) $>$ 30 Gy (19.7, 7.1-54.2)	Actinomycin (3.8, 1.3-11.3) Methotrexate (IV/IM) (3.3, 1.0-10.2)	Carmustine (12.3, 3.1-48.9) Lung Radiation $>$ 10 Gy (15.6, 2.6-92.7)
Five-Year Survival after SOT (95% CI)	93.5% (81.0-97.9)	80.6% (63.6-90.3)	27.8% (4.4-59.1)	34.3% (4.8-68.6)

†3 patients had different prior SOT, *only HR with p $<$ 0.05 shown.

10560 Poster Session (Board #317), Sun, 8:00 AM-11:30 AM

Relationship between the cumulative burden (CB) of chronic health conditions (CHC) and health-related quality of life (HRQoL) among childhood cancer survivors (CCS): The St. Jude Lifetime (SJLIFE) cohort. *First Author: Nickhill Bhakta, St. Jude Children's Research Hospital, Memphis, TN*

Background: Adult CCS experience an excess burden of CHC. The association between disease burden (estimated using CB) and HRQoL has not been extensively assessed. **Methods:** 2878 CCS (mean [range] age 32.1 [18.3-66.2] years; time from diagnosis 25.0 [10.2-51.0] years) were enrolled in SJLIFE (eligibility: survived >10 years and >18 years of age) and clinically evaluated for 168 graded CHC using the St. Jude modified Common Terminology Criteria for Adverse Events. HRQoL was assessed using the Short Form 36 survey and categorized into Low (< -0.5 SDs), Average (-0.5 to 0.5 SDs), and High (> 0.5 SDs) subgroups from the Physical and Mental Component Summary (PCS, MCS) and Vitality Scale using cohort age- and sex-specific values. CB (average number of grade 3-4 [severe/life-threatening] CHC/survivor) for each CHC was calculated and summed for each HRQoL subgroup. **Results:** Survivors with low PCS had, on average, more CHC CB compared to those with High and Average PCS. Higher CHC CB was also associated with poorer Vitality and MCS, but the differences in effect size were smaller than PCS. When CB for each of the 3 HRQoL scores were compared by subgroups across 12 organ systems and subsequent neoplasms, CB at age 50 differed significantly ($p<0.05$) across PCS, MCS, and Vitality in 9, 3 and 7 of the 13 systems, respectively. **Conclusions:** Survivors with lower HRQoL scores have more CHC, but the patterns of this association vary in PCS, MCS and Vitality by CHC organ systems, suggesting adult CCS adjust better to certain types of CHC than others. Future research will focus on CHC with greatest impact on functioning.

CB (average number of grade 3-4 CHC/Survivor) and HRQoL by subgroups and age.

		HRQoL Score				
	Age	Low	Average	High	P	Organ Systems that Differed Significantly at Age 50
PCS						
	30	3.6	2.0	1.4	*	Auditory, Cardiovascular (CV), Endocrine (Endo),
	40	5.5	3.4	2.3	*	Gastrointestinal (GI), Infection, Musculoskeletal
	50	7.9	5.2	3.6	*	(MSK), Neurology (Neuro), Pulmonary (Pul), Reproductive
MCS						
	30	2.5	2.1	2.0	+	CV, Endo, Neuro
	40	3.9	3.4	3.3	+	
	50	6.1	5.1	4.9	+	
Vitality						
	30	2.8	2.1	1.7	*	CV, Endo, GI, MSK, Neuro, Pul, Renal
	40	4.5	3.4	2.8	*	
	50	6.7	5.2	4.3	*	

*p<0.001, +p<0.05

10561 Poster Session (Board #318), Sun, 8:00 AM-11:30 AM

Late complications among adult survivors of neuroblastoma in the St. Jude Lifetime Cohort Study (SJLIFE). *First Author: Carmen Louise Wilson, St. Jude Children's Research Hospital, Memphis, TN*

Background: Assessment of late outcomes in neuroblastoma survivors has generally consisted of self-reported health events within retrospective cohorts. We aimed to characterize the health outcomes of a clinically-assessed cohort of long-term survivors of neuroblastoma diagnosed between 1963-2003. **Methods:** In a cohort of 239 ten-year survivors of neuroblastoma, of whom 137 (57%) underwent comprehensive clinical assessments, chronic conditions were graded using a modified version of the Common Terminology Criteria of Adverse Events, version 4.03. Comparisons were made using 272 clinically assessed community controls. Log-binomial regression was used to compare the prevalence of chronic conditions (grade 1-5) between survivors and controls and to calculate prevalence ratio (PR) and 95% confidence intervals (CI). Mean cumulative count (treating death as a competing risk) of chronic conditions by age was used to estimate cumulative burden with imputation of outcomes for non-clinically assessed survivors. **Results:** The median age at diagnosis was 0.9 (range: 0.0-14.4) and the median age at follow-up was 31.9 (range: 20.2-54.6) years for clinically assessed survivors. Median age of controls was 34.7 (range: 18.3-70.2). Treatment consisted of chemotherapy (75%), radiation (23%) and surgery (91%). Survivors were more likely than controls to have hearing loss (31.4% vs. 2.9%, PR = 10.7, 95% CI = 5.2-22.0), cardiomyopathy (8.8% vs. 0.7%, PR = 11.9, 95% CI = 2.7-52.5), hypothyroidism (10.9% vs. 5.2%, PR = 2.1, 95% CI = 1.1-4.3) or neurological disorders (56.9% vs. 32.4%, PR = 1.8, 95% CI = 1.4-2.2). At 35 years of age, the cumulative incidence of survivors experiencing at least one grade 3-5 condition was 67.3% (95% CI = 58.3-76.0%). By age 35 survivors experienced, on average, 8.5 (95% CI = 7.6-9.3) grade 1-5 and 2.4 (95% CI = 2.0-2.8) grade 3-5 conditions per 100 survivors, which was higher than the burden of grade 1-5 (3.3 [95%CI = 2.9-3.7]) and grade 3-5 (0.9 [95%CI = 0.7-1.0]) conditions identified among controls. **Conclusions:** Two-thirds of survivors are affected by severe or life-threatening health conditions. Continued follow-up, screening and intervention provide opportunities to optimize health.

10562 Poster Session (Board #319), Sun, 8:00 AM-11:30 AM

Long-term incidence of venous thromboembolism (VTE) among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Arin L Madenci, Boston Children's Hospital, Boston, MA*

Background: This study aimed to estimate the incidence of late-occurring VTE among survivors of childhood cancer, and to identify associated demographic and clinical factors that define high-risk subgroups for potential screening and prevention. **Methods:** Using data from CCSS, a multi-institutional, longitudinal cohort of 5-year survivors of childhood cancer (diagnosed 1970-1999) and their siblings, the primary endpoint of self-reported late VTE (occurring ≥5 years after diagnosis) was estimated using multivariable piecewise exponential models adjusted for age, sex, and race. Generalized estimating equations accounted for potential within-family correlation where applicable. **Results:** Among 23,601 survivors and 5051 siblings, the incidence of VTE was 1.15 and 0.48 events per 1000 person-years, respectively. For survivors, median age at last follow-up was 28.6 years (range 5.6-58.3) and median follow-up time from diagnosis was 21.2 years (range 5.0-39.3). The adjusted rate ratio (RR) for survivors compared to siblings was 2.2 (95% confidence interval [CI] = 1.7-2.8, $P< 0.01$). Among survivors, risk factors for VTE included BMI≥30kg/m^2 (ref. BMI 18.5-24.5; RR = 1.5, CI = 1.2-2.0, $P< 0.01$), increasing number of severe or life-threatening (i.e. CTCAE grades 3 or 4) non-VTE chronic conditions (ref. 0 conditions; 1-2 conditions: RR = 2.5, CI = 2.0-3.1, $P< 0.01$; ≥3 conditions: RR = 3.5, CI = 2.5-4.9, $P< 0.01$), and cancer recurrence or second malignant neoplasm (RR = 3.5, CI = 2.7-4.6, $P< 0.01$). Incidence of late VTE was associated with increased subsequent mortality, independent of non-VTE chronic conditions (RR 2.2, 95% CI = 1.7-2.8, $P< 0.01$). **Conclusions:** Survivors of childhood cancer remain at increased risk for VTE across their lifespan. While typically not causal, late VTE was associated with subsequent mortality. Care providers should be aware of this increased risk and consider interventions that target modifiable co-morbidities such as obesity. Surveillance and education should be directed toward high-risk survivors.

10563 Poster Session (Board #320), Sun, 8:00 AM-11:30 AM

Infection related late mortality in survivors of childhood cancer with asplenia or radiation-induced hyposplenism: A report from the Childhood Cancer Survivor Study. *First Author: Brent Weil, Boston Children's Hospital, Boston, MA*

Background: Asplenia or hyposplenism can develop in survivors of childhood cancer following splenectomy or radiotherapy exposure to the left upper quadrant of the abdomen (LUQ). Knowledge regarding long-term infection related outcomes for these survivors is limited. **Methods:** Infection related late mortality (sepsis, meningitis or pneumonia) was evaluated in 20,805 5-year survivors (diagnosed <21 years of age from 1970-1999, median follow-up 26 years, range 5-44) using cumulative incidence and Poisson regression models to calculate adjusted relative risk (RR) and 95% confidence intervals (CI). Average LUQ radiation was calculated as a surrogate for splenic radiation. **Results:** Treatment included splenectomy for 1328 survivors (6%). An additional 10,295 (49%) were exposed to LUQ radiotherapy without splenectomy. The cumulative incidence of infection related late mortality was 1.4% (95%CI: 0.7%-2.2%) at 35 years after splenectomy and 0.6% (95%CI: 0.4%-0.8%) after LUQ radiotherapy, with a total of 78 deaths attributable to infectious causes (25 sepsis, 1 meningitis, 52 pneumonia). Splenectomy (RR=8.4, $p<0.001$) and increasing LUQ radiotherapy dose ($p<0.001$) were independently associated with infection related late mortality (Table). **Conclusions:** Splenectomy and LUQ radiotherapy increased risk for infection related late mortality. While infectious mortality increased with increasing LUQ radiation dose, even lower dose exposure (<10Gy) increased risk substantially. Accordingly, cancer survivors exposed to LUQ radiotherapy should be considered at risk for functional asplenia and managed similarly to asplenic individuals with respect to vaccinations and febrile illnesses.

Multivariate analysis of factors associated with infection related late mortality.*

Treatment	RR (95% CI)	P
No splenectomy; no RT (Ref.)	1.0	
Splenectomy	8.4 (3.5 - 20.1)	<0.001
No splenectomy, 0.1-10 Gy LUQ RT	2.4 (1.1 - 5.2)	0.028
No splenectomy, 10-19 Gy LUQ RT	6.1 (2.5 – 14.9)	<0.001
No splenectomy, 20+ Gy LUQ RT	9.3 (3.2 – 27.0)	<0.001

*Adjusted for age at diagnosis, attained age, sex, race and chronic health conditions. *RT*, radiotherapy.

10564 Poster Session (Board #321), Sun, 8:00 AM-11:30 AM

Endothelial dysfunction in adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort study. *First Author: Daniel A. Mulrooney, St. Jude Children's Research Hospital, Memphis, TN*

Background: Endothelial dysfunction, as an indicator of vascular disease in childhood cancer survivors (CCS) has not been widely studied. **Methods:** Markers of vascular inflammation (high sensitivity C-reactive protein [hsCRP]), hemostasis (fibrinogen), activation (endothelial cell expression of vascular cell adhesion molecule [VCAM-1]) and functional testing (large/small artery elasticity [L/SAE], pulse wave velocity [PWV]) were assessed in 200 CCS, ≥10 years from diagnosis, and 192 age/gender matched healthy controls. Exclusion criteria included: inflammatory processes, use of anti-inflammatory or cardiovascular medications, or pregnancy. Differences were assessed by adjusted multivariable linear regression. **Results:** CCS (53% male) of leukemia/lymphoma (59%), central nervous system tumors (6%), sarcomas (11.5%), embryonal tumors (22.5%), and other (1%) had a mean age at diagnosis 7.3 years (SD ±5.7). CCS and controls did not differ in current age (mean 34.1 ±9.2 vs. 33.5 years ±9.8), body mass index, smoking, mean systolic (124 mm Hg ±11.7 vs. 123 ±11.9) or diastolic blood pressure (73 ±9.5 vs. 71 ±9.5). Fasting low- (110 mg/dl ±31 vs. 102 ±30) and high-density (52 ±16 vs. 56 ±18) cholesterol levels differed between survivors and controls ($p<0.01$). Endothelial expression of VCAM-1 and PWV were statistically significantly increased in CCS; arterial elasticity was significantly reduced (table). Therapeutic exposures (anthracyclines and radiation) were not significantly associated with endothelial dysfunction. **Conclusions:** Childhood cancer survivors have greater endothelial dysfunction, a sign of atherosclerosis, and preventive measures should be investigated.

Vascular biomarkers and functional testing.

	Survivors		Controls		
	Mean	(95%CI)	Mean	(95%CI)	P-value*
Vascular Biomarkers					
hsCRP (mg/L)	1.5	(1.1 – 2.0)	1.3	(1.0 – 1.8)	0.36
Fibrinogen (mg/dl)	166	(147 – 184)	182	(163 – 201)	0.06
Surface VCAM-1 (%)	67	(61 – 73)	44	(38 – 51)	<0.01
Vascular Function					
LAE (ml/mm Hg x 10)	16.9	(15.8 – 18.0)	18.1	(17.0 – 19.2)	0.02
SAE (ml/mm Hg x 100)	6.9	(6.3 – 7.5)	8.5	(7.8 – 9.1)	<0.01
PWV (m/s)	7.1	(6.8 – 7.3)	6.5	(6.2 – 6.8)	<0.01

*adjusted for age, race, BMI, smoking, physical activity, education, employment

10565 Poster Session (Board #322), Sun, 8:00 AM-11:30 AM

Mental healthcare use and severe psychiatric diagnoses in adult survivors of childhood cancer: A population-based study using health services data. *First Author: Sumit Gupta, Hospital for Sick Children, Toronto, ON, Canada*

Background: Though physical late effects in childhood cancer survivors are well documented, their risk for adverse mental health outcomes is less clear; existing evidence is contradictory. Health services data offer an objective method for measuring population-based mental health outcomes. **Methods:** Using a provincial registry with detailed patient, disease, treatment, and outcome data, we assembled a cohort of all five-year survivors of childhood cancer diagnosed before age 18 years and treated in an Ontario pediatric cancer centre between 1987-2008. Patients were linked to population-based healthcare data capturing inpatient, outpatient, and emergency department (ED) visits. The primary outcome was the rate of mental healthcare visits (primary care, psychiatrist, ED or hospital). Secondary outcomes included the time to a severe mental health event (ED visit, hospitalization, or suicide) both overall and by psychiatric diagnostic categories. Outcomes were compared between survivors and matched controls using recurrent event and survival analyses, and predictors of adverse outcomes modeled. **Results:** When compared to 20,269 controls, 4,117 survivors had a significantly higher rate of mental health visits [47.1 vs. 36.1 visits/100 person years; adjusted relative rate (RR) 1.3, 95% confidence interval (CI) 1.2-1.5]. Higher rates of visits were associated with female gender (RR 1.4, CI 1.1-1.7; $p = 0.008$) and adolescent age at diagnosis (RR 2.0, CI 1.3-3.0; $p = 0.004$). Cancer type, treatment intensity or treatments targeting the central nervous system were not significant predictors. The hazard of a severe mental health event did not differ between survivors and controls. Though rare in both groups, survivors were at increased risk of a severe event due to a psychotic disorder (HR 1.8, CI 1.1-2.8; $p < 0.05$). **Conclusions:** Childhood cancer survivors experience higher rates of mental health visits than the general population, but are no more likely to experience a severe mental health event. Their risk is not attributable to a specific diagnosis or aspect of treatment. An increased risk of severe psychotic disorders requires confirmation in other cohorts.

10566 Poster Session (Board #323), Sun, 8:00 AM-11:30 AM

Human papillomavirus (HPV)-associated malignancies as subsequent malignant neoplasms (SMN) in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Tara O. Henderson, The University of Chicago, Chicago, IL*

Background: It is not known whether childhood cancer survivors (CCS) develop human papillomavirus (HPV)-associated malignancies more frequently than the general population. **Methods:** We assessed the cumulative incidence of SMN in sites typically associated with HPV (HPV-SMN) and evaluated standardized incidence ratios (SIR) and absolute excess risks (AER) using age-, sex- and calendar-year specific rates from the Surveillance, Epidemiology and End Results (SEER) program. Multivariate Cox regression models identified associations between key risk factors and HPV-SMN development. **Results:** Among 27,620 CCS, 36 developed an HPV-SMN at a median age of 27 years (range: 8-42) and a median of 15 years (range: 5-29) after their primary cancer. The 30-year cumulative incidence of an HPV-SMN was 0.20% (95% confidence interval [CI]: 0.13%-0.28%). HPV-SMN locations included oral cavity/pharynx (N = 26, 72%), rectum (N = 4, 11%), cervix/uteri (N = 3, 8%), and vulva (N = 3, 8%). The incidence of HPV-SMN was almost 3-fold higher among CCS than the general population (SIR = 2.8, 95% CI 2.0-4.1) with an AER of 6.0/100,000 person-years. Rates were elevated in those exposed (SIR = 3.3, CI 2.1-5.2) and not exposed to radiotherapy (RT; SIR = 2.6, CI 1.4-4.8). Risk of oral cavity/pharynx SMN was elevated in both those exposed (SIR = 7.3, CI 3.9-13.6) and not exposed (SIR = 4.2, CI 2.2-8.1) to head or neck RT, whereas, risk in GU locations was elevated in those exposed (SIR = 4.1, CI 1.9-9.2) but not in those not exposed to pelvic RT (SIR = 0.8, CI 0.3-2.1). Male sex (HR = 2.9, CI 1.3-6.1), exposure to head/neck/pelvic RT (HR = 2.6, CI 1.2-6.1), and platinum chemotherapy (HR = 6.1, CI: 2.6-13.9) increased the risk. Among 15 deceased HPV-SMN cases, 10 (67%) died of their HPV-SMN. **Conclusions:** While the overall incidence is low, CCS are at increased risk of developing malignancies in locations commonly associated with HPV infection in the general population. Further research examining the role of HPV in the etiology of these SMNs is warranted. As HPV-SMNs are potentially preventable, promotion of HPV vaccination efforts should be considered in this population.

10567 Poster Session (Board #324), Sun, 8:00 AM-11:30 AM

Hepatic injury after treatment for childhood cancer: A report from the St. Jude Lifetime Cohort study. *First Author: Daniel M. Green, St. Jude Children's Research Hospital, Memphis, TN*

Background: We assessed hepatic injury (HI) in a large cohort of childhood cancer survivors (CCS). **Methods:** We measured aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in 2751 SJLIFE CCS (> 10 years (yrs) post-diagnosis, age ≥18 yrs), and graded using the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. Multivariable log binomial regression was used to estimate associations between demographic and clinical factors and grades 1–4 ALT and AST. Variables with a $p < 0.1$ were examined in multivariable models. **Results:** 1339 (48.7%) CCS were female. 2271 (82.6%) were non-Hispanic white (NHW). Median age at diagnosis - 7.4 yrs, median age at evaluation - 31.4 yrs, and median time from diagnosis to evaluation - 23.2 yrs. 177 (6.4%) had grades 1-4 AST (grade 1 = 164, grade 2 = 9, grade 3 = 4), and 421 (15.3%) had grades 1-4 ALT (grade 1 = 394, grade 2 = 18, grade 3 = 8). The multivariable results are shown in the table below. **Conclusions:** Male gender, obesity, hepatitis C virus infection, and treatment with busulfan are risk factors for increased AST and ALT. V10 is an additional risk factor for increased ALT. These results may guide future treatment designs and lifestyle interventions.

	Grades 1-4 ALT		Grades 1-4 AST	
	Odds ratio (95%CI)	p-value	Odds ratio (95% CI)	p-value
Male vs female	2.93 (2.33 to 3.68)	< 0.001	2.18 (1.52 to 3.14)	< 0.001
Non-Hispanic black vs NHW	0.66 (0.46 to 0.94)	0.021	*	*
Other vs NHW	1.09 (0.67 to 1.78)	0.737	*	*
BMI ≥ 25 to < 30 vs ≥ 13 to < 25	1.98 (1.47 to 2.68)	< 0.001	1.16 (0.73 to 1.83)	0.536
BMI ≥ 30 vs ≥ 13 to < 25	3.07 (2.24 to 4.23)	< 0.001	1.58 (1.04 to 2.40)	0.033
Hepatitis C (Yes vs No)	2.70 (2.01 to 3.63)	< 0.001	7.66 (4.70 to 12.49)	< 0.001
Busulfan (Yes vs No)	2.52 (1.38 to 4.59)	0.003	4.83 (1.45 to 16.07)	0.01
V10 (per 10%)	1.09 (1.06 to 1.12)	< 0.001	1.04 (1.00 to 1.08)	0.058

* - univariable $p > 0.1$; V10 – percentage of the lung that received ≥ 10 Gy

10568 Poster Session (Board #325), Sun, 8:00 AM-11:30 AM

Impact of a formal human papilloma virus (HPV) education program in a childhood cancer survivor center. *First Author: Karen Cristly Burns, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: The HPV vaccine has proven efficacy in preventing secondary cancers. It was approved for females age 11-26 in 2006 and for males age 11-21 in 2011. Despite this, vaccination rates in the US have been poor. The Cancer Survivorship Center (CSC) at Cincinnati Children's Hospital Medical Center (CCHMC) instituted an education program in July, 2016 to improve education and vaccination rates in a childhood cancer survivor population. The following is a summary of program effectiveness. **Methods:** Providers in the CSC identified females age 11-26, and males age 11-21, presenting for annual visit from 7/1/16 thru 12/31/16. Patients received HPV education materials published by the CDC at registration. Materials were also displayed in exam and waiting rooms. During the visit, providers reviewed and documented vaccination history and discussed the importance of the HPV vaccine in preventing cancer. Patients interested in starting the vaccine series received the first vaccine in clinic and a follow-up schedule for further vaccination. Education and immunization status was documented in the electronic medical record using smart phrase trackable format. All patients were asked to sign a release to obtain vaccine records from the primary physician. A comparison group consisted of HPV eligible patients seen in the CSC during the six months prior to program initiation. Groups were compared for education completed and vaccination rate. **Results:** A total of 156 eligible patients were seen in the comparison group. None received HPV-directed education during their visit. Only 37 (23.7%) had any HPV vaccine, with 5 given during the clinic visit (13.5%). By comparison, 176 eligible patients were seen after initiation of the education program. All patients received materials at registration and 89% had documented education completed by a health care provider. Ninety one (55%) had any HPV vaccine, with 30 given during the clinic visit (33%). **Conclusions:** Through the implementation of a standardized education program in the CSC, we saw more than a 200% increase in rate of HPV vaccination. This demonstrates the importance of knowledgeable providers and the value of a dedicated HPV education program.

10569 Poster Session (Board #326), Sun, 8:00 AM-11:30 AM

Second malignant neoplasms in a nationwide population-based cohort of childhood cancer survivors in Taiwan. *First Author: Chu-Ling Yu, Taipei Cancer Center, Taipei Medical University, Taipei, Taiwan*

Background: Childhood cancer survivors have excess risk of second malignant neoplasms, but data are limited in Asian populations. We established a nationwide retrospective cohort of childhood cancer survivors in Taiwan to study the risk of second malignant neoplasms in the population. **Methods:** Children and adolescents diagnosed with cancer before age 21 years between 1990 and 2011 were identified from the Taiwan Cancer Registry, the national cancer registry in Taiwan. One-year survivors of childhood cancer were ascertained through data linkage with the national death registry. Survivors were followed up through December 2012. Standardized incidence ratios (SIRs), absolute excess risks (AERs), and cumulative incidence of second malignant neoplasms were calculated. **Results:** A total of 186 second malignant neoplasms occurred among 15,263 1-year survivors of childhood cancer after a mean follow-up time of 8.0 years (SIR = 5.4, 95% confidence interval [CI] = 4.6-6.2; AER = 12.4 per 10,000 person-years). The most common types of second malignant neoplasms were gastrointestinal cancers (n = 37), leukemia (n = 28), endocrine cancers (n = 18), and brain cancer (n = 17). Cancers in the liver (n = 11, including 9 hepatocellular carcinoma) and colorectum (n = 16) accounted for 73% of second gastrointestinal malignant neoplasms in this population. The cumulative incidence of second malignant neoplasms at 10 and 20 years from follow-up was 1.0% (95% CI = 0.8-1.2%) and 3.0% (95% CI = 2.3-3.6%), respectively. **Conclusions:** Childhood cancer survivors in Taiwan experience excess risk of second malignant neoplasms, in particular gastrointestinal cancers, compared with the general population.

10570 Poster Session (Board #327), Sun, 8:00 AM-11:30 AM

Accuracy of self-reported smoking status in adult survivors of childhood cancer: A report from St. Jude Lifetime Cohort study. *First Author: I-Chan Huang, St. Jude Children's Research Hospital, Memphis, TN*

Background: Although clinicians often evaluate smoking behavior in cancer survivors via self-report, the validity of this approach is unknown. We validated self-reported smoking status by serum cotinine data in clinically assessed adult survivors of childhood cancer and identified factors contributing to misclassification. **Methods:** The study sample consists of 287 randomly selected adult survivors of childhood cancers participating in the St. Jude Lifetime Cohort Study and undergoing a risk-based clinical assessment in a survivorship clinic. Self-reported smoking status was classified as never (N = 105), past (N = 111), and current (N = 71) smokers. Age, sex, and race/ethnicity were balanced among the three groups (p's $>$ 0.05). Blood samples were obtained and serum cotinine levels were quantified by liquid chromatography tandem mass spectrometry. Misclassification was determined by the discrepancies between self-reported smoking status and race/ethnicity-specific serum cotinine thresholds (Benowitz et al. Am J Epidemiol 2009). Multiple logistic regression model was used to identify factors related to misclassification. **Results:** Of the 287 survivors (mean age = 34 years [range = 19-61]; mean time from diagnosis = 24 years [range = 11-46]), 55.4% were male and 84.0% non-Hispanic white. Cotinine levels consistent with recent active smoking were present in 39.4% compared to 24.7% who self-reported as being a current smoker (X^2 = 14.1; p = 0.0002). Rates of misclassification were 36.9%, 8.4%, and 6.7% in survivors who reported themselves as past, current, and never smokers, respectively. Among self-reported past smokers, 18-30 years of age at survey, male, and current marijuana use increased the risk of misclassification: RR = 3.0 (95%CI = 1.2-7.6), 2.5 (95%CI = 1.1-5.4) and 3.2 (95%CI = 1.1-9.3), respectively. **Conclusions:** Within a clinical setting, reliance on self-report of smoking status by survivors results in a high misclassification rate. For research, serum cotinine levels should be utilized to assign smoking status. For clinical care and health promotion, clinicians need to be aware of the high rate of misclassification when relying upon self-reported smoking status.

10571 Poster Session (Board #328), Sun, 8:00 AM-11:30 AM

Genome-wide discovery of novel susceptibility loci for treatment-associated hypothyroidism among survivors of pediatric medulloblastoma. *First Author: Austin L Brown, Baylor College of Medicine, Houston, TX*

Background: Pediatric medulloblastoma patients exposed to craniospinal radiation (CSI) are at high risk of developing endocrinopathies, including hypothyroidism. We sought to evaluate the role of genetic variation on hypothyroidism susceptibility among survivors of pediatric medullobastoma. **Methods:** Records from 61 medulloblastoma survivors treated at Texas Children's Hospital between 1997 and 2013 were reviewed. All patients completed baseline and yearly follow-up thyroid assessments. Genome-wide genotyping was performed on Illumina HumanOmni1 and HumanOmni2.5 BeadChip single nucleotide polymorphism (SNP) arrays. Following standard quality control measures and exclusion of rare variants (minor allele frequency [MAF] $<$ 5%), 572,562 autosomal SNPs were included in our analyses. The association between each SNP and hypothyroidism was tested using Fisher's exact test and logistic regression, assuming additive allelic effects. **Results:** A total of 25 patients (41%) developed hypothyroidism with median follow-up of 8.3 years from diagnosis (range: 1.8-17.2 years). Primary hypothyroidism was identified in 9 (36%) cases, while the remaining 16 (64%) developed central hypothyroidism. Hypothyroidism was detected in 13 of 40 (33%) individuals exposed to $<$ 30 Gy CSI and 12 of 21 (57%) individuals exposed to $\geq$30 Gy CSI (p = 0.06). Genome-wide association analysis identified several risk loci, including 3 variants associated with hypothyroidism (p-value $< 1x10^{-5}$) at chromosome 2q11.2 (*NPAS2* gene). The top overall SNP (MAF = 27.5%, p-value = $6.5x10^{-7}$) remained strongly associated with hypothyroidism after accounting for possible confounders, including CSI dose, CSI type (proton/photon), age, sex, and genetic ancestry. **Conclusions:** Our findings suggest susceptibility to treatment-related hypothyroidism is strongly influenced by common genetic variation in *NPAS2*. The *NPAS2* gene, a central component of the circadian rhythm network, is a transcriptional activator and regulator of DNA damage response and DNA repair genes.

10572 Poster Session (Board #329), Sun, 8:00 AM-11:30 AM

Prevalence of attention-deficit/hyperactivity disorder in pediatric brain tumor survivors. *First Author: Emily Kauvar Shabason, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Pediatric brain tumor survivors (PBTS) often have neurodevelopmental late effects, including attention and concentration deficits, which may impact cognitive and academic functioning. Such symptoms are also seen in attention-deficit/hyperactivity disorder (ADHD), which affects ~5-8% of children and adolescents. This study examined the prevalence of ADHD diagnosis and ADHD medication use in PBTS and identified higher risk subsets of patients. **Methods:** A retrospective chart review was completed of PBTS (n = 106), diagnosed from 1999-2013, who were at least 2 years from the end of tumor-directed therapy (surgery, chemotherapy and/or radiation therapy) and without a multi-system genetic disorder or severe developmental delay prior to brain tumor diagnosis. Subjects were already screened for or enrolled in 3 other studies of PBTS late effects. Statistical analysis involved chi-squared analysis. **Results:** Among the 106 patients, 55.7% were male, with an average age at time of brain tumor diagnosis of 5.9 years (0-12.2 years). The most common tumor types were glioma (51.9% with 47.2% low grade, 4.7% high grade), medulloblastoma (13.2%) and ependymoma (11.3%), with 50% of tumors supratentorial, 46.2% infratentorial and 3.8% either extending or multifocal across the tentorium. Of the patients, 42.5% received radiation therapy, 38.7% chemotherapy and 86.8% surgery. Nineteen patients (17.9%) had ADHD diagnoses, and 20 (18.9%) had been on ADHD medications. Clinical factors associated with an ADHD diagnosis were supratentorial vs. infratentorial tumors (28.3% vs. 6.1%, p = 0.013), no radiation therapy vs. radiation therapy (27.9% vs. 4.4%, p = 0.002) and no chemotherapy vs. chemotherapy (24.6% vs. 7.3%, p = 0.024). ADHD diagnosis was not associated with age of brain tumor diagnosis or surgical treatment. **Conclusions:** Our study suggests that PBTS have over twice the ADHD prevalence as the general population, most notably in patients with supratentorial tumors or without a history of radiation therapy or chemotherapy. The results suggest that a closer look at this population is warranted and that select patients may benefit from behavioral or pharmacologic ADHD treatments to optimize functioning.

10573 Poster Session (Board #330), Sun, 8:00 AM-11:30 AM

Predictors of specialized pediatric palliative care involvement and impact on patterns of end-of-life care in children with cancer: A population-based study. *First Author: Sumit Gupta, Hospital for Sick Children, Toronto, ON, Canada*

Background: Children with cancer are at risk of receiving high-intensity (HI) care at the end-of-life (EOL) and associated high symptom burden. The impact of palliative care (PC) delivered by generalists or of specialized pediatric palliative care (SPPC) on patterns of EOL care is unknown, with previous studies limited by small sample sizes or low response rates. **Methods:** Using a provincial registry, we assembled a retrospective cohort of Ontario children with cancer who died between 2000-2012 and who received care through a pediatric institution with a SPPC team and a clinical PC database. Patients were linked to population-based healthcare data capturing inpatient, outpatient, and emergency visits. Clinical PC databases were used to identify patients receiving SPPC. Remaining patients were categorized as having received either general PC (GPC) or no PC depending on the presence of PC associated physician billing or inpatient codes. We determined predictors of SPPC involvement, and whether either SPPC or GPC was associated with HI-EOL outcomes: ICU admission $<$ 30 days from death, mechanical ventilation $<$ 14 days from death, or in hospital death. Sensitivity analyses excluded treatment-related mortality (TRM) cases. **Results:** 572 patients met inclusion criteria. Children less likely to receive SPPC services included those with hematologic cancers [odds ratio (OR) 0.33, 95th confidence interval (CI) 0.30-0.37; $p < 0.001$)], in the lowest income quintile (OR 0.44, 95CI 0.23-0.81; p = 0.009), and living at increased distance from the treatment center (OR 0.46, 95CI 0.40-0.52; $p <$ 0.0001). In multivariate analysis, SPPC was associated with a 3-fold decrease in the odds of an EOL ICU admission (OR 0.32, 95CI 0.18-0.57), while GPC had no impact. Similar associations were seen with all other HI-EOL indicators. Excluding TRM had little impact. **Conclusions:** SPPC, but not GPC, is associated with lower intensity care at EOL. Access to such care however remains uneven. In the absence of randomized trials, these results provide the strongest evidence to date supporting the creation of SPPC teams. These results can be used to support PC advocacy and policy efforts.

10574 Poster Session (Board #331), Sun, 8:00 AM-11:30 AM

Intensity of end-of life-care in children with cancer: A population-based study. *First Author: Emily E. Johnston, Stanford University Medical Center, Palo Alto, CA*

Background: There is growing evidence that adult oncology patients who know they are dying choose less intense care. Further, high intensity care is associated with worse caregiver outcomes. Little is known about pediatric oncology end-of-life care intensity. **Methods:** Using the California Office of Statewide Health Planning and Development administrative database linked to death certificates, we performed a retrospective population based analysis of cancer patients aged 0-21 who died between 2000 and 2011. The frequency of previously defined end-of-life intensity markers (hospital death, intense medical interventions, IV chemotherapy, and gastrostomy and tracheostomy tube placement) were calculated and multivariable logistic regression was used to determine clinical and sociodemographic factors associated with $>$ 2 intensity markers (as above), intense medical intervention (cardiopulmonary resuscitation, intubation, ICU admission, or hemodialysis), and hospital death. **Results:** The 3,732 pediatric cancer decedents were 34% non-Hispanic whites and 45% Hispanic; 41% had hematologic malignancies and 59% solid tumors. The most prevalent intensity markers included: hospital death (63%) and ICU admission (20%). 65% had $>$ 1 intensity marker, 23% $>$ 2, and 22% $>$ 1 intense medical intervention. There was a bimodal association between age and intensity: the youngest patients (age $<$ 5) and adolescent patients (age 15-21) were more likely to receive intense care: $<$ 5y (intense medical intervention: OR = 1.42; 95% CI, 1.1-1.9; hospital death: OR = 1.72; 95% CI, 1.4-2.2; $>$ 2 markers: OR = 1.37, 95% CI 1.1-1.8); 15-21y (intense medical: OR = 1.48; 95% CI, 1.2-1.9; hospital death: OR = 1.39; 95% CI, 1.1-1.7; $>$ 2 markers: OR = 1.35, 1.1-1.7) (references: 5-9y). Other factors associated with intensity included, hematologic malignancies, minority status, and death between 2008 and 2011 vs. $<$ 2008. **Conclusions:** Nearly two-thirds of the pediatric cancer decedents had $\geq$1 marker of intense care and disparities exist. Patients $<$ 5 and adolescents were more likely to receive intense end-of-life care. Further research needs to determine if these rates and variation are consistent with patient goals and factors associated with goal concurrent care.

10575 Poster Session (Board #332), Sun, 8:00 AM-11:30 AM

Fosaprepitant use in children and adolescents at Memorial Sloan Kettering Cancer Center. *First Author: Dazhi Liu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recent NCCN guidelines recommend the addition of a neurokinin-1(NK1) receptor antagonist (e.g. fosaprepitant) to the serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist-corticosteroid combination for controlling both acute and delayed chemotherapy induced nausea and vomiting(CINV) associated with high emetogenic chemotherapy (HEC) in adults. Fosaprepitant is bioequivalent to aprepitant and could offer benefits to patients who are unable to tolerate oral antiemetics. However, little is known about the efficacy and safety of fosaprepitant in children. **Methods:** This retrospective chart review included all pediatric patients less than 18 years of age who received fosaprepitant at Memorial Sloan Kettering Cancer Center from July 2011 to November 2016. **Results:** Thirty-one patient charts representing a total of 105 doses of fosaprepitant were reviewed. Median age was 15 (range 2-17) years. Fifty-one doses (49%) were administered for primary prophylaxis for 11 patients; 40 doses (38%) for 12 patients who had a history of severe CINV and 14 doses (13%) as rescue for CINV in 10 patients after chemotherapy. Seventy-eight of the 101 chemotherapy cycles were highly emetogenic including 39 containing cisplatin. In the first two groups, patients did not have any episodes of vomiting in 97% and 88% of chemotherapy cycles respectively after fosaprepitant therapy. Seven of 12 patients receiving fosaprepitant for $>$ 3 episodes of breakthrough vomiting within 24 hours had no vomiting episodes during the first 24 hours post fosaprepitant administration. No fosaprepitant-related side effects were reported. **Conclusions:** Fosaprepitant appears to be safe and tolerable in children with cancer in whom it may provide benefit as prophylaxis and treatment of CINV. However a phase III study is warranted to formally study its role in pediatrics.

TPS10576 Poster Session (Board #333a), Sun, 8:00 AM-11:30 AM

Phase 1 multicenter trial of CUDC-907 in children and young adults with relapsed or refractory solid tumors, CNS tumors, and lymphoma. *First Author: David Stephen Shulman, Dana-Farber Cancer Institute/Boston Children's Hospital, Boston, MA*

Background: CUDC-907 is an oral first-in-class small molecule inhibitor of histone deacetylases (HDACs) and phosphatidylinositol-3-kinases (PI3Ks), two enzyme classes commonly implicated in pediatric malignancies. Preclinical data demonstrate that inhibition of these enzymes decreases tumor growth across a range of histologies. Data from preclinical and clinical studies suggest that down-regulation of Myc or Mycn signaling may be important in the antineoplastic effects of CUDC-907. Myc or Mycn signaling appears to drive a number of pediatric cancers, heralds a poor prognosis in many of these diseases and has proven difficult to target. CUDC-907 has completed adult phase I testing in patients with hematologic malignancies. The drug was tolerable using a 5 days on/2 days off (5/2) dosing strategy, with a recommended phase II dose of 60 mg. Diarrhea, fatigue, nausea and thrombocytopenia were the most commonly reported side effects. Partial and complete responses were observed in patients with Myc-altered diffuse large B cell lymphoma. **Methods:** This study is a phase I, open-label, multicenter trial of CUDC-907 in patients 1-21 years of age with relapsed/refractory solid tumors, brain tumors and lymphomas (NCT02909777). The primary objectives are to determine the recommended phase II dose, describe toxicities, and describe pharmacokinetic parameters of CUDC-907 in this population. Other objectives include evaluation of disease response and exploration of the pharmacodynamic effects of CUDC-907. Patients receive CUDC-907 orally on a 5/2 schedule in 28-day cycles, with a pediatric mini-tab formulation available for younger children. Part A consists of a standard 3+3 design evaluating up to three dose levels. Following dose escalation, Part B consists of two expansion cohorts for patients with Mycn/Myc-driven neuroblastoma or mature B-cell lymphoma. Up to 44 patients may be enrolled across Parts A and B. Detailed pharmacokinetic testing is required in the first two cycles. Optional pharmacodynamic testing will quantify histone acetylation, Myc protein, and phospho-S6 in serial blood samples. Enrollment began in October 2016 and is ongoing. Clinical trial information: NCT02909777.

TPS10577 Poster Session (Board #333b), Sun, 8:00 AM-11:30 AM

Phase 1/2 study of the selective TRK inhibitor larotrectinib in pediatric patients with cancer. *First Author: Noah Federman, University of California, Los Angeles, Los Angeles, CA*

Background: Neurotrophin ligands and their receptors TRKA, TRKB, and TRKC (encoded by *NTRK1, NTRK2, and NTRK3)* are important for growth regulation, differentiation and survival of neurons. Translocations involving the *NTRK1/2/3* kinase domain, mutations involving the TRK ligand-binding site, and amplifications of *NTRK*, have been described in diverse tumor types and may contribute to tumorigenesis. A broad range of pediatric malignancies have been found to harbor *NTRK* fusions, including infantile fibrosarcoma (IFS), spindle-cell sarcoma, congenital mesoblastic nephroma, pediatric papillary thyroid cancer, pediatric gliomas and Ph-like acute lymphoblastic leukemia. Larotrectinib is the first small-molecule selective inhibitor of TRKA, -B, and -C in clinical development and preliminary data from the adult phase 1 trial demonstrate prolonged responses in patients with TRK fusions and a favorable safety profile. **Methods:** We have initiated an open-label, multi-center, international Phase 1/2 study with larotrectinib in pediatric patients with solid tumors and primary CNS tumors (NCT02637687). Patients with advanced cancer between the ages of 1 year and 21 years are eligible, as well as patients as young as 1-month of age with a documented *NTRK* fusion. Patients with IFS who have not had definitive surgery are also eligible. Larotrectinib is administered orally twice daily on a continuous 28-day schedule. Dosing is based on body surface area. Larotrectinib is available in an oral liquid formulation and capsules. Following identification of the maximum tolerated dose of larotrectinib in the phase 1 portion, the phase 2 portion will commence. The phase 2 portion will enroll patients with *NTRK*-translocated tumors and measurable disease into three cohorts: 1) infantile fibrosarcoma; 2) extracranial solid tumors; and 3) primary CNS tumors. The primary endpoint for the phase 2 portion is objective response rate, with duration of response and progression free survival as secondary efficacy endpoints. Each phase 2 cohort will enroll in a single stage of up to 10 patients per cohort. Molecular abnormalities will be characterized through the analysis of archival tissue. Enrollment began in December 2015 and is ongoing. Clinical trial information: NCT02637687.

TPS10578 Poster Session (Board #334a), Sun, 8:00 AM-11:30 AM

Comparative genomic analysis for pediatric cancer patients evaluated in a California Initiative to Advance Precision Medicine Demonstration Project. *First Author: Olena Morozova, University of California, Santa Cruz, Santa Cruz, CA*

Background: California Kids Cancer Comparison (CKCC), a demonstration project for the California Initiative to Advance Precision Medicine, evaluates the utility of incorporating gene expression information into the genomic analysis of difficult-to-treat pediatric cancers. CKCC is a partnership between UC Santa Cruz and clinical genomic trials conducted by Children's Hospital of Orange County, UC San Francisco (Pacific Pediatric Neuro Oncology Consortium), and Stanford University. **Methods:** CKCC compares each prospective tumor's RNA sequencing profile to over 11,000 uniformly analyzed tumor profiles from pediatric and adult cancer patients. These comparisons are used to identify genes and pathways that are significantly over expressed in each patient's tumor. The pathways are reviewed by data analysis for the potential for clinical impact and presented to the treating oncologist in a molecular tumor board setting.

TPS10579 Poster Session (Board #334b), Sun, 8:00 AM-11:30 AM

Phase 1 trial of lyso-thermosensitive liposomal doxorubicin (LTLD) and magnetic resonance guided high intensity focused ultrasound (MR-HIFU) for pediatric refractory solid tumors. *First Author: AeRang Kim, Children's National Health System, Washington, DC*

Background: Prognosis for children and young adults with refractory solid tumors remains unacceptably poor. Current approaches have reached the limits of maximal dose intensification, and the acute and late side effects of therapy are substantial. MR-HIFU is an innovative therapy that uses an external applicator to focus ultrasound energy inside a tumor non-invasively and without radiation. The resulting heating is precisely controlled and accurately targeted with the aid of MR thermometry and anatomic imaging. The flexibility and control over local heating by MR-HIFU provide an ideal system to be used with LTLD, a novel formulation of liposomal doxorubicin with the unique property of rapid heat-activated release of doxorubicin, an active agent in most pediatric solid tumors. The potential synergistic effects include enhanced permeability of the tumor vasculature, enhanced extravasation of the drug and subsequent high local concentrations of doxorubicin in the targeted tumor, inhibition of DNA repair, and stimulation of immune responses. **Methods:** This is the first pediatric trial of LTLD with MR-HIFU in refractory solid tumors (NCT02536183). Part A is a phase 1 dose escalation study to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of LTLD combined with MR-HIFU ablation in children. Part B combines LTLD at the MTD/RP2D with MR-HIFU induced mild hyperthermia (MHT) in an expanded cohort. Patients $\leq$21 (Part A) and $\leq$30 (Part B) years of age with refractory solid tumors at sites accessible to MR-HIFU, adequate organ function including cardiac function, and prior anthracycline dose of $\leq$ 450 mg/m^2 are eligible. LTLD is administered intravenously over 30 min followed immediately by MR-HIFU on day 1 of a 21-day cycle. Patients can receive a maximum of 6 cycles (or lifetime of 600 mg/m^2 of cumulative anthracycline) provided treatment is tolerated and have at least stable disease. Secondary objectives evaluate changes in quality of life and pharmacodynamic immune markers in children treated with LTLD and MR-HIFU. Clinical trial information: NCT02536183.

11000 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Phase III study of aldoxorubicin vs investigators' choice as treatment for relapsed/refractory soft tissue sarcomas. *First Author: Sant P. Chawla, Director, Sarcoma Oncology Center, Santa Monica, CA*

Background: Aldoxorubicin (A) is a novel drug that binds covalently to albumin in the circulation, accumulates in tumors and releases doxorubicin in the acidic tumor environment. It has demonstrated enhanced antitumor activity in several murine models and in a phase IIb STS study when compared with doxorubicin. *Trial Design*: Phase III open-label study evaluating efficacy and safety of A compared to investigators' choice (IC) of treatment in subjects with soft tissue sarcomas (STS) who have relapsed or were refractory to prior chemotherapy. *Objectives*: (1) Primary: Efficacy of A vs IC: progression-free survival (PFS); (2) Secondary: Efficacy of A vs IC: tumor response (ORR), disease control rate (DCR; CR+PR+SD > 4 months), overall survival (OS) and safety. **Methods:** A: 350 mg/m^2 (260 mg/m^{2}dox. equiv.) iv q3 wks. IC drugs: dacarbazine, doxorubicin, pazopanib, ifosfamide, gemcitabine/docetaxel administered per package insert or study site's standard practice; provided, with G-CSF, by the sponsor. AEs, serum chemistries, CBCs, EKG and ECHOs obtained frequently. CT scans every 6 weeks for 30 weeks, then every 12 weeks; analyzed using RECIST 1.1 by Blinded Independent Central Review. **Results:** Randomized 433 subjects; 79 countries; 313 (72%) in North America (NA) and 121 (28%) in Rest of World (ROW). Leiomyosarcoma 42.5%, liposarcoma 15%, synovial sarcoma 9%, others 33.5%, L-sarcomas (lipo+leiomyo) 57.5%. Median PFS Total Pop. (months): A= 4.06; IC= 2.96; p = 0.12; HR = 0.82 (0.64-1.06). Median PFS NA (months): A= 4.21; IC= 2.96; p = 0.027; HR = 0.71 (0.53-0.97). Median PFS L-sarcomas (months): A= 5.32; IC= 2.96; p = 0.007; HR = 0.62 (0.44-0.88). DCR Total Pop.(%): A= 30.3; IC= 20.9; p = 0.028; DCR NA (%): A= 32.9; IC= 19.2; p = 0.007; DCR L-Sarcomas (%): A= 37.5; IC= 23.0; p = 0.018. ORR and OS will be reported. TEAEs gr 3 or 4 (%): A= 61.0; IC= 46.4. Trtmt Rel. SAEs (%): A= 27.0; IC= 14.0. TEAEs leading to Drug Discontinue (%): A= 4.2; IC= 6.3. Trtmt Related Deaths (#); A= 3; IC= 0; LVEF < 50% expected (%): A= 2.8%; Dox = 12.8%. **Conclusions:** Aldox is an active, well-tolerated drug for treating relapsed or refractory STS and is significantly better than standard treatments for patients with L-sarcomas. Clinical trial information: NCT02049905.

11001 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Impact of next-generation sequencing (NGS) on diagnostic and therapeutic options in soft-tissue and bone sarcoma. *First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: The utility of NGS in management of sarcoma pts remains undefined. **Methods:** We retrospectively analyzed the NGS profile of patients who were sequenced using a panel of 405 cancer-related genes in DNA and 265 genes rearranged in RNA. Diagnostic and therapeutic implications of mutations (mut) were evaluated through published literature (OncoKb.org, Pubmed). An algorithm was applied to determine germline mut. Following IRB approval, we evaluated the clinical outcomes of pts who underwent NGS at MSKCC. **Results:** From 2012–2016, 5635 pts worldwide with 56 histologies were tested. Median age of 52 yrs (< 1-88), 52% females and sarcoma NOS (n = 858) was most frequent. Tumors were sequenced to a mean coverage of 634X; 1165 fusions and > 60,000 mut were found. Mut suspicious for germline defects were seen in 542 pts (9.6%) in known and novel genes (*BRCA*, *ARID1*, *FANC*). Tumor mutational burden was 2.5/Mb (0–329) and glomus tumors and EHE had the highest and lowest mut, respectively. 16% and 7% of pts had treatment-linked alterations (TLA) known to respond to an FDA approved or study drug, respectively. 42% of pts had TLA eligible for NCI-MATCH, ASCO-TAPUR or other studies. Novel TLA include *AKT*, *ESR1*, *BRCA*, *NTRK*, *PTCH1, SMARCB1 and others.* Of the 107 MSKCC pts with clinical data, 60/107 (57%) had at least one TLA, of which 31 (30%) enrolled on a matched trial and 26 pts were ineligible or lacked access to trials. Partial/complete responses were seen with inhibitors to NTRK, IDH1, BRAF, PI3K/mTOR, MDM2, SMARCB1 and others. NGS changed the initial pathology diagnosis and treatments in 5% pts (e.g. LMS to liposarcoma, clear cell to melanoma). Resistance mutations averted futile therapies in 5% pts (e.g. Rb loss and palbociclib in liposarcoma). **Conclusions:** Our data suggests that NGS has a significant impact in aiding diagnosis and selecting matched therapies in sarcoma. Suspected germline aberrations, while intriguing, needs further validation.

11002 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Genetic landscape of soft-tissue sarcomas: Moving toward personalized medicine. *First Author: Antoine Italiano, Institut Bergonié, Bordeaux, France*

Background: Patients with advanced soft-tissue sarcomas have a very poor outcome with a median overall survival of less than 18 months. Identification of molecular abnormalities for which targeted therapies are available or can be developed is critical for improving their outcomes. **Methods:** We have analyzed the mutational and copy number profiles of patients with sarcoma sequenced through the AACR Project GENIE Consortium in order to identify the proportion of cases bearing actionable mutation. **Results:** 587 patients (pts) were included in the study (295 males). 331 pts (56%) had complex genomics sarcomas, 144 (25%) translocation-related sarcomas and 112 (19%) others sarcomas (inactivating mutation, simple amplicon). The five most frequent histology were: Leiomyosarcoma (n = 112; 19.1%); Undifferentiated Pleomorphic Sarcomas (n = 74, 12.6%), dedifferentiated liposarcoma (n = 55, 9.4 %), angiosarcoma (n = 43, 7.3%), synovial sarcoma (n = 38, 6.5%). 430 pts (73%) had at least one mutation. The ten most frequently mutated genes were: *TP53* (34.7%); *ATRX* (9.1%), *RB1* (8.4%), *KMT2D* (5.8%), *NF1* (5.3%), *ATM* (5.1%), *PI3KCA* (4.9%), *ERBB4* (4.2%), *PTEN* (4%), and *ARID1A* (3.7%). 504 patients (85.9%) presented at least one copy number alteration. The 5 five most frequently amplified genes were: *MDM2* (20%), *CDK4* (16.7%), *GLI1*, *MAP2KA*, and *TERT* (3.2% for each gene), and the most frequently deleted were *RB1* (12.7%), *CDKN2A* (10.3%), *CDKN2B* (9.7%), *TP53*(9.5%), *PTEN* (8.5). 92.5% of pts had at least one targetable mutation, copy number alteration and/or fusion gene (Leiomyosarcoma n = 100/17%, UPS n = 74/12%, dedifferentiated diposarcoma n = 54/9%, angiosarcoma n = 41/7%, synovial Sarcoma n = 36/6%), with incidences reported that will be reported in details at the meeting. **Conclusions:** This is the first large report of genomic landscape including mutation and copy number profiling through NGS of soft-tissue sarcomas. Our results indicate a significant proportion of actionable mutations and represent a rationale for the MULTISARC study: the first study implementing Exome Seq and RNA Seq for clinical decision making in patients with advanced STS. The design of this study supported by the French government and launched in 09/2017 will be presented at the meeting.

11003 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Multi-institutional European single-arm phase II trial of pazopanib in advanced malignant/dedifferentiated solitary fibrous tumors (SFT): A collaborative Spanish (GEIS), Italian (ISG), and French (FSG) sarcoma groups study. *First Author: Javier Martin Broto, Virgen del Rocio University Hospital, Institute of Biomedicine Research (IBIS), Seville, Spain*

Background: SFT is a rare soft tissue tumor. In advanced SFT chemotherapy has only limited activity. With the rationale of a rich vascular network & VEGF (tumor cells and endothelium) and VEGFR1/2 (endothelial cells) expression in SFT, we designed an international, single-arm phase II trial to test pazopanib (P) in advanced SFT. Clinical and preclinical evidence suggesting that anti-angiogenics was less effective in more aggressive compared with less aggressive SFT (Stacchiotti et al), led us to conduct the trial on two different cohorts: typical and malignant (M)/dedifferentiated (DD) SFT. Here we present the outcome of the latter cohort. **Methods:** Most relevant inclusion criteria were: unresectable or metastatic, M/DD SFT confirmed by central pathologic review with evidence of STAT6 (IHC and /or FISH or RT-PCR), ≥ 18 years, ECOG 0-2, progressive and measurable disease. Main endpoint was response rate (RR) according Choi criteria. Central radiological assessment was mandatory. P was administered at 800 mg/d continuously until progression or toxicity. **Results:** From June 2014 to November 2016, 34 patients (pts) were enrolled with a median age of 61 y (23-87). Median tumor size and mitosis at diagnosis were 77 mm and 8x10 HPF. Most relevant grade 3-4 toxicity were neutropenia (9%) and hypertension (12%). At the time of the present analysis, 31 pts are evaluable for response. RR according to Choi and RECIST were: PR 16 (52%), SD 7 (22%), PD 8 (26%) and PR 1 (3%), SD 19 (61%), PD 11 (35%) respectively. With a median follow-up of 15 months, the median PFS was 5.53 months (4.24-6.82), while 72% survived at 18 months. Size > 5 cm, mitosis > 8 and DD subtype showed significantly worse PFS. The 18-month OS was 90% for those with SD and PR and 25% for PD according to Choi ($p < 0.001$), while 94% for SD and PR and 45% for PD according RECIST ($p = 0.002$). In multivariate analysis, only Choi was an independent prognostic factor for OS with PD showing a HR of 11.9 (2.3-63.1), $p = 0.003$ for the risk of death. **Conclusions:** Pazopanib showed activity in malignant SFT. Choi criteria exhibited a more accurate assessment of response than RECIST. Clinical trial information: NCT02066285.

11004 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Activity of cediranib in alveolar soft part sarcoma (ASPS) confirmed by CASPS (cediranib in ASPS), an international, randomised phase II trial (C2130/A12118). *First Author: Ian Robert Judson, Cancer Research UK Centre for Cancer Therapeutics, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: ASPS is a rare disease (0.5-1% of soft tissue sarcomas) mainly affecting young people. It is unresponsive to conventional chemotherapy. Cediranib (C), an inhibitor of vascular endothelial growth factor receptors and other receptor tyrosine kinases, has shown significant activity in ASPS in single arm phase II trials. CASPS (NCT01337401) was designed to permit discrimination between the impact of cediranib and the often intrinsically indolent nature of the disease. **Methods:** CASPS compared C (30mg od) with placebo (P) in a 2:1 double blind randomisation in patients (pts) age ≥16 years with metastatic ASPS progressive in the previous 6 months. Pts were unblinded at week 24, or at progression if sooner, when those on P started C. The primary endpoint of percentage change in the sum of target marker lesions (TML_{sum}) between baseline and week 24 (or progression if sooner) was compared between groups by Mann-Whitney test. Secondary endpoints were progression-free survival (PFS), week 24 response rate and best response (RECIST v1.1), safety/tolerability and overall survival (OS). One-sided p-values and two-sided 90% confidence intervals are reported. **Results:** 48 pts were recruited between 07/2011 and 07/2016 from 12 centres (UK, Australia & Spain). 52% of pts were female, median age was 31. Most common grade ≥3 adverse events on C were hypertension (23%), diarrhoea (14%) and fatigue (9%). In the evaluable population (N = 44) median change in TML_{sum} on C was minus 8.3% (IQR minus 26.2% to +5.9%); versus P: +13.4% (IQR minus 0.6% to +21.3%), p = 0.0013. Best response by week 24 was partial response for 6/28 (21%) C pts compared with 0/16 on P (p = 0.053) and stable disease for an additional 19/28 (68%) on C and 12/16 (75%) on P. The PFS HR (C versus P) was 0.54 (90% CI 0.30-0.97, p = 0.041), median PFS: 10.8 mths on C versus 3.7 mths on P, OS at 12 mths was C: 96%; P: 64.3%. **Conclusions:** CASPS, the largest randomised trial to date in this disease, confirms the activity of C in ASPS, showing a significant reduction in tumour burden and improvement in PFS. Tumour tissue and serial blood samples will subsequently be investigated to identify potential predictive and prognostic biomarkers. Clinical trial information: NCT01337401.

11005 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

A phase II trial of regorafenib (REGO) in patients (pts) with advanced Ewing sarcoma and related tumors (EWS) of soft tissue and bone: SARC024 trial results. *First Author: Steven Attia, Mayo Clinic, Jacksonville, FL*

Background: Pazopanib is approved for soft tissue sarcoma pts after failure of other therapy, but there are few subtype-specific data regarding kinase inhibitor activity. We report on a single arm, phase II trial of REGO in advanced EWS. **Methods:** EWS pts (age > 18, ECOG 0-2, good organ function) who had at least 1 line of therapy and had PD within 6 mo were eligible. Prior oral kinase inhibitors were not allowed. Initial REGO dose was 160 mg PO QD x21 q28d. Dose reductions were employed for toxicity and AEs. The primary endpoint was PFS at 8 weeks (PFS8w) employing RECIST 1.1. Sample size of 30 allowed determination of the difference between PFS8w of 50% vs 25% with alpha = 0.05 and power of 91%. **Results:** 30 pts (median age 32, range 19-65; M/F = 20/10; ECOG 0/1/2 = 16/13/1; bone, 12; soft tissue, 18; median prior treatments 5, range 1-10) enrolled at 14 US sites (09/2014-03/2016). Most common grade (G3) toxicities were hypophosphatemia (6), hypertension (2), high ALT (2) and 1 each: fatigue, abd pain, diarrhea, hypokalemia, oral mucositis, neutropenia and rash; no G4 toxicities were noted. 13 pts required ≥1 dose reduction, most commonly hypophosphatemia (n = 7); 2 stopped REGO for toxicity. There was 1 death in the 30 day post study period, not REGO related. Median dose at study end: 140 mg (3.5 tabs, range 80-160 mg) 3 wks on/1wk off. 18/30 pts were without PD at 8 wks. Median PFS: 3.6 mo (95%CI 2.8-3.8 mo). PFS8w by KM was 73% (95%CI 57-89%). Best responses: PR/SD/PD/not evaluable of 3/18/7/2, for RECIST RR 10%. Two pts with PR had *EWSR1* translocation by FISH; a third had *CIC-DUX4*. Median duration of response: 5.5 mo (95%CI 2.9-8.0). Median OS is not reached. **Conclusions:** The substudy met its primary endpoint. REGO toxicity was similar to that seen previously. Enrollment continues in LPS and OGS cohorts, and is being expanded to further study variant EWS without *EWSR1-FLI1* fusion. Study of the existing tissue may elucidate which EWS patients may benefit from REGO. Clinical trial information: NCT02048371.

11006 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Immune response, safety, and survival impact from CMB305 in NY-ESO-1+ recurrent soft tissue sarcomas (STS). *First Author: Neeta Somaiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: CMB305 is an active immunotherapy regimen designed to generate and expand anti-NY-ESO-1 T cells. It consists of LV305, a dendritic cell targeting lentiviral vector encoding NY-ESO-1, and a boost with G305, an NY-ESO-1 recombinant protein plus GLA-SE, a TLR-4 agonist. An LV305 phase 1 study demonstrated a 1-yr survival of 81% and induction of anti-NY-ESO-1 T cells in sarcoma patients (pts). This first-in-human study of CMB305 examined safety, immunogenicity, and efficacy in pts with NY-ESO-1 positive (+) solid tumors. **Methods:** Adults with previously treated NY-ESO-1^+ sarcomas, NSCLC, ovarian cancer were enrolled in a 3+3 dose-escalation with an expansion phase 1 study. The CMB305 regimen included 4 intradermal injections of LV305 at 10^9 or 10^{10} vector genomes, alternating with 3 intramuscular G305 injections at 250 μg for 3 months, then bimonthly G305 injections up to 1 yr. **Results:** As of 31Dec2016, 25 pts with STS (15 synovial (SS), 8 myxoid/round cell liposarcoma (MRCL), 2 other) were evaluable for safety; 23 SS/MRCL pts were evaluable for immune response (IR) and efficacy. All SS and MRCL pts received prior therapy for locally advanced/metastatic disease, 67% > = 2 prior chemo regimens. No DLTs were observed; treatment related AEs were grade 1 and 2, except 1 pt with grade 3 SAE (prostatic pain). Of 11 SS/MRCL pts tested, 64% pts developed NY-ESO-1 specific T cells and 72% pts anti-NY-ESO-1 antibodies. T cell receptor sequencing indicated increased clonality, and antigen spreading after CMB305. Best response by immune related response criteria was stable disease in 8/15 (53%) SS pts and 6/8 (75%) MRCL pts. The 3 month PFS rate was 74% and 75% for SS and MRCL pts. Median survival has not been reached with 1-yr survival rate of 86% and 100% for SS and MRCL pts. **Conclusions:** CMB305 is safe, well tolerated, and demonstrates a survival rate that is favorable when compared with approved agents for recurrent STS. CMB305 resulted in a stronger and broader integrated IR than LV305, including antigen spreading. These data warrant further investigation of CMB305 as a monotherapy in a randomized clinical study in STS. A randomized study of CMB305 in combination with atezolizumab in SS/MRCL pts is ongoing. Clinical trial information: NCT02387125.

11007 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

A multi-center phase II study of nivolumab +/- ipilimumab for patients with metastatic sarcoma (Alliance A091401). *First Author: Sandra P. D'Angelo, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients (pts) with metastatic sarcoma (SAR) have limited options. Nivolumab(N), a fully human anti-PD-1 mAb and ipilimumab (I), a humanized anti-CTLA-4 mAb, have favorable safety & efficacy in other tumors. Pembrolizumab demonstrated a response rate (RR) of 12% in SAR pts. We evaluated N, independently from N+I, in SAR pts. **Methods:** This open-label multi-center phase II study enrolled pts failing prior regimens. Randomized (non-comparative) pts received either N3 [N (3 mg/kg q2W)] or N3+I1 [N(3 mg/kg Q3W x4, then Q2W) & [I(1 mg/kg q3W x4)]. Treatment continued beyond progressive disease (PD) in 1^{st}12 weeks. 5 confirmed responses in 38 evaluable pts yielded 90% power (0.05 1-sided alpha) to detect a 20% (vs 5%) confirmed RR. Other endpoints: adverse events (AEs), progression-free, overall survival (PFS, OS), and correlative studies including PD-L1 expression by IHC, mutational burden/neoantigen analysis, TCR clonality and TIL characterization. **Results:** 85 pts (43 - N3; 42 - N3+I1) were enrolled [mean age 54 yrs (21–81), 52% female). No significant differences in histological subtypes across cohorts: 36% LMS, 4% LPS, 10% UPS/MFH, 6% synovial, 5% bone, 5% Ewing's, and 34% other. Pts were refractory to 1(20%), 2(22%), and ≥3 (58%) regimens. Grade 3-4 treatment related adverse events (TRAE) occurred in 7% (N3) and 14% (N3+I1) and 0 Gr 5 TRAEs. 8% of pts stopped due to AEs (2% N3, 14% N3+I1). 2/3 confirmed responses on N3, with 2 ongoing (range 1.1-3.2 months). 6/7 confirmed responses (2 complete) on N3+N1, with 5 ongoing (range 6-13 months). Responses occurred in 7 histologies. See Table for pt outcomes. **Conclusions:** N + I showed acceptable safety and encouraging antitumor activity with most responses ongoing across multiple SAR histologies, passing efficacy criteria. There was minimal activity observed with N alone. Increased TRAEs were observed in N3+I1. Correlative analyses ongoing. NCT02500797. Support: U10CA180821, U10CA180882, Conquer Cancer Foundation, BMS. Clinical trial information: NCT02500797.

	N3 (n = 38)	N3+I1 (n = 38)
Confirmed RR, n (%, 90% CI)	2 (5%, 1-16%)	6 (16%, 7-29%)
PFS[a]	2.6 (2.1-4.3)	4.5 (3.9-6.3)
OS[a]	8.7 (5.5-NE)	11.2 (9.9-NE)
6 Month PFS Rate	16% (7.5-34.7%)	36% (23.6-55.5%)

[a] In months. Median (95% CI)

11008 Oral Abstract Session, Fri, 3:00 PM-6:00 PM

Multicenter phase II study of pembrolizumab (P) in advanced soft tissue (STS) and bone sarcomas (BS): Final results of SARC028 and biomarker analyses. *First Author: Melissa Amber Burgess, University of Pittsburgh Physicians, Pittsburgh, PA*

Background: SARC028 is the first multicenter Phase II study of P monotherapy in patients (pts) with STS and BS. Designed to detect clinical efficacy signals in multiple histologies, the study collected blood & tissue samples on all pts. We report extended clinical follow-up and in-depth biomarker correlates of response. **Methods:** The primary endpoint was objective response rate (ORR) by RECIST 1.1. Secondary endpoints were safety, 12 wk progression-free survival (PFS), and overall survival (OS). The STS arm had 10 pts in each of 4 cohorts: undifferentiated pleomorphic sarcoma (UPS), dedifferentiated liposarcoma (DDLPS), synovial sarcoma (SS) and leiomyosarcoma (LMS). The BS arm included 40 pts with osteosarcoma (OS), Ewing sarcoma (ES) or dedifferentiated chondrosarcoma (CS). Pre- and on-P biopsies were required as well as blood at multiple time points. Tumor was assessed for PD-L1 expression (clone 22C3) and immune infiltrates by multi-color IHC (Vectra). Ongoing analyses include circulating cytokine and checkpoint levels and exome (DNA), transcriptome (RNA), and T-cell receptor (TCR) sequencing. **Results:** 86 pts were enrolled, 80 were evaluable for response. For STS, median follow-up was 14.5 months. The ORR in the overall STS cohort was 18% and the 12-wk PFS 55% [95% CI, 42-71]). Clinical activity was variable by histologic subtype with 40% ORR in UPS (1 CR and 3PR out of 10 evaluable pts), 2 PR/10 were seen in DDLPS, 1PR/10 in SS and 0/10 in LMS. For BS, median follow-up was 12.3 months (ORR 5%; 12-wk PFS 28% [95% CI, 14-41]), with 1PR/22 OS, 1PR/5 CS and 0/13 ES. 70 pre-P tissues were analyzed (11 excluded for insufficiency), with PD-L1+ in 3/70 (4%); all 3 were UPS. Of the 2 evaluable pts, 1 had CR and 1 PR. 2 OS were PD-L1+ on multi-color IHC, 1 had PR. All PD-L1+ samples had CD8+ T-cell infiltration. There were no post-P PD-L1+ samples. **Conclusions:** P has clinical activity in UPS and LPS, and expansion cohorts in those subtypes are planned. Pre-treatment PD-L1 expression was infrequent, but correlated with T-cell infiltration and response in UPS & OS. Ongoing biomarker analyses that may guide combination strategies are ongoing and will be presented at the meeting. Clinical trial information: NCT02301039.

11009 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

Extended treatment with adjuvant imatinib (IM) for patients (pts) with high-risk primary gastrointestinal stromal tumor (GIST): The PERSIST-5 study. *First Author: Chandrajit P. Raut, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

Background: Adjuvant IM reduces risk of recurrence and improves survival in pts with high-risk primary GIST. Joensuu et al 2016 demonstrated higher 5-yr overall survival (OS) rates of 91.9% vs 85.3% in pts treated with adjuvant IM for 3 vs 1 yr, respectively. It is unknown if further extension of treatment duration can improve outcome. **Methods:** PERSIST-5 is a single-arm, phase II trial that enrolled pts ≥18 yrs of age, who underwent macroscopically complete resection of primary KIT (+) GIST with high risk of recurrence within 12 wks prior to IM treatment. High risk was defined as primary GIST (any site) ≥2 cm with a mitotic count ≥ 5/50 HPF or non-gastric primary GIST ≥5 cm. Pts were treated with IM 400 mg/d for 5 yrs or until progression, relapse, or intolerance. Primary endpoint was recurrence-free survival (RFS, defined as time of treatment start to first recurrence or death). **Results:** IM was administered to 91 pts with a median age of 60 yrs (range 30-90). Median tumor size was 6.5 cm (range 2.3-30 cm; 55% gastric origin). Median treatment duration was 55.7 mos (range, 0.5-75). Forty-six (50.5%) pts completed study treatment. The 5- and 8-yr estimated RFS rates were 90% (95% CI, 80-95) and 81% (95% CI, 62-91), respectively. The 5- and 8 year OS rate was 95% (95% CI, 86-99). There were 7 recurrences; 1 pt recurred and died while on IM (*PDGFRA* D842V mutation) and 6 pts recurred after IM discontinuation. Two pts died after IM discontinuation, unrelated to study treatment and without recurrence. Forty-five pts discontinued study treatment; common reasons included patient choice (20%), adverse events (AEs, 17%), protocol deviation (4%), and loss of follow-up (4%). The most common AEs of all grades (regardless of relationship to IM) were nausea (71%), diarrhea (63%), fatigue (50%), muscle spasm (41%), vomiting (39%), and periorbital edema (34%). **Conclusions:** Five yrs of IM treatment was effective in preventing recurrence in pts with sensitive mutations who underwent resection of primary GIST. Nearly half of the patients discontinued treatment early, and most recurrences occurred after IM discontinuation. Clinical trial information: NCT00867113.

11010 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

The clinical impact of performing routine next generation sequencing (NGS) in gastrointestinal stromal tumors (GIST). *First Author: Ciara Marie Kelly, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The majority of GISTs harbor activating mutations in KIT or PDGFRα but the clinical relevance of other genomic alterations is unknown. We sought to determine the clinical impact of performing routine NGS and to describe the molecular landscape in GIST. **Methods:** From April 2014 to August 2016, 177 patients (pts) consented to an IRB-approved protocol. Tumor and matched normal samples were prospectively analyzed in a CLIA-compliant laboratory, with MSK-IMPACT, a NGS assay of up to 468 cancer-associated genes. **Results:** 191 samples were analyzed. NGS was most often performed in the setting of advanced disease (n = 108 (57%)). The primary tumor was most commonly tested (n = 120 (63%)). NGS guided clinical management in 79% (n = 150) of cases [matched therapy (MT) offered, n = 120/150 (80%); MT not offered, n = 24/150 (16%)]. In 25/41 cases (61%) where NGS did not influence management, treatment was not indicated because the GISTs were low risk. Most samples had ≤ 3 mutations (muts) (range: 0-17). Actionable muts were identified in 155/191 samples (81%). These included muts in KIT, PDGFRα and BRAF [oncoKB stratification: level 1 (84%), 2A (13%), 2B (2%), 3A(1%)]. 33/177 pts did not have a KIT/PDGFRα mut [SDH deficiency, n = 15 (45%), NF1, n = 10 (30%), BRAF, n = 1(3%), NF1&BRAF, n = 1 (3%)]. 5pts had quadruple wild type GIST. Most GISTs had at least one genetic alteration in a non-driver allele (74%, n = 141/191)[frequently mutated genes in KIT exon 11 driven i) primary tumors include TP53, MAX, MLL2, SETD2, PIK3CA, TSC1; and ii) metastatic tumors include RB1, SETD2, PTEN, ANKRD11, TP53, TSC1]. CDKN2A deletion was the most common copy number alteration identified in KIT driven GIST and occurred most often in metastatic samples (with and without co-occurring, secondary KIT muts) and those with high mitotic rate. **Conclusions:** NGS of GIST informs clinical management in the majority of pts through the identification of muts in canonical driver genes. NGS also identifies a high prevalence of tumor-specific genetic alterations in non-canonical driver genes. These genes function in multiple pathways including intracellular signaling, chromatin remodeling, proteasomal degradation and cell cycle regulation.

11011 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

Clinical activity of BLU-285 in advanced gastrointestinal stromal tumor (GIST). *First Author: Michael C. Heinrich, Knight Cancer Institute, Oregon Health & Science University, Portland, OR*

Background: Oncogenic mutations in KIT or PDGFRα drive > 85% of GIST. However, primary and acquired mutations in the activation loop of PDGFRα and KIT are not effectively treated by approved therapies. A phase 1 study (NCT02508532) was initiated in advanced GIST to assess the safety, PK and clinical activity of BLU-285, a potent, highly-selective oral inhibitor that targets KIT Exon 17 and PDGFRα D842 activation loop mutants. **Methods:** Adult patients (pts) with unresectable GIST, who had received ≥2 kinase inhibitors including imatinib or who had a primary PDGFRα D842 mutation regardless of prior therapy, were given BLU-285 once daily on a 4-week cycle following a 3+3 escalation design, which allowed additional accrual to dose levels demonstrated to be safe. Adverse events (AEs) per CTCAE v4.03, PK and plasma/tumor mutant DNA levels were assessed. Response was determined by RECIST 1.1 every 8 weeks. **Results:** At a 01JAN17 cutoff, 40 pts (21 PDGFRa/19 KIT) have been treated with BLU-285 at doses of 30-600 mg. Median number of prior kinase inhibitor regimens was 4.5 (2-12) KIT/2.5 (0-4) PDGFRα. RECIST 1.1 responses were seen across all dose levels for PDGFRα GIST and at higher dose levels for KIT GIST. Of 17 PDGFRα D842V pts with ≥1 radiographic assessment, 7 had confirmed PR (ORR 41%) and 10 had SD. Of 11 evaluable KIT pts treated at doses ≥ 135 mg, 2 had PR (1 confirmed; ORR 18%) and 5 SD. BLU-285 is rapidly absorbed (T_{max} 2-8 h), exposure increases linearly with dose, and half-life is > 24 h supporting QD dosing. Most AEs were grade 1 or 2, most commonly nausea (48%), fatigue (45%), peripheral edema, periorbital edema, vomiting (30% each), diarrhea (25%), anemia, dizziness, and lacrimation (23% each). There were no grade 4 or 5 BLU-285-related AEs, dose limiting toxicities, or discontinuations. 29 pts (all 21 PDGFRα pts) remain on treatment (duration 1-14 mo). Updated results including MTD, ct-DNA and central radiographic assessments will be presented. **Conclusions:** Precision targeted therapy with BLU-285 demonstrates important clinical activity in pts with both PDGFRα- and KIT-mutant GIST that is resistant to available therapies. Clinical trial information: NCT02508532.

11012 Poster Discussion Session; Displayed in Poster Session (Board #335), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Pathologic complete response and survival outcomes in patients with localized soft tissue sarcoma treated with neoadjuvant chemoradiotherapy or radiotherapy: Long-term update of NRG Oncology RTOG 9514 and 0630. *First Author: Dian Wang, Rush University Medical Center, Chicago, IL*

Background: We sought to determine the prognostic significance of pathologic complete response (pCR) in soft tissue sarcoma (STS) in patients (pts) receiving neoadjuvant chemoradiotherapy (RTOG 9514) or radiotherapy (RTOG 0630) with long-term outcomes. **Methods:** RTOG has completed two phase II trials (RTOG 9514 and RTOG 0630) for pts with localized STS. Pts with high-grade STS ≥8 cm of extremities or body wall were enrolled to 9514 from 1997-2000 and received 3 cycles neoadjuvant chemotherapy (CT), interdigitated with RT, and 3 cycles postop CT. Pts with STS of extremities were enrolled to 0630 from 2008-2010 and received preoperative RT without CT. One pathology expert (DL) assessed pts for pCR at time of surgery without knowledge of disease outcomes. Overall and disease-free survival (OS and DFS) were calculated from the date of surgery. Pts that did not have surgery or had an amputation were excluded. Hazard ratios (HR) and p-values were estimated by multivariate Cox model stratified by study, where possible (i.e., > 0 events in both groups); otherwise p-values were calculated by stratified log-rank test. **Results:** Of 135 who had surgery, 123 were evaluable for pCR: 14/51 (27.5%) on 9514 and 14/72 (19.4%) on 0630 had pCR. With median follow-up of > 5 years for surviving pts, OS is 100% for pts with pCR vs. 5-year 76.5% (95% confidence interval 62.3-90.8) and 56.4% (43.3-69.5) for pts with < pCR in 9514 and 0630, respectively. pCR is associated with improved OS (p = 0.01) and DFS [HR 4.91 (1.51-15.93); p = 0.008] relative to < pCR. Local failure rate was 0% in pts with pCR vs. 5-year 11.7% (3.6-25.1) and 9.1% (3.3-18.5) for pts with < pCR in 9514 and 0630, respectively. Leiomyosarcoma/liposarcoma/myxofibrosarcoma are associated with better OS [hazard ratio 2.24 (1.12 and 4.45)] while liposarcoma/myxofibrosarcoma are associated with better DFS [hazard ratio 2.42 (1.23-4.76)]. **Conclusions:** Results from this analysis have demonstrated that pCR is associated with improved survival outcomes in pts with STS treated with either neoadjuvant RT or CT-RT. pCR should be considered as a survival surrogate for future STS studies. Clinical trial information: RTOG 9514 and RTOG 0630.

ABSTRACT RETRACTED

11014 Poster Discussion Session; Displayed in Poster Session (Board #337), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Clinical, radiological and genetic features, associated with the histopathologic response to neoadjuvant chemotherapy (NAC) and outcomes in locally advanced soft tissue sarcoma (STS) patients (pts). *First Author: Sophie Cousin, Institut Bergonié, Bordeaux, France*

Background: Two large phase III studies have shown an improved overall survival in soft-tissue sarcoma (STS) pts treated with neoadjuvant chemotherapy. The prognostic impact of pathologic response is not known neither the clinical, radiological and genetic features associated with response. **Methods:** Data from pts with localized STS of the extremities or trunk wall and treated with anthracyline-based NAC at Institut Bergonie (Bordeaux, France) were reviewed. Central pathology (diagnosis, histological response) and radiology (MRI, DCE-MRI) reviews were performed for all the cases. A good histological response (GR) was defined as <10% residual viable tumor. Exome and RNA sequencing of pre-treatment tumor samples was performed in order to identify genetic aberrations predictive of response. **Results:** 150 patients (88 male) were included in the study. Median age was 60 years (17-84). 40 pts (26.7%) were good responders. GR was associated with undifferentiated pleomorphic sarcomas and very large tumors (> 20 cm). Median OSwas 10.3 year [IC95 : 5.8 ; 14.9]. On multivariate analysis, only GR (HR= 0.36, 95%CI 0.184-0.703, p=0.0028) and performance status (PS) (HR= 3.799, 95%CI 1.72-8.387, p=0.001 for PS=2-3) were prognostic factors for OS. Early *DCE-MRI* parameters (after 2 cycles of treatment) such as, area under the contrast concentration vs. time curve for 90 seconds after contrast injection (*IAUC90*) were strongly associated with histological response (p=0.027) whereas RECIST 1.1 was not. **Conclusions:** As for bone sarcomas, histological response to NAC is a crucial prognostic factor in STS. Multiparametric MRI parameters obtained post-2nd cycle of NAC are predictive of histological response and should be considered to adjust the therapeutic strategy. Genetic features (including the CINSARC signature) associated with response to NAC will be presented at the meeting.

11016 Poster Discussion Session; Displayed in Poster Session (Board #339), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

The sarculator stratified prognosis of patients with high-risk soft tissue sarcomas (STS) of extremities and trunk wall treated with perioperative chemotherapy in a randomised controlled trial (RCT). *First Author: Sandro Pasquali, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Patients with extremity and trunk wall STS with high malignancy grade and size larger than 5cm are considered at high risk of death, but in fact this risk varies broadly depending on histologic subtype and size. The Sarculator, a nomogram for STS, can improve prognostic assessment of these patients. This tool was evaluated for stratifying risk of distant metastasis (DM) and overall survival (OS) in a RCT investigating perioperative chemotherapy. **Methods:** High-risk STS patients were randomly assigned to receive either three cycles of preoperative chemotherapy with epirubicin (120 mg/m2) and ifosfamide (9 g/m2) or the same three preoperative cycles followed by two further postoperative cycles. The Sarculator was used to stratify patient risk according to predicted 10-year cumulative incidence of DM and OS rates. **Results:** The Sarculator identified three different prognostic groups of patients at low (N = 101), intermediate (N = 102), and high (N = 107) risk. Cumulative incidence of DM was 0.26 (SE: 0.04), 0.31 (SE: 0.05), and 0.48 (SE: 0.05) for low, intermediate, and high risk patients, respectively. Similarly, OS rates were 0.78 (95%CI 0.68-0.85), 0.63 (95%CI 0.53-0.72), and 0.42 (95%CI 0.32-0.52), respectively. Patients in the low risk group were at significantly lower risk of death compared to those in the intermediate (HR 0.51, 95%CI 0.34-0.78, P = 0.002) and high (HR 0.28, 95%CI 0.17-0.46, P < 0.001) risk groups. Subgroup analysis performed by jointly considering these three groups and the two study arms did not identify statistically significant survival differences between the treatment arms within each risk category. **Conclusions:** Patients with high-risk STS included in this RCT were not a homogeneous population. The Sarculator identified different risk groups for DM and OS even in patients included in a RCT investigating perioperative treatments. This tool should be considered for redefining high-risk STS and stratifying patient risk in future RCT investigating perioperative chemotherapy. Clinical trial information: 2004-003979-36.

11017 Poster Discussion Session; Displayed in Poster Session (Board #340), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Factors impacting contemporary management of high-grade extremity sarcoma: An analysis of 12,020 patients. *First Author: Stephen Ramey, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Previous studies noted racial/ethnic disparities in high-grade extremity soft tissue sarcoma (ESS) treatment and overall survival (OS). Retrospective series have noted worse OS for Amputation (Amp) vs limb salvage surgery (LSS) and for LSS alone vs LSS plus radiation (RT). Given superior functional outcomes, LSS is now favored over Amp when possible. This study examines racial/ethnic disparities in receipt of Amp vs LSS and impact on OS using modern data from a national registry. **Methods:** The National Cancer Database was used to identify patients (pts) with stage II-III, high-grade ESS diagnosed between 2004-2014 and treated definitively with 1) Amp alone, 2) LSS alone, 3) Preoperative RT [pre RT] + LSS or 4) LSS + Post-operative RT [post RT]. Multivariate analyses (MVA) utilized logistic regressions for patterns of local treatment and Cox proportional hazards regression for OS. The Kaplan-Meier method was used to estimate 5-year OS. **Results:** Among 12,020 pts, receipt of LSS vs Amp did not differ significantly by race, ethnicity, age, insurance status, income, or educational attainment on MVA. The rate of Amp was higher in academic centers (OR 2.42; p = .006) or integrated network programs (OR 2.30; p = .014) vs community programs and rural vs. Metro settings (OR 1.88; p = .035). Actuarial 5-year OS by treatment was Amp 43%, LSS 59%, pre RT + LSS 61%, and LSS + post RT 66% ($p < .001$). On MVA, OS was worse with Amp vs. LSS alone (HR 1.37; $p < .001$) while pre RT + LSS (HR 0.70; $p < .001$) and LSS + post RT (HR 0.72; $p < .001$) had improved OS vs LSS alone. Treatment at a comprehensive community, academic, or integrated network programs vs community program; private insurance vs none; Hispanic vs. non-Hispanic (HR 0.85, p = .048); and higher educational attainment were associated with improved OS. More comorbidities, other primary cancers, older age, and no transitions in care were associated with worse OS. **Conclusions:** The only racial/ethnic disparity identified when evaluating rates of Amp and OS for ESS was a small OS benefit for Hispanic pts. OS was inferior with Amp and best with LSS with either pre RT or post RT. OS was improved at non-community programs, potentially indicating a need for referral to experienced centers.

11018 Poster Discussion Session; Displayed in Poster Session (Board #341), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Radiation-associated versus sporadic osteosarcoma: A single-institution experience. *First Author: Brittany Siontis, University of Michigan, Ann Arbor, MI*

Background: Osteosarcoma (osarc) can be a rare complication from radiation (rt) therapy. Radiation-associated osarc (RAO) is reported to have a worse prognosis than non rt-associated osarc with limited objective data comparing the two. We conducted a retrospective study comparing demographics, therapy and outcomes of sporadic osarc (SO) to RAO. This study was confined to adults. **Methods:** We identified patients (pts) > age 18 years (yr) with osarc treated at our institution between 1990 and 2016 using an institutional database. We categorized tumors as SO or RAO based on history of prior rt within field of osarc. We extracted data on demographics, treatment, and primary malignancy characteristics. **Results:** We identified 159 pts with osarc, 28 were RAO tumors. Results are in Table 1. Median follow-up was 2.8 yr (0.1-19.6 yr). For RAO, median time from rt to diagnosis was 11.5 yr (1.5-28 yr) with a median cumulative dose of 60 Gy (44-75.8 Gy). Median progression free survival (PFS) and overall survival (OS) were not significantly different in pts presenting with metastatic osarc; PFS 10.3 mo vs 4.8 mo (p=0.45) and OS 15.6 mo vs 6.1 mo (p=0.96) in SO vs RAO pts, respectively. For pts with localized osarc, median relapse-free survival (RFS) and OS were significantly different, not reached vs 12.2 mo ($p<0.001$) and not reached vs 27.6 mo (p=0.001) in SO vs RAO, respectively. **Conclusions:** In our series, there was a significant difference in age, size and location of RAO vs non rt-associated osarc. Overall, all osarc pts with metastatic disease at diagnosis fared poorly. Pts presenting with localized RAO had worse outcomes than patients with localized SO. This was not associated with a detectable difference in therapy rendered or treatment effect in resection specimens.

Variable	SO	RAO	p value
Age, median (range)	38 (18-79)	61 (18-77)	<0.001
Tumor size cm, median (range)	8.7 (1.8-20)	5.6 (2-12)	0.003
Primary location, n (%)			
Axial	41 (31.3)	22 (78.6)	< 0.001
Appendicular	90 (68.7)	6 (21.4)	< 0.001
Neoadjuvant Chemotherapy, n (%)	77 (58.8)	17 (60.1)	0.899
Resection, n (%)	115 (87.8)	21 (77.8)	0.216
< 10% viable tumor, n (%)	16/54 (29.6)	3/12 (25)	0.752
Adjuvant Chemotherapy, n (%)	22 (16.8)	5 (17.9)	0.889
Mets at diagnosis, n (%)	20 (15.3)	6 (21.4)	0.409

11019 Poster Discussion Session; Displayed in Poster Session (Board #342), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Analysis of osteosarcoma subtypes by clinical genomic testing to identify clinically actionable alterations. *First Author: John Andrew Livingston, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Genomic testing is being utilized with increasing frequency to identify matched therapies for patients (pts) with advanced disease; however, the utility of such testing has not been defined in osteosarcoma (OS). We report our experience with 36 pts with recurrent/metastatic OS who underwent testing on a genomic testing protocol, including actionable alterations across multiple histologic subtypes of OS. **Methods:** Standardized hotspot mutation analysis was performed in 36 pts with recurrent/metastatic OS, using either a 46-, 50-gene, or 128-gene CLIA certified multiplex platform. 12 pts had a 200-gene analysis on a companion research protocol. We used the Catalogue Of Somatic Mutations In Cancer (COSMIC) database to identify alterations that are in mutation hotspots in OS or in other cancers. Clinical outcomes were retrospectively collected. Histologic subtype classifications were made by an experienced sarcoma pathologist based upon the pre-treatment and resection specimens. Cases with only metastatic samples available were classified as "other high-grade osteosarcoma." Additional clinical correlations are ongoing. **Results:** A total of 36 pediatric and adult pts were analyzed. All osteosarcomas were high grade; the most common osteosarcoma histologic subtypes were chondroblastic, osteoblastic, and other. Samples analyzed were from primary tumor in 15/36 (42%), with the remaining from metastatic specimens (58%). Mutations were identified in 26 pts (72%). The most common mutations were in *TP53*. An activating *PIK3CA* E545K mutation was found in chondroblastic OS. Other notable hotspot mutations include a *GNAS* R201 mutation in osteoblastic osteosarcoma and a *KRAS*G12V mutation in a fibroblastic osteosarcoma. **Conclusions:** Clinical gene panel sequencing can identify a limited number of potentially actionable mutations in patients with osteosarcoma. Given the heterogeneity of osteosarcoma at the molecular level, clinical genomic testing may be warranted to identify patients for participation on matched clinical trials.

11020 Poster Discussion Session; Displayed in Poster Session (Board #343), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Osteosarcoma prognostic nomograms for predicting the 10-year probability of mortality and recurrence. *First Author: Haotong Wang, Massachusetts General Hospital, Boston, MA*

Background: The multidisciplinary approach in treatment of osteosarcoma has been well established and well adopted nationwide. This study combined the clinical prognostic factors at initial presentation into a nomogram to predict local control (LC), metastasis free survival (MFS), and overall survival (OS) for patients with non-metastatic bone osteosarcoma. **Methods:** We reviewed 397 osteosarcoma patients treated from 1995 to 2014. Patients with metastatic disease at diagnosis or limited follow up were excluded, resulting in 283 cases for analysis. Clinical and pathologic variables were recorded. Predictive variables included age at diagnosis, gender, previous radiation history, site, tumor size, histologic subtype, histologic grade, extra-osseous extension (EOE), lymphovascular invasion (LVI), necrosis rate and margin. The multivariate Cox proportional hazards regression was used to analyze survival outcomes and risk variables. **Results:** At 10 years, LC was 70.4% (95% confidence interval, CI: 64.0%-76.7%), MFS was 64.7% (95% CI: 58.1%-71.3%), and OS was 61.5% (95% CI: 54.9%-68.1%). Multivariate Cox model identified age (p = 0.033), site (p = 0.020), EOE (p = 0.017), LVI (p = 0.011), and margin (p = 0.039) were correlated with LC; age (p = 0.028), tumor size ($p < 0.001$), histologic grade (p = 0.039), and LVI (p = 0.014) were correlated with MFS; whereas age ($p < 0.001$), prior radiation history (p = 0.010), tumor size (p = 0.002), histologic subtype (p = 0.012), EOE (p = 0.002), and LVI (p = 0.001) were associated with OS. The nomograms were drawn on the basis of the Cox regression model and were internally validated using bootstrapping, with predictive accuracy of ±7.2% for 10-year LC, ±7.4% for 10-year MFS, and ±7.5% for 10-year OS. **Conclusions:** Nomograms have been developed to predict the 10-year local-control failure, recurrence and death. We suggest that this tool at presentation may be useful for individualized risk evaluation, patient counseling, and making clinical decisions.

11021 Poster Discussion Session; Displayed in Poster Session (Board #344), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Cost effectiveness of surveillance for distant recurrence in extremity soft tissue sarcoma. *First Author: Trevor Joseph Royce, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA*

Background: Optimal surveillance strategies for extremity soft tissue sarcoma (STS) are unknown. We performed a cost-effectiveness analysis of competing imaging modalities performed at National Cancer Comprehensive Network guideline-specified intervals. **Methods:** We developed a Markov model simulating lifetime outcomes for 54-year-old patients after definitive treatment for Stage II-III extremity STS using four surveillance strategies: watchful waiting (WW), chest x-ray (CXR), chest computed tomography (CCT) and positron emission tomography-computed tomography (PET/CT) performed every 3-6 months for the first 3 years, every 6 months until year 5, and then annually. We used probabilities, utilities and costs extracted from the literature and Medicare claims to determine incremental cost-effectiveness ratios (ICER). **Results:** While the model showed that CCT is the most effective strategy, CXR is the most cost-effective strategy at a societal willing-to-pay (WTP) of $100,000/quality-adjusted life year (QALY). The ICER is $14,306/QALY for CXR versus $117,683/QALY for CCT while PET/CT is never cost effective (Table). Sensitivity analyses demonstrated CCT becomes the preferred imaging modality as the lifetime risk of DR increases beyond 38% or as the societal WTP increases beyond $130,000/QALY. **Conclusions:** Optimal DR surveillance imaging for Stage II-III extremity STS should be individualized based on patients' risks for DR. CXR, or CCT at more protracted intervals, may be preferred for lower risk patients (i.e. DR risk less than 38%), whereas CCT may be preferred for higher risk patients (i.e. DR risk greater than 38%). These findings can help refine guidelines to reduce resource overutilization during surveillance of sarcoma patients.

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER ($/QALY)
WW	1,290		7.29		
CXR	4,006	2,715	7.48	0.19	14,306
CCT	7,952	3,947	7.51	0.03	117,683
PET/CT	24,304	16,351	7.47	-0.04	-382,006

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WW, watchful waiting; CXR, chest x-ray; CCT, chest computer tomography; PET/CT, positron emission tomography-computed tomography.

11022 Poster Discussion Session; Displayed in Poster Session (Board #345), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Prospective development of a patient reported outcomes (PRO) tool in desmoid tumors: A novel clinical trial endpoint. *First Author: Jean Paty, QuintilesIMS, New York, NY*

Background: Desmoid tumors (DT) are locally aggressive and cause significant morbidity. Clinical trials in DT typically utilize response rates and progression free survival as primary endpoints. However, these endpoints do not capture improvements in clinical symptoms. To date, there are no validated PRO tools in DT to capture the patient experience and efficacy of a drug. **Methods:** A review of the published literature and interviews with sarcoma clinicians were used to formulate a list of signs and symptoms and impact on patients (pts). These were collected to build a conceptual model. DT pts (n = 31) with a range of anatomical locations and presentations were interviewed, initially in an open-ended fashion, followed by interrogating the conceptual model. For the concepts that pts reported, they were asked to rate how disturbing each was on a 0-10 scale (0 being not at all, and 10 being as bad as they can imagine). The pts interview data was then used to refine the conceptual model and generate two new PRO instruments **Results:** Pt interviews demonstrated that across tumor locations, the most frequent and disturbing symptoms were: 'muscle' pain (65% pts, median disturbance (MD) of 6.8), 'nerve' pain (73%, MD 6.0), and fatigue (65%, MD 5.0). Some symptoms were specific to tumor locations, especially abdominal tumors. Restricted range of motion (68%, MD 4.0), fear (84%, MD 6.5), sleep disturbance (77%, MD 7.5) , disfigurement (81%, MD 6.8), and impact on daily activities (65%, MD 6.8) were the most frequent and disturbing impact on pts lives. These concepts were then used to develop two new PRO instruments: the sign and symptom PRO includes 11 items; the impact on pts lives instrument includes 17 items. The instruments vary in asking pts about the last 24 hours, or the last week. **Conclusions:** This is the first validated PRO tool in DT. This tool adequately captures symptoms central to the DT pts experience and its impacts on their lives. The instruments are ready for implementation in a DT clinical trial for further evaluation of their measurement properties.

11023 Poster Discussion Session; Displayed in Poster Session (Board #346), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Toxicity and efficacy of bolus (BOL) versus continuous intravenous (CIV) dosing of doxorubicin (DOX) in soft tissue sarcoma (STS): Post hoc analysis of a prospective randomized trial. *First Author: Lee D. Cranmer, University of Washington Seattle Cancer Care Alliance, Seattle, WA*

Background: DOX remains critical in STS treatment. Controversy exists regarding its optimal administration route (BOL vs CIV). BOL vs CIV could affect toxicity and/or efficacy. A randomized trial to assess this is unlikely. We conducted a *post hoc* analysis to explore differences in these routes of DOX administration. **Methods:** Data from a prospective randomized phase III study of doxorubicin with or without evofosfamide (TH-302) were used. At the discretion of treating physician, BOL or CIV DOX could be used. Grade 3-5 hematologic, non-hematologic and cardiac toxicities and treatment response were explored using multivariable logistic regression. OS and PFS were analyzed using Kaplan-Meier and Cox proportional hazards. **Results:** 640 subjects were enrolled (556 BOL, 84 CIV). Baseline differences in age, extent of disease and prior radiotherapy were controlled for in regression models. Hematologic toxicity was associated with age, performance status (PS) and cumulative (CUM) DOX dose. Non-hematologic toxicity was associated with age, PS, receipt of prior radiotherapy and CUM TH-302 dose. Cardiac toxicity was only associated with CUM DOX dose. Odds of response were strongly associated with CUM DOX dose (mg/m^2, OR = 1.011, $p < 0.0001$), and, to a lesser extent, with CUM TH-302 dose (g/m^2, OR = 1.081, p = 0.0008), STS subtype and prior radiotherapy. Comparing CIV to BOL DOX, neither OS (median 21.7m vs 18.3m, HR = 0.85, p = 0.29) nor PFS (median 6.1m vs. 6.1m, HR = 0.89, p = 0.43) was affected by manner of DOX administration (CIV vs BOL). Cox analyses indicated that factors reflecting tumoral biology and host status, rather than treatment received, were associated with OS (PS, histologic STS subtype, histologic grade, receipt of prior radiotherapy) and PFS (PS, treatment-related toxicity). **Conclusions:** Our analyses provide no evidence for superiority of either BOL or CIV administration of DOX as regards toxicity or efficacy in STS treatment. Thus, the logistically simpler BOL administration of DOX should be favored over CIV administration.

11024 Poster Session (Board #347), Sun, 8:00 AM-11:30 AM

Weekly paclitaxel (WP) +/- bevacizumab (B) in angiosarcoma (AS) patients (pts): Analysis of prognostic/predictive factors from a randomized phase 2 trial. *First Author: Loic Lebellec, Centre Oscar Lambret, Lille, France*

Background: WP is an active regimen for treatment of AS pts (Ray-Coquard JCO 2015). We report here the correlative analysis conducted during a phase 2 trial assessing WP +/- B. **Methods:** Circulating pro/anti-angiogenic factors (FGF, PlGF, SCF, Selectin, thrombospondin, VEGF, VEGF-C) were collected at D1 and D8. Prognostic value for PFS was assessed using Cox model (biomarkers as continuous variables). We attempt to identify subgroups of pts benefiting from adding B using interaction tests (predictive factors). **Results:** Among the 51 pts enrolled in this trial, 45 were analyzable: 20 in Arm A (WP without B) and 25 in Arm B (with B). Median PFS was 5.5 and 6.1 months, respectively (p = 0.84). Samples were collected in 45 pts at D1 and 42 pts at D1 and 8. Baseline biomarkers were similar in both arms (excluding Selectin, significantly lower in arm A: median of 25 *vs.* 35 ng/mL, p = 0.03). In arm A, there was no significant difference between values at D1 and D8. In arm B, there were a significant decrease in VEGF (from a median of 0.49 to 0.08 ng/mL; $p < 0.01$) and selectin (from a median of 35.3 to 31.7 ng/mL; $p < 0.01$), and a significant increase in PlGF (from a median of 16.1 to 30.0 pg/mL; $p < 0.01$). In univariate analysis, factors associated with PFS were: de novo *vs.* radiation-induced AS (HR = 2.39 ($p < 0.01$), visceral *vs.* superficial AS (HR = 2.04; $p < 0.03$), VEGF-C at D1 (HR = 0.77; $p < 0.03$), FGF at D8 (HR = 1.17; $p < 0.01$), difference in FGF D8-D1 (HR = 1.24; $p < 0.01$), and PlGF value at D1 (HR = 1.02; $p < 0.05$). In multivariate analysis, factors associated with PFS were: de novo AS (HR = 2.39; p = 0.03), VEGF-C at D1 (HR = 0.73; $p < 0.02$) and FGF difference between D8 and D1 (HR = 1.16; $p < 0.02$). None of these factors were associated with benefit of adding B. **Conclusions:** Baseline VEGF-C levels and change in FGF were independent prognostic factors in pts with or without B. Addition of B significantly decreased the level of circulating VEGF and selectin and increased the level of circulating PlGF in AS patients. We did not identify subgroup of pts benefiting from adding of B to WP. Clinical trial information: NCT01303497.

11025 Poster Session (Board #348), Sun, 8:00 AM-11:30 AM

Immune-infiltrate characterization in localized osteosarcoma patients treated within protocol ISG-OS1. *First Author: Emanuela Palmerini, Istituto Ortopedico Rizzoli, Bologna, Italy*

Background: We hypothesized that immune-infiltrates were associated with survival, and examined a primary osteosarcoma tissue microarrays (TMAs) to test this hypothesis. **Methods:** Biopsies of patients (pts) treated from 04/2001 to 11/2006 were analyzed. TMAs from representative areas were assembled. Clinical and pathological characteristics at diagnosis, expression of CD8, CD4, CD3, FOXP3, CD20, CD68/CD163 (tumor associated macrophage), Tia-1 (cytotoxic T cell), CD303 (plamacytoid dendritic cells: pDC), Arginase-1 (myeloid derived suppressor cells: MDSC), PD-1 on immuno-cells (IC), and PD-L1 both on tumor cells (TC) and IC were correlated with patients outcome. A TMA of surgical specimens of the same cases also was assembled, and chemotherapy-induced changes analysis is ongoing. **Results:** 86 pts identified. Median age: 16 (range 4-39); high LDH: 36/86; high serum alkaline phosphatase (SAP): 18/86. All pts underwent neoadjuvant chemotherapy and surgery. A good pathologic response (≥90% necrosis) was achieved by 45/86 pts. IHC results are displayed in the Table. With a median follow-up of 8 years (range 1-13), the 5-year overall survival (5-yr OS) was 74% (95% CI 64-85). Univariate analysis showed better 5-yr OS for: a) good responders (good 89% vs poor 57%, p=0.0001); b) pts with CD8/Tia1 tumoral infiltrates (+/+ 81% vs +/- 60% vs -/- 45% p=0.002); c) pts with normal SAP (normal 85% vs high 44%, p=0.04). A numerically lower 5-yr OS was found in PD-L1 (IC) positive (+ 58% vs - 77%, p=0.14) and CD163 negative (+ 81% vs - 56%, p=0.17) cases. After multivariate analysis, poor histologic response (p=0.007) and lack of CD8/Tia1 infiltration (p=0.02) were independently correlated with poorer survival. In the subset of CD8+ patients, poorer (p= 0.02) OS was observed for PD-L1 (IC) + cases. **Conclusions:** Our findings support the hypothesis that CD8/Tia1 (cytotoxic T cells) infiltrate in tumor microenvironment at diagnosis is associated with superior survival for patients with localized osteosarcoma, while PD-L1 expression is associated with poorer survival.

	CD3 %	CD8 %	CD20 %	FOXP3 %	Tia1 %	CD68 %	CD163 %	CD303 %	Arg1 %	PD-L1 (TC) %	PD-1 (IC) %	PD-L1 (IC) %
Pos	89	86	29	33	73	37	67	4	21	0	22	14
Neg	11	14	71	67	27	63	33	96	79	100	78	86

11026 Poster Session (Board #349), Sun, 8:00 AM-11:30 AM

Neoadjuvant denosumab treatment of locally advanced giant cell tumor of bone (GCTB). *First Author: Piotr Rutkowski, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland*

Background: Retrospective study on locally advanced GCTB patients (pts) treated with neoadjuvant Denosumab (Db) outside clinical trials in 6 European reference centers. **Methods:** From 138 pts (median age 30yrs) with histologically confirmed advanced GCTB treated with Db(2011-2016), we included into analysis 87pts who underwent surgery after preoperative Db. All 87 patients had locally advanced tumors with extensive soft tissue involvement(54) or penetration to joint, not amenable to limb-sparing surgery/ primary curettage or with high risk of recurrence. In 39/42(93%) cases diagnosis was confirmed by *H3F3A*gene mutation. Median follow-up time -22 months. **Results:** Primary tumor was located in lower limb(54%; n = 47) -mostly in tibia(25%) and femur(23%), upper limb(33%; n = 29), and pelvis/axial skeleton/ribs(13%; n = 11). 68(78%) patients had primary tumors, 19(22%) recurrent tumors after surgery (+/-radiotherapy). Median Db duration was 7months (range 1.5-35months), 17pts received also Db postoperatively. 39(45%) had wide en-bloc resection -WE (+17 implantation of prosthesis), 48(55%) cases had intralesional curettage -C, no extremity amputation. Pts who underwent prosthetic replacement had longer median preoperative Db therapy as compared to pts without prosthesis. All pts demonstrated a response to Db Progression after surgical treatment was observed in 15 pts -13 of them after intralesional curettage (13/48, 27%); 9 patients underwent D re-challenge -all responded. Two-year progression-free survival (PFS; from Db start) rate was 80%, 91% in WE group vs 73% in C group (p = 0.04), one-year PFS (from operation date) rate was 84%: 92% in WE and 79% in C group(p = 0.01). Treatment was well tolerated with only 1 grade 3 toxicity. **Conclusions:** Our study confirms that Db is active in a neoadjuvant setting with excellent efficacy and short-term tolerability. It implies that neoadjuvant therapy with Db is the option for treatment of initially locally advanced tumors to facilitate complete surgical resection or avoid mutilating surgery. The risk of recurrences after curettage of GCTB following Db raises questions about the optimal duration of preoperative treatment and if Db is indicated postoperatively.

11027 Poster Session (Board #350), Sun, 8:00 AM-11:30 AM

Characterizing the end-of-life period in young patients with sarcomas. *First Author: Sujana Movva, Fox Chase Cancer Center, Philadelphia, PA*

Background: There is a paucity of data surrounding the end-of life transition (EOLT) in young adult (YA) patients with sarcoma. Discussions surrounding prognosis, goals of care (GOC), hospice and death can be challenging in these patients as they may be at a particularly hopeful stage of their life. The purpose of this study is to better understand the EOLT in YA patients with sarcoma by determining the survival and number of lines of treatment at different periods in the disease course. In addition, the study aims to determine what impacts the decision to discontinue anti-cancer therapy. **Methods:** Fox Chase Cancer Center (FCCC) patients, 18-39 years old who died from sarcoma between January 2013 and December 2016 were included in this study. Patient demographics, tumor specific data, treatment and treatment decisions were collected from electronic medical records and retrospectively analyzed. **Results:** 38 FCCC patients who were diagnosed between the ages of 18-39 died between January 2013 and December 2016. Of these 21 patients were between the ages of 18-39 at the time of their death. Median age at death was 30 (range: 22-40). The most common histologies were Ewing Sarcoma, GIST (n = 3) and osteosarcoma, synovial sarcoma (n = 2). Median time from diagnosis of metastatic disease to death was 21.4 months. Median time from metastatic disease to discussion of GOC and hospice by any provider was 9.6 and 16.7 months respectively. The hospice discussion was held by the treating oncologist 87.5% (n = 16) of the time (outpatient 35.7% and inpatient 64.3%). 60% (n = 15) of patients/family selected hospice when it was originally presented to them (multi-organ failure, unarousable, paralysis). The hospice discussion was held at a median of 21 days prior to death and median time on hospice was 13 days (range: 1-63). Patients were treated a median of 54 days prior to their death (range: 6-1823). Median times on first, 2ndto last and last treatments were 273, 67 and 22.5 days respectively (P = 0.002). **Conclusions:** Focusing on this particular group of patients will generate benchmark data that can help counsel them about their specific expected survival and changes in clinical status as their disease progresses. We plan to compare this data with that of older patients.

11028 Poster Session (Board #351), Sun, 8:00 AM-11:30 AM

Failure rate of standard rescue with leucovorin for high-dose methotrexate (HDMTX) in osteosarcoma. *First Author: Mikael Eriksson, Skane University Hospital and Lund University, Lund, Sweden*

Background: HDMTX followed by leucovorin rescue is well established as part of MAP chemotherapy for osteosarcoma. However, leucovorin rescue is not always effective as rescue, resulting in delays to subsequent courses of chemotherapy. **Methods:** This retrospective observational study involved patients ≥2 years of age with osteosarcoma treated with MAP during 2009 - 2014. Data was extracted from medical records from five clinics in Poland, Hungary, Norway and Sweden. The study objective was to determine to what extent patients treated with MAP encountered treatment delays due to MTX-related toxicity or delayed MTX elimination. **Results:** All patients fulfilling the inclusion criteria were included. Of 116 patients (ages 5-39 with a mean of 14 years; 59% males), 97% completed their first MAP cycle while only 48% completed six treatment cycles. The analysis of the primary endpoint included 114 evaluable patients. At least one treatment delay due to MTX toxicity or delayed MTX elimination was reported for 89 patients (78%) and only six patients (5%) completed the entire MAP treatment according to plan. Delay in subsequent treatment was observed following 183 of 369 evaluated MAP cycles (50%). About three quarters of the delays were found to be due to MTX-related toxicity while only a small number were related to delayed MTX elimination. The treatment related issues most commonly registered were increased liver enzymes, hematological disturbances, increased bilirubin and mucositis. **Conclusions:** We found at least one treatment delay due to MTX toxicity or delayed MTX elimination in 78% of all MAP-treated patients and that 50% of the administered MAP cycles resulted in a delay in subsequent treatment, mostly due to MTX toxicity. Only six patients (5%) completed the entire MAP treatment according to plan. The retrospective methodology with broad inclusion criteria implies that the results can be extrapolated to the entire target population. Thus, there appears to be an unmet need for a more effective HDMTX rescue that could reduce MTX toxicity and be expected to enable more patients to maintain planned MAP treatment intensity and duration, thereby improving the overall efficacy of the MAP regimen.

11029 Poster Session (Board #352), Sun, 8:00 AM-11:30 AM

The genomic and evolutionary landscape of osteosarcoma progression and lung metastasis. *First Author: Jin Wang, Department of Musculoskeletal Oncology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China*

Background: Osteosarcoma (OS) is a primary malignant bone tumor that has a high potential to metastasize to lungs. Recent studies have characterized somatic mutations of primary OS tumors. Nevertheless, lung metastases of OS are poorly studied, and whether they harbor distinct genetic alterations beyond those observed in primary tumors is largely unknown. **Methods:** We performed whole-exome sequencing (WES) of matched primary tumors and lung metastases in a cohort of 15 OS patients. Somatic single nucleotide variations (SNV) and copy number alterations (CNA) were analyzed to characterize the genomic and evolutionary landscape of metastatic OS. **Results:** Compared to matched primary tumors, lung metastases exhibited higher transversion rate for base substitution, and poor overlap ($< 10\%$) of genetic alterations was observed between primary and metastasis tumors. Multiple novel significantly mutated genes were identified, including *ZNF717* in lung metastases, *SPDYE1* in primary tumors, and *CRIPAK* in both. Copy number analysis indicated recurrent CNAs, including *NEURL1B* deletion and *FLG* amplifications in lung metastases, *GSTT1* deletion in primary tumors, and *CEACAM* gene family deletion in both. Furthermore, phylogenetic analyses revealed that paired primary tumors and metastases underwent parallel evolution with few ubiquitous clonal mutations, suggesting that OS metastases are likely to be derived from primary tumors at a very early stage of their evolution. **Conclusions:** This study for the first time provides important evidence that OS metastases harbor distinct genetic alterations compared with primary tumors. Our findings strongly support a parallel evolution model of primary and metastatic tumors. Moreover, several novel CNAs and significantly mutated genes that are specifically associated with lung metastases may provide future therapeutic insight for OS.

11030 Poster Session (Board #353), Sun, 8:00 AM-11:30 AM

Does *MGMT* (O6-methylguanine–DNA methyltransferase) have a role in metastatic Ewing sarcoma (ES) patients (pts) undergoing temozolomide (TMZ) and irinotecan (IRI)? *First Author: Emanuela Palmerini, Istituto Ortopedico Rizzoli, Bologna, Italy*

Background: TMZ+IRI has significant activity in metastatic ES. Epigenetic silencing of the *MGMT* DNA gene by promoter methylation has been associated with response to TMZ in glioblastoma. Our aim was to assess if *MGMT* methylation 1) has a role in ES progression and 2) is predictive of response to TMZ. **Methods:** 1) In 10 ES cell lines presence of *MGMT* gene (Real-time PCR), methylation of its promoter (methylation-specific PCR) and protein expression (western blot) were assessed. MGMT protein (IHC) and methylation of its promoter was searched in 97 ES pts samples (74 localized; 23 metastatic). 2) In metastatic ES pts treated with TMZ+IRI, with pre-treatment FFPE tissue and measurable disease, the relation between RECIST response, PFS and MGMT expression (IHC) was assessed. **Results:** 1) The expression of *MGMT* gene and its protein was detected and concordant ($p = 0.02$) in all ES cell lines evaluated; methylation was a rare event. In ES tissue samples the methylation of the *MGMT* gene was found at a low intensity as compared with the unmethylated gene, but the protein expression was relatively low: 36% in localized, 65% in metastatic pts (p 0.03). 2) 24 pts (median age 19 years, range 3-50 years; F/M: 7/17) treated with TMZ + IRI from 2010 to 2015 were identified. Line of treatment: 8 patients were in 1st line; 16 ≥ 2nd line. Median n of cycles was 6 (range: 2-31). Pattern of metastases: 16 multiple sites, 4 lungs, 3 multiple sites + bone marrow, 1 bone. MGMT was positive in 63% of cases. ORR: 16.5% (1 CR , 3 PR); SD: 50% (13 pts); PD: 33.5% (7 pts). According to MGMT expression the ORR was 11% in negative and 20% in MGMT positive patients ($p = 0.8$). 6-mos PFS rate was 59% (38-80 %IC), no differece according to MGMT expression (pos 61% vs neg 56%, p 0.7). **Conclusions:** Whereas in cell lines the *MGMT* gene and its protein expression is a generalized event, in tissue samples MGMT protein is present in a minority of localized pts, and might be associate with tumor progression. Methylation of *MGMT* gene does not seem responsible for its regulation in ES, and post-transcriptional mechanisms are more likely to be involved. The presence of MGMT protein does not predict the response to TMZ + IRI in this small series.

11031 Poster Session (Board #354), Sun, 8:00 AM-11:30 AM

Apatinib for patients with unresectable high-grade osteosarcoma progressing after standard chemotherapy: A multi-center retrospective study. *First Author: Wenxi Yu, Affiliated Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, China*

Background: Prognosis for patients with relapsed/metastatic osteosarcoma is dismal and the optimal treatment strategy remains to be refined. Sorafenib and sorafenib plus everolimus are the only two second-line targeted therapies recommend by FDA. The median progression-free survival (PFS) was 4–5 months. In this study, the efficacy and safety of apatinib, another oral tyrosine kinase inhibitor targeting VEGFR-2, were evaluated in patients (pts) with inoperable high-grade osteosarcoma progressing after standard multidisciplinary treatment. **Methods:** This retrospective study reviewed the medical records of 26 pts with metastatic osteosarcoma who received apatinib at a dose of 500 mg qd or 250 mg bid after failure of standard treatment including doxorubicin, cisplatin, ifosfamide and high-dose methotrexate from Jul 2015 to Nov 2016. **Results:** Among all pts, 25 (96.2%) had pulmonary metastases and 4 (15.4%) had metastases in the bone (Table). Eleven pts achieved partial response, 10 stable disease and 5 progressive disease, yielding an objective response rate of 42.3% and a clinical benefit rate of 80.8%. Followed up to Dec 31 2016, the median PFS was 8 months (95%CI, 3.2–12.8 months), and the median overall survival (OS) was not reached. The 12-month PFS and OS rates were 22.5% (95%CI, 1.6%–58.1%) and 68.7% (95%CI, 37.5%–86.5%), respectively. Noteworthy, the 12-month PFS rate for patients treated with apatinib in the second-line setting was 51.3% (95%CI, 9.1%–83.1%). The most frequent treatment-related adverse events (AEs) were hand-foot skin reaction (HFSR) (84.6%), hypertension (46.2%), and diarrhea (23.1%). Severe AEs included grade 3 HFSR (7.7%) and hypertension (3.8%). No unexpected AE was found. **Conclusions:** Apatinib was well tolerated and demonstrated activity as a second- or later-line treatment in patients with metastatic osteosarcoma, which deserves further investigations.

Baseline characteristics.

Characteristics		N	%
Age	Median (range), years	18.5 (8–63)	
	<18	11	42.3
Gender	Male	18	69.2
Karnofsky performance score	<90	24	92.3
Previous chemotherapy	1 line	13	50.0
Sites of metastases	Lung only	22	84.6
	Lung and bone	3	11.5
	Bone only	1	3.8

11032 Poster Session (Board #355), Sun, 8:00 AM-11:30 AM

Clone evolution and genomic alteration analysis of osteosarcoma and matched lung metastasis. *First Author: Di Wang, Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China*

Background: Lung metastasis (LM), as the most common metastatic site, is the main reason resulting in treatment failure and death of osteosarcoma (OS). But there was no report about the clone evolution and genomic alteration in the process of LM of OS. **Methods:** Multiregion whole-genome sequencing and whole-exome sequencing were performed on ten patients with primary OS and matched lung metastatic tumors. A set of high confident somatic nucleotide variants (SNV), small insertion and deletion (indel) and copy number variation (CNV) in each sample were identified, then the *n*-dimensional Bayesian Dirichlet process was applied to define the constituent mutation clusters as clone or subclone. Neoantigen prediction and HLA typing were performed using NetMHC3.0 and POLYSOLVER algorithm, respectively. **Results:** There were diversified metastatic progression during lung metastasis of OS including linear evolution (7/10) and parallel evolution (3/10), and metastasis-to-metastasis spread was also found in a patient with multiple metastasis; Mutation accumulative effect during the metastasis of OS was evident, LM had much higher mutation load (fold change = 4.1, P-value < 0.01) and neoantigen burden (fold change = 4.5, P-value < 0.001) than the primary tumor; DNA mismatch repair (MMR) genes relevant deleterious mutation events were found in germline in 8/10 metastatic OS cases and MMR genes mutation were much more in LM than primary cancer; The genome instability of LM was prevalently much more significant than primary tumor, with higher copy number variation frequency (fold change = 7.01, P-value < 0.01). **Conclusions:** The evolution of OS during LM was very complex with diversified metastatic progression. For the LM of OS, the novel therapy should be considering the much higher mutation load, especially those causing tumor neoantigens, higher genomic instability which were associated with tumor immune therapy. Furthermore, the findings of germline MMR genes mutation in primary OS which had occurred LM and more MMR genes mutation in LM of OS indicated potential clinical benefit on immune checkpoint inhibitor therapy and other small molecular drugs for MMR genes.

11033 Poster Session (Board #356), Sun, 8:00 AM-11:30 AM

Multicentric randomized phase II trial of gamma knife surgery (GKS) versus image-guided, intensity-modulated radiation therapy (IG-IMRT) in patients with sacrococcygeal chordoma. *First Author: Shun Lu, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*

Background: Chordoma is a rare slow-growing neoplasm arisen from cellular remnants of the notochord. About 30% occur in the sacrococcygeal region. Surgical resection is recommended treatment. Due to the high recurrence rate, adjuvant radiation therapy was suggested to receive as an effective method to improve local control rates. **Methods:** Thirty eight patients were pathologically diagnosed as non-metastatic sacrococcygeal chordoma from Aug. 2003 to May. 2015 were recruited retrospectively to analysis. All patients received surgical resection after diagnosed. Initial surgery included subtotal resection (24% of patients), and gross total resection (76% of patients). Among these patients, 25 patients treated with adjuvant IG-IMRT, while 13 patients treated GKS after surgical resection. The median follow-up was 40 months (range, 6–151 month) for all patients, The PTV of IG-IMRT group received total doses were 60 Gy (range, 56-74Gy), delivered with 2-2.2 Gy/fraction, while GKS group underwent a total of 6-8 sessions treatment. **Results:** For the IG-IMRT group and the GKS group, the 5-year overall survival and local control rates were 87.5% and 67.7%, respectively. And 5-year local control rates were 35% and 22.2%, respectively. In total, 18 patients progressed locally: 11 were in the IG-IMRT group and 7 in the GKS group. In comparison with GKS group, the IG-IMRT group has a better overall recurrence-free survival ($p = 0.03$), the significance remained after adjusted for surgery results, age and gender. Moreover, there is no significant difference of overall survival was found between these two groups. **Conclusions:** We report favorable local control and adverse event rates following IG-IMRT, and suggested IG-IMRT is the first choice of adjuvant radiation therapy for sacrococcygeal chordoma treatment.

11034 Poster Session (Board #357), Sun, 8:00 AM-11:30 AM

A DNA methylation-based classifier for accurate molecular diagnosis of bone sarcomas. *First Author: Shengyang Wu, NYU School of Medicine, New York, NY*

Background: Bone sarcomas present a unique diagnostic challenge because of the considerable morphologic overlap between different entities. The choice of optimal treatment, however, is dependent upon accurate diagnosis. Genome-wide DNA methylation profiling has emerged as a new approach to aid in the diagnosis of brain tumors, with diagnostic accuracy exceeding standard histopathology. In this work we developed and validated a methylation based classifier to differentiate between osteosarcoma, Ewing's sarcoma, and synovial sarcoma. **Methods:** DNA methylation status of 482,421 CpG sites in 15 osteosarcoma, 10 Ewing's sarcoma, and 11 synovial sarcoma samples were measured using the Illumina HumanMethylation450 array. From this training set of 36 samples we developed a random forest classifier using the 400 most differentially methylated CpG sites (FDR q value < 0.001). This classifier was then validated on 10 synovial sarcoma samples from TCGA, 86 osteosarcoma samples from TARGET-OS, and 15 Ewing's sarcoma from a recently published series (Huertas-Martinez et al., Cancer Letters 2016). **Results:** Methylation profiling revealed three distinct molecular clusters, each enriched with a single sarcoma subtype. Within the validation cohorts, all samples from TCGA were correctly classified as synovial sarcoma (10/10, sensitivity and specificity 100%). All but one sample from TARGET-OS were classified as osteosarcoma (85/86, sensitivity 98%, specificity 100%) and all but one sample from the Ewing's sarcoma series was classified as Ewing's sarcoma (14/15, sensitivity 93%, specificity 100%). The single misclassified osteosarcoma sample was classified as Ewing's sarcoma, and was later determined to be a misdiagnosed Ewing's sarcoma based on RNA-Seq demonstrating high EWRS1 and ETV1 expression. An additional clinical sample that was misdiagnosed as a synovial sarcoma by initial histolopathology, was accurately recognized as osteosarcoma by the methylation classifier. **Conclusions:** Osteosarcoma, Ewing's sarcoma and synovial sarcoma have distinct epigenetic profiles. Our validated methylation-based classifier can be used to provide an accurate diagnosis when histological and standard techniques are inconclusive.

11035 Poster Session (Board #358), Sun, 8:00 AM-11:30 AM

Association of genomically unstable Ewing sarcoma tumors with HOTAIR overexpression and clinical outcome. *First Author: Jamie D. Gardiner, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Ewing sarcoma (ES) is the second most common bone cancer in children, characterized by the EWS-FLI1 fusion protein. Like most translocation-driven pediatric cancers, ES is a genomically "quiet" cancer with a low mutational burden and strong epigenetic regulation. However, recurring copy number alterations (CNAs) still arise in some ES tumors (e.g., chromosome 1q gain, 8 gain, 12 gain, and 16q loss) while other ES tumors completely lack genomic CNAs. We hypothesized that clinical, molecular, and epigenetic differences exist between these two unstable vs. stable genomic subtypes of ES. **Methods:** We performed CNA analysis on over 200 ES FFPE tumors. 30% of ES tumors had stable genomes while 60% had one or more CNAs across the genome. We performed gene expression and methylation microarray analyses on 24 ES FFPE tumors (11 stable, 13 unstable). Expression and methylation signatures were compared between stable vs. unstable ES and combined with clinical outcome. **Results:** Patients with unstable vs. stable ES tumors revealed worse 5-year overall (OS) and event-free survival (EFS) (38% vs. 67% EFS, $p = 0.005$; 58% vs. 84% OS, $p = 0.0016$). The subtypes had distinct expression and methylation signatures and clustered by methylation patterns. We identified differentially expressed and methylated genes, including upregulation ($p = 0.0005$) and unmethylation ($p = 0.0009$) of the long non-coding RNA *HOTAIR* in unstable vs. stable ES tumors. *HOTAIR* expression is higher in metastatic ES tumors compared to primary ES tumors ($p = 0.02$). Per the Cancer Cell Line Encyclopedia (Broad), ES cell lines have increased HOTAIR expression compared to 36 other cancers. **Conclusions:** ES genomic profiling through copy number, gene expression, and methylation identified at least two subtypes of ES (stable and unstable) that differ in outcome, gene expression and methylation. This data suggests *HOTAIR's* involvement in ES pathogenesis, particularly in unstable tumors that have worse prognosis. Investigation is ongoing for *HOTAIR* expression as a prognostic and therapeutic target for ES, including a marker for LSD-inhibitor response.

11036 Poster Session (Board #359), Sun, 8:00 AM-11:30 AM

Inhibition of autophagy sensitizes gastrointestinal stromal tumor cells to TKI/Bcl-2 inhibitors-induced apoptosis. *First Author: Shuchao Zhang, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the GI tract. Most GISTs are driven by mutations in KIT or platelet-derived growth factor receptor-α (PDGFRA), which responds well to imatinib, a tyrosine kinase inhibitor (TKI) that blocks KIT and PDGFR-α signaling. Bcl-2 family plays a critical role in the regulation of cell apoptosis in GISTs. ABT-737 as an inhibitor of Bcl-2/Bcl-xL can result in a time and dose-dependent activation of apoptosis. Autophagy is a key mechanism to promote tumor cells survival, inhibition of which can induce the cell death in GISTs. Chloroquine, an antimalarial drug, has been also identified as an autophagy inhibitor. In this study, we assessed the combinational effects of imatinib, ABT-737 and chloroquine in GIST cells. **Methods:** Human GIST cell lines, GIST-T1 and GIST-882, were employed in our study. Cells were treated with imatinib, ABT-737 and chloroquine either separately or in different combinations. Cell viability was tested by means of MTS and synergistic effects were analyzed by isobologram software. The levels of related proteins of apoptosis (PARP, Caspase-3) and autophagy (LC3-II, beclin-1) were measured by western blot. Cell apoptosis and cell cycle were tested by flow cytometry. **Results:** Cell viability assay indicated cell survival percentage of double or triple drug combinations ($< 5\%$) dramatically decreased compared to single drug treatments (42%, 36% or 12%) ($P < 0.05$). Isobologram analysis revealed triple drugs combination had stronger synergistic effects than double drugs combinations (CI = 0.204 vs 0.309 or 0.356, $P < 0.05$). Cell apoptosis percentage of double (32.9% or 36.6%) or triple drugs combinations (66.5%) significantly increased compared to single treatments (6.1%, 6.1% or 13.1%) ($P < 0.05$). Western blot showed drugs combinations increased cleavage of PARP and Caspase-3 levels, but inhibited autophagy. **Conclusions:** The combination of imatinib, ABT-737 and chloroquine has collaborative effects on the treatment of GISTs *in vitro*. The combined strategy may enhance the clinical efficacy, which provides a rationale for the clinical evaluation of these drug combinations in GISTs treatment.

11037 Poster Session (Board #360), Sun, 8:00 AM-11:30 AM

The role of neoadjuvant imatinib therapy of patients with primary locally advanced GIST. *First Author: Peter Arkhiri, N. N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia*

Background: percutaneous biopsy of gastrointestinal tumors is contraindicated, that is why prospective randomized trials of efficiency of preoperative imatinib therapy weren't conducted. According to the results of theRTOG S-0132/ACRIN 6665, CST1571-BDE43 and other studies, neoadjuvant imatinib therapy increase tumor resectability and improve progression-free and disease-specific survival. The optimal timing of surgical intervention is likely during the maximal response on treatment (6 to 12 months as a rule). **Methods:** We have analyzed the treatment results of 86 patients with locally advanced GIST which were treated since January 1st 2002 till 20 January 2016 at N.N. Blokhin Russian Cancer Centre. The primary tumor was located in the stomach - 32 pts (37,2%), duodenum and small bowel - 37 (43,1%), other (colon, rectum and extraorgan) – 17 pts (19,7%). The median follow-up time was 4.9 years. There are 4 groups in the trail: group 1 - 29 patients received only surgical treatment, group 2 - 12 pts– surgical resection with adjuvant imatinib therapy for 1 year; group 3 - 25 pts – adjuvant imatinib therapy for 3 years and group 4 - 17 pts– surgical resection with neoadjuvant and adjuvant imatinib therapy (1 - 3 years). The remained 3 patients received surgical resection with adjuvant imatinib therapy for 5 years. **Results:** Survival analyses showed a significant improvement of RFS and OS in patients who received combined treatment with neoadjuvant and adjuvant imatinib therapy. The five-year RFS in first group of patients was 10,8%, in 2 group - 16,7%, in 3 group - 68,4%, and 4 group - 79,8% (p = 0.0001). The 5-year overall survival in these groups was 42,6%, 66,7%, 76,1% and 91.6% (p = 0,0072) respectively. In the patients with 5-years adjuvant therapy, diseases progression was not noted. During neoadjuvant therapy disease progression has been registered in two patients. The median time of preoperative imatinib therapy was 11 month (from 3 to 24 month). Neoadjuvant imatinib therapy increased the rate of R0 (14 pts – 82,4%) and organ-sparing (12 pts – 70,6%) resections. **Conclusions:** The optimal approach in patients with locally advanced GIST is combined surgical treatment with neoadjuvant and adjuvant (at least for 3 years) imatinib therapy.

11038 Poster Session (Board #361), Sun, 8:00 AM-11:30 AM

Rechallenge in advanced GIST progressing to imatinib, sunitinib and regorafenib: An Italian survey. *First Author: Bruno Vincenzi, Medical Oncology Department, University Campus Bio-Medico, Rome, Italy*

Background: We retrospectively collected data from metastatic Italian GIST patients treated with imatinib or sunitinib reintroduction after progression to conventional three or four lines of therapy. **Methods:** 82 eligible advanced GIST patients, previously treated with imatinib, sunitinib and regorafenib, were collected in the present analysis from 6 cancer centres. All patients received all three standard kinase inhibitors. Imatinib dose increase as active second line or 800 mg upfront in exon 9 mutant GIST were allowed. Specific mutations were recorded if available (deletion versus others) and correlated with survival and response according to RECIST 1.1 or CHOI criteria. **Results:** Seventy-four of 82 patients received Imatinib 400 mg as rechallenge, while 8 patients were treated with sunitinib at personalised dose and schedule according to the physician's choice. Mutational status was available in all patients and in 68 patients details about type of mutation were achievable. The median follow-up was 13 months (range 1-42 months). The median time to progression (TTP) in patients receiving a rechallenge therapy was 5.4 months (95% CI 1.9-13.5) and Overall Survival (OS) was 10.6 months (95% CI 2.8-26.9). Apparently, in this setting a correlation between mutational status and response rate, TTP or OS was not found. On the contrary, considering only exon 11 mutated patients and comparing patients with deletion vs non deleted ones a significant difference was identified both in terms of TTP and OS (respectively, P = 0.04 and P = 0.02). **Conclusions:** Our retrospective data confirm that the rechallenge of imatinib or sunitinib is a reasonable option in advanced GIST patients after failure of previous treatments. As expected, imatinib is the most frequently prescribed option in the Italian real-life setting, demonstrating a TTP and OS longer than those observed in previous studies. Also the prognostic value of the specific type of exon 11 KIT mutations has been confirmed in our series.

11039 Poster Session (Board #362), Sun, 8:00 AM-11:30 AM

A phase Ib study of BGJ398 in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST). *First Author: Ciara Marie Kelly, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Preclinical studies suggest that imatinib resistance (IR) in GIST can be mediated by MAP-kinase activation via FGF signaling. In FGF stimulated GIST cell lines, BGJ398, a pan-FGFR inhibitor in combination with imatinib, is cytotoxic and superior to imatinib alone, or imatinib in combination with MEK-inhibition. In GIST with FGF signaling, the combination of BGJ398 and imatinib may provide a mechanism to overcome IR. **Methods:** This phase Ib study of BGJ398 in combination with imatinib was performed in patients (pts) with imatinib resistant advanced GIST. A standard 3+3 dosing schema was utilized to determine the recommended phase II dose. Two treatment schedules were evaluated incorporating imatinib 400mg daily continuously in combination with (A) BGJ daily 3 wks on, 1 wk off or (B) BGJ daily 1 wk on, 3 wks off. Response was evaluated by RECIST and CHOI every 8 wks x4 and then every 12 wks. **Results:** 16 pts enrolled. Median age 54 (range: 44-77), 81% male, median prior therapy 4 [range: 2-6, 13/16 pts had $\geq$ 3 prior therapies (81%)]. 12 pts received treatment on schedule A [dose level (DL)1 (BGJ 75mg), n = 6; DL-1 (BGJ 50mg), n = 3; DL-2 (BGJ 25mg), n = 3]: 3 DLTs (myocardial infarction, grade (G)4 CPK elevation, G3 ALT elevation) were observed on schedule A at DL1, hyperphosphatemia (on target effect) was not observed raising concern for therapeutic efficacy at the maximum tolerated dose. Following protocol amendment that allowed an alternative dosing schedule, 4 pts enrolled on schedule B [DL1 (BGJ 75mg), n = 3; DL2 (BGJ 100mg), n = 1]: one DLT occurred (G3 intra-abdominal hemorrhage) at DL2. The most common non-DLT G3/4 toxicity was HTN (2/16pts) and G2 toxicity was prolonged QTc interval (3/16pts). Of the 12 pts with evaluable CT scans, stable disease (SD) was the best response observed in 7 pts by RECIST and 9 pts by CHOI. 3pts achieved SD for $>$ 6 months. 2 pts remain on study at data cut-off (range: 1 – 67 wks). Median progression free survival is 8 weeks. Pharmacokinetic analysis of imatinib and BGJ is forthcoming. **Conclusions:** In heavily pre-treated pts, durable disease control was observed in 3/16 pts. This signal of efficacy suggests that further evaluation of FGF signaling in the development of IR is warranted. Clinical trial information: NCT02257541.

11040 Poster Session (Board #363), Sun, 8:00 AM-11:30 AM

Numerical, dimensional or mixed progression disease to imatinib as prognostic factor in patients with metastatic GIST. *First Author: Giuseppe Badalamenti, Department of Surgical, Oncological, and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy*

Background: The majority of GIST patients with advanced disease initially achieves disease control from imatinib treatment. Approximately 10% of patients progresses within 6 months of starting therapy (primary resistance) and also 50-60% of the responding patients develops progression disease within two years (secondary resistance). Progression disease (PD) can be numerical, dimensional or mixed. The known prognostic factors of risk stratification in local disease are tumor size, mitotic activity and anatomic site. In this retrospective analysis we explore several clinical factors affecting survival in metastatic setting. **Methods:** The population included in this large database of 128 patients with metastatic GIST was obtained examining data collected from four Oncologic Centres with expertise for the GIST management. The clinical factors analyzed were sex, tumor size, mitotic activity, anatomic site, *KIT* and *PDGFRa* mutational status, site of metastasis, FDG-PET status at progressing disease and pattern of tumor progression to I line imatinib 400, II line Imatinib 800 or Sunitinib, evaluated with CT scan or MRI: PD with dimensional growth (dimensional, dPD), with new lesions appearance (numerical, nPD) and with both numerical and dimensional growth (Mixed, mPD). Every factor has been correlated with Overall Survival (OS) measured in months. Survival analyses were performed by using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard regression models were executed to search for association with the outcome. **Results:** Univariate analysis showed significant value for primary tumor site ($p < 0.0001$), mitotic activity (p = 0.02), tumor size (p = 0.05) and PD pattern (p = 0.008): OS nPD group was 102.7 months, in dPD group 87 and in mPD group 70. The multivariate analysis confirm significant prognostic factors for OS tumor site (p = 0.0004) and PD pattern (p = 0.02). **Conclusions:** with the limitations of a retrospective analisys, this study shows for the first time the impact of pattern of progression on OS: patients with dPD have a worse prognosis than those with nPD or mPD, suggesting type of PD as an independent prognostic factor for OS in advanced GISTs.

11041 Poster Session (Board #364), Sun, 8:00 AM-11:30 AM

Long-term survival (over 10 years) of inoperable/metastatic GISTs: A retrospective series of 141 patients (pts) of the french sarcoma group (FSG). *First Author: Florence Duffaud, Hopital de la Timone, Marseille, France*

Background: A subset of metastatic GIST exhibit very long-term survival after imatinib (IM) introduction. The aim of this study was to analyse the clinico-biological characteristics of GIST pts alive > 10 years (yrs) after diagnosis (dx) of metastases (mets) and identify possible factors associated with long-term survival. **Methods:** Pts were identified from 2 sarcoma databases; NetSarc and ConticaGIST. Clinical data prospectively registered in the databases were supplemented with retrospective review of medical records. **Results:** We identified 141 pts (75 men, 66 women) with median age 54 (17-84) yrs and median ECOG 0 (0-2). Primary tumors (T) were all CD117+, and mainly gastric or intestinal (64 & 45 pts), with median size 10 (2-40) cm, CD34+ (82 pts), mitoses/50 HPF ≤ 5 (n = 36), or > 5 (n = 81). Genotype was documented in 82 (58%) pts with 73 (89%) *KIT* mutations (in exons 11,9 and 12 of 69, 3, and 1 pts respectively) and 9 WT *KIT*. 129 (91%) T were resected, 124 upfront, 5 post IM, with R0/R1/R2 resections in 61, 11, and 10 pts. Mets were mainly hepatic or peritoneal (78 & 51 respectively). 1st line TKI was given to 139 pts: 130 received IM; 88 (63%) within a clinical trial (CT), 41 (29%) had mets resection. Second, 3d and 4th line TKI were given to 81, 51 and 37 pts respectively, comprising 27, 7 and 10 from CT. Median number of TKIs was 2 (0-7), but 60 (44%) pts received only 1st line with no GIST progression within or after 10 yrs. 2 pts never received TKI but had mets resection. After median FU of 14.3 yrs (10-34.5), 104 remain alive, 37 died. Mean and Median OS from initial dx are 24 yrs (CI95% 21.6-27) and 20,8 yrs. Median PFS on TKIs are 127, 29, 21 and 22 mos on 1st, 2d, 3d and 4th line of TKI. In univariate analysis no factor is significantly associated with OS, but T size (≤ 10 vs > 10 cm) and oligometastatic disease (≤5 vs > 5 mets) are borderline significant (p = 0.056 and 0.07), and good PS (ECOG ≤ 1) at 2dline TKI initiation is associated with better PFS (p = 0.03). **Conclusions:** This large series of long-term (> 10 yrs) survivors of metastatic GIST shows a high proportion of mets resection and a longer duration of PFS for TKI at any line. In this selected population, no prognostic factor is associated with long OS.

11042 Poster Session (Board #365), Sun, 8:00 AM-11:30 AM

Analysis of tumor-infiltrating immune cells in gastrointestinal stromal tumors (GIST) after tyrosine kinase inhibitor therapy. *First Author: Peter Hohenberger, Division of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Centre, University of Heidelberg, Mannheim, Germany*

Background: There is initial evidence that immune-infiltrates of tumor may correlate with the clinical course of patients with GIST beyond the response to tyrosine kinase inhibitors (TKI) according to the mutational status. We were interested to analyze the composition of tumor-infiltrating immune cells in GIST tumor tissues after different TKI regimens vs untreated controls. **Methods:** From 40 GIST patients who were treated with imatinib alone (neoadjuvant group) and other TKIs (M1 HEP group, progressing on more than ≥2 TKI inhibitors) prior to tumor removal, surgical specimens were available at ten 10 cases each,. They were compared with 20 untreated primary tumors graded for malignant behaviour (low vs high risk) acc. to Miettinen&Lasota 2006. 2-μm sections of formalin-fixed, paraffin-embedded tissue samples were used for IHC-staining anti-CD68 (Dako); anti-CD11c, anti-CD11b, anti-FOXP3 (all Abcam); anti-CD163, anti-CD4 , anti-CD8 (all Leica). Evaluation was performed with Dako REAL EnVision Detection System (K5007). The phenotypes of immune cells were compared in the defined GIST groups. In the neoadjuvant group we used recurrence-free survival (RFS) for correlation, and overall survival (OS) after TKI failure in the M1 HEP group. **Results:** Foxp3+ Tregs, CD163+ M2 macrophages and CD11b+ myeloid cells are significantly higher in TKI resistance or neoadjuvant (viable cells > 30%) tissues compared with neoadjuvant (viable cells < 10%) cases. The rate of CD11c+ M1 macrophages is higher in low-risk GISTs compared to high risk GISTs, but CD11b+ myeloid cells are exactly the opposite. Kaplan-Meier curves show high CD163+ M2 macrophages or CD11b+ myeloid cells to correlate significantly with worse RFS in after neoadjuvant IM (p 0.01). In the TKI resistant condition, patients with high CD11c+ M1 macrophages show better median OS (p = 0.07, ns). **Conclusions:** Our study reveals dynamic changes of tumor-infiltrating immune cell protagonists in GISTs after different TKI therapeutic regimen and after neoadjuvant treatment. We could not detect a different immune infiltrate in untreated primary tumors of different risk categories.

11043 Poster Session (Board #366), Sun, 8:00 AM-11:30 AM

Impact of pharmacogenomics on imatinib toxicity in gastrointestinal stromal tumors. *First Author: Wei Zhuang, Sun Yat-Sen University, Guangzhou, China*

Background: Imatinib-induced side effects are common, although most of these side effects are mild, some will be severe and lead to disruption of Imatinib treatment in gastrointestinal stromal tumor (GIST). It is necessary to explore a biological predictors to predict and optimal therapeutic strategy. But there were few studied conducted to explore the mechanisms of Imatinib-induced side effects. The present study comprehensively investigated the effects of genetic polymorphisms of cytokines involved in cell proliferation and metabolic enzymes and transporters involved in Imatinib metabolism on these side effects. **Methods:** A total of 154 GSIT patients treated with Imatinib were enrolled. 22 SNPs (single nucleotide polymorphisms) in *KIT/ PDGFRA/ PDGFRB/ SHC1/ FLT1/ MAPK1/ EGFR/ CCL5/ CXCL14*were detected using Agena Massarray matrix-assisted laser desorption / ionization-time of flight (MALDI-TOF) platform. Logistic regression analyses were performed to evaluate their effects on Imatinib-induced toxicities. This study was approved by the ethical committee of Sun Yat-Sen University Cancer Center. **Results:** Imatinibdose, *FLT1* rs9951465, *MAPK1* rs13515, *PDGFRB* rs55712339 and *SHC1* rs3766920 were found to be correlated with the incidence of myelosuppression (*P*= 0.027, 0.009, 0.002, 0.008, < 0.001, respectively), moreover, *FLT1* rs9554314 was correlated with severe myelosuppression (Grade 0,1 vs. 2+, *P*= 0.009, OR (95%CI) = 3.042 (1.314-7,042)). Meanwhile, *EGFR* rs10228436 was found to be correlated with the incidence of skin rash (*P*= 0.027), moreover, *CCL5* rs4796120 and *CXCL14* rs7716492 were correlated with severe skin rash (Grade 0,1 vs. 2+), with OR (95%CI) and p value were 8.542 (0.934-78.107), 13.504 (2.308-79.004) and 0.057, 0.020, respectively. **Conclusions:** This is the first comprehensive report on the biomarkers for Imatinib toxicities. These biomarkers might be able to distinguish patients with mild or more severe forms of Imatinib toxicities, thus enabling the optimization of Imatinib therapy and lead patients benefit from Imatinib treatment in a long-term.

11044 Poster Session (Board #367), Sun, 8:00 AM-11:30 AM

LMTK3 as a novel regulator of oncogenic KIT in KIT-mutant cancers. *First Author: Lillian Rose Klug, Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR*

Background: Multiple cancers, such as gastrointestinal stromal tumors (GIST) and melanoma, have been shown to be caused by somatic activating mutations in the receptor tyrosine kinase KIT. The major cause of death in patients with advanced KIT-mutant cancers is due to the development of KIT tyrosine kinase inhibitor-resistant (TKI-resistant) metastatic disease. Drug resistance arises almost exclusively from secondary mutations within KIT, highlighting the importance of KIT in the proliferation and survival of these tumors. **Methods:** We performed a human kinase siRNA screen in multiple KIT-mutant cancer cell lines using viability as a read out. We defined candidate targets as those whose knockdown decreased viability in all cell lines. Validation and mechanistic studies were done using a library of KIT-mutant GIST and melanoma cells. **Results:** We identified lemur tyrosine kinase 3 (LMTK3) as candidate target in three KIT-mutant cell lines. LMTK3 silencing reduced the viability of all KIT-mutant GIST and melanoma cells tested to date, including cell lines with KIT TKI-resistance mutations. Importantly, LMTK3 silencing decreased the viability of KIT-mutant cells specifically, but not that of KIT-independent GIST and melanoma cells. Further, we found that decreased cell viability was due to induction of apoptosis, as assessed by measuring caspase 3 and 7 activity within 96 hours of LMTK3 silencing. LMTK3 knockdown also reduced tumor growth *in vivo* in a GIST xenograft model. Because these cells depend so heavily on KIT and the loss of KIT signaling results in cell death, we hypothesized that LMTK3 silencing may affect this pathway. Indeed, LMTK3 silencing decreased levels of autophosphorylated KIT. We also observed a significant decrease in total KIT protein expression. This phenotype and corresponding viability was rescued with exogenous expression of full length LMTK3. **Conclusions:** LMTK3 is an important regulator of oncogenic KIT expression and activity in KIT-mutant GIST and melanoma and represents a novel, tractable target.

11045 Poster Session (Board #368), Sun, 8:00 AM-11:30 AM

Prognostic factors of recurrence and survival of gastrointestinal stromal tumors: First multicentric study of Mexico. *First Author: Rafael Medrano Guzman, Hospital De Oncologia Centro Medico Nacional Siglo XXI, Mexico, Mexico*

Background: Gastrointestinal stromal tumors are mesenchymal lesions arising from the interstitial cells of Cajal. In GIST the location, size, number of mitosis and risk group are accepted as prognostic factors; some factors in which there are still controversies about their value as prognostic factors include male gender, tumor cellularity, the margins of resection, the presence or absence of p16 or intraperitoneal tumor breakdown. **Methods:** Observational, retrospective and longitudinal study. Patients admitted to the Oncology Hospital, CMN Siglo XXI of January 1, 1991 to April 30, 2012. **Results:** We identified 384 patients, the mean follow-up time was 55.86 months, the mean age was 58 years, 80.3% had symptoms and only 4.54% the finding was incidental. The most common site was the stomach (66.6%), followed by small intestine (28.7%) and colon (1.54%). The 7.57% had metastases at diagnosis, 4.54% in liver and 3.03% in the peritoneum. Were expressed by abdominal pain (39.39%) and gastrointestinal bleeding (30.30%), intestinal obstruction in 1.5%. The most common site was the stomach (66.6%), followed by small intestine (28.7%) and colon (1.54%). The 7.57% had metastases at diagnosis. The average tumor size was 10.84 cm (2.2 to 38 cm). Immunohistochemical markers were studied: 94.28% positive for CD117, CD34 74.28%, 11.42% S100 protein, desmin 5.71% and 51.72% for smooth muscle actin (AML). Overall rate at 5 years and 82% rate of recurrence-free survival at 5 years and 61% survival. The location of the tumor ($p = 0.0002$), size ($p = 0.03145$), the number of mitosis ($p = 0.008$), risk group ($p = 0.020$) and adjuvant treatment with Imatinib showed a statistically significant difference for Survival Recurrence-free. For overall survival, lesion location was the only factor that showed statistical significance with $p = 0.0054$. **Conclusions:** The tumor location, size, number of mitosis, the risk group and adjuvant treatment with Imatinib were statistically significant prognostic factors for disease recurrence. The location of the lesion was the only factor that showed statistical significance as a predictor of overall survival.

11046 Poster Session (Board #369), Sun, 8:00 AM-11:30 AM

Influence of chemotherapy combined with radiotherapy on the time-to-development of radiation-induced sarcomas: A multicenter, retrospective analysis. *First Author: Alison Yan Zhang, Northern Beaches Cancer Service, Manly, Australia*

Background: An increasing number and proportion of cancer patients with apparently localised disease are treated with chemotherapy and radiation therapy in contemporary oncology practice. In a pilot study of radiation-induced sarcoma (RIS) patients, we demonstrated that chemotherapy was associated with a reduced time to development of RIS. We now present an international multi-centre collaborative study to validate this association. **Methods:** This was a retrospective cohort study of RIS cases across five large international sarcoma centres between the 1st January, 2000 to 31st December, 2014. The primary endpoint was time to development of RIS, defined as the date of diagnosis of the first malignancy to date of the RIS diagnosis. We also assessed the relationship between chemotherapy, patient and cancer characteristics, and time to RIS. **Results:** We identified 419 patients with RIS, who were predominantly diagnosed with their first malignancy at adulthood. The median interval from the index cancer to development of RIS for the entire cohort was 11 years (range 1-64). Chemotherapy for the first malignancy was associated with a shorter time to RIS development (HR 1·37; 95% CI: 1·08-1·72; $P = 0·009$). In the multi-variable model, older age (HR 2·11; CI 1·83-2·43; $P < 0·001$) and chemotherapy for the first malignancy (HR 1·61; CI 1·26-2·05; $P < 0·001$) were independently associated with a shorter time to RIS. Anthracyclines and alkylating agents significantly contribute to the effect. **Conclusions:** This study confirms an association between chemotherapy given for the first malignancy and a shorter time to development of a RIS. Our data highlights the importance of vigilance in surveillance for RIS after chemotherapy and radiation therapy, particularly in younger patients who also have a longer potential time to develop a second malignancy.

11047 Poster Session (Board #370), Sun, 8:00 AM-11:30 AM

Prognosis of desmoid tumors (DT): A prospective nationwide survey of 771 patients (pts). *First Author: Thomas Ryckewaert, Centre Oscar Lambret, Lille, France*

Background: Prognostic factors and optimal management of DT are not yet established. **Methods:** We analyzed the outcome of 771 consecutive DT pts treated between 01/2010 and 12/2016 in France. We have calculated event-free survival (EFS) defined as local relapse after surgery, progressive disease during non surgical approach or change in treatment strategy (e.g. from wait and see to systemic treatment or local treatment). **Results:** The sex ratio M/F was 219/552, the median age was 39 (2-90), and the median size 57 mm (4-700). 596 DT are found *CTNNB1*-mutated (71%). The 1st treatment was wait and see (369, 48%), surgery (343, 44%), systemic treatment (25, 3%), or radiotherapy (3, 0%). The median follow-up was 32 mo. 230 events occurred (including 1 death). The median EFS was 27 mo. After initial wait and see, pts required systemic treatment in 61 cases (15%), radiotherapy (4; 1%), cryotherapy (3; 1%), surgery (2; 0%) and radiofrequency (1, 0%). After initial surgery, DT pts required wait and see for relapse in 88 cases (25%), systemic treatment in 17 cases (5%), radiotherapy (6; 2%), cryotherapy (2; 0%) and surgery (1, 0%). Univariate analysis identified 3 factors associated with EFS: favorable locations (median not reached (NR) vs. 21 mo; $p = 0.0001$), nature of sampling (core needle biopsy: 31 mo; resection 26 mo and open biopsy 15 mo, $p = 0.046$) and superficial DT (NR vs. 28 mo, $p = 0.00001$). Favorable locations included: abdominal wall (236 pts), intra-abdominal (78 pts), breast (27 pts) and digestive viscera (42 pts). Chest wall (209 pts), head and neck (28 pts), lower limb (90 pts), upper limb (25 pts) and pelvis (18 pts) were all associated with poor EFS. Multivariate analysis identified only 1 prognostic factor for EFS: favorable location HR = 0.52 [0.39-0.69]. Compared to surgery, wait and see as 1st treatment was associated with better EFS in unfavorable DT locations (HR = 0.74 [0.74-0.56]; $p = 0.001$) but not associated with EFS in favorable locations (HR = 0.89 [0.69-1.13]; $p = 0.420$). **Conclusions:** Since primary location of DT is the major determinant of DT outcome, stratified approach according to location has to be prospectively assessed. Correlative biology analyses are warranted to better understand these findings.

11048 Poster Session (Board #371), Sun, 8:00 AM-11:30 AM

Tumor volume score (TVS), modified recist, and tissue damage score (TDS) as novel methods for assessing response in tenosynovial giant cell tumors (TGCT) treated with pexidartinib: Relationship with patient-reported outcomes (PROs). *First Author: Charles Peterfy, Spire Sciences, Inc., Boca Raton, FL*

Background: TGCT is a locally aggressive neoplasm of joint and tendon sheath synovia that may cause pain, limit joint function and destroy bone and local tissues. Measuring TGCT with RECIST is a challenge due to irregular shape and asymmetrical growth, and local tissue damage is not assessed. We reported earlier results of a longitudinal trial of pexidartinib, a selective CSF1R kinase inhibitor, using RECIST as well as novel TVS, modified RECIST and TDS. Here we examine concordance of these MRI measures with PROs. **Methods:** Patients (pts) with progressive TGCT in a single-arm, multi-center trial of pexidartinib (1000 mg po daily) were assessed by MRI every 2 months by 2 central radiologists (blind to visit order). For RECIST, longest measurable dimensions of up to 2 tumors per joint or tendon sheath were summed (SLD). Modified RECIST summed short axis dimensions (SSD). TVS was based on 10% increments of the estimated maximally distended normal synovial cavity or tendon sheath. TDS scored bone erosion (ERO), cartilage loss (CAR) and bone marrow edema (BME) in multiple regions of each joint. The relationship with PROs (Worst Pain numerical rating scale [NRS] and Worst Stiffness NRS) was assessed. **Results:** 15 pts (7 knees, 3 hips, 2 ankles, 1 elbow, 1 wrist, 1 thigh) with PRO data and evaluable MRI scans at baseline and Month 7 were assessed. All SLD, SSD and TVS scores improved with respective median changes of -25%, -39% and -50%. Baseline ERO, CAR, and BME ranged 0-19, 0-34, and 0-15, respectively. Median change for each was 0%: ERO worsened in 1 pt, CAR did not change, and BME improved in 4 and worsened in 2. Worst Pain NRS and Worst Stiffness NRS improved in 11 and 9 pts, respectively. **Conclusions:** TVS demonstrated the greatest pexidartinib effect size, followed by SSD and then conventional RECIST. All had good concordance with PROs. Clinical trial information: NCT01004861.

Concordance of MRI measures with PROs.

	Pain improved (Yes)	Pain improved (No)	Stiffness improved (Yes)	Stiffness improved (No)
SLD improved (Yes)	11	1	9	3
SLD improved (No)	0	0	0	0
SSD improved (Yes)	11	2	9	4
SSD improved (No)	0	0	0	0
TVS improved (Yes)	10	2	8	4
TVS improved (No)	1	0	1	0

11049 Poster Session (Board #372), Sun, 8:00 AM-11:30 AM

Elevated preoperative peripheral blood neutrophil-to-lymphocyte ratio to predict clinical outcome in patients with localized soft tissue sarcoma. *First Author: Jason Yongsheng Chan, National Cancer Centre Singapore, Singapore, Singapore*

Background: Recent studies suggest that markers of systemic inflammation such as blood neutrophil-to-lymphocyte ratio (NLR) may be prognostic for various cancers, though its clinical utility has not been widely accepted. This study aims to investigate its clinical relevance in patients (pts) with soft tissue sarcoma (STS). **Methods:** Five hundred and twenty-nine pts with localized STS who had available pre-operative blood counts at the time of diagnosis were retrospectively examined. An optimal cutoff for high NLR (>2.5) in predicting overall survival (OS) and relapse-free survival (RFS) in pts who underwent curative surgery (n = 473) was determined using receiver operating curve analyses. Cutoffs for platelet-lymphocyte ratios (PLR, >180) and lymphocyte-monocyte ratios (LMR, <3.6) were similarly obtained. Survival analysis was performed using the Kaplan-Meier method and multivariate Cox proportional models. Median follow-up was 40 months. **Results:** A high NLR was present in 311 (58.8%) pts, which was significantly associated with tumor grade ($p<0.0001$), depth ($p=0.003$) and size >5 cm ($p=0.0242$), but not with age at diagnosis, sex or ethnicity. High NLR was associated with both worse OS (HR 1.78; 95%CI 1.28-2.47; $p=0.0005$) and RFS (HR 1.54; 95%CI 1.17-2.03; $p=0.0019$), as were age at diagnosis, tumor grade, size, PLR and LMR. In multivariate models adjusted for clinicopathological predictors of survival, only NLR, in addition to tumor grade and size, were independently associated with worse OS (HR 1.52; 95%CI 1.09-2.11; $p=0.0131$) and RFS (HR 1.42; 95% CI 1.08-1.85; $p=0.0114$). Analysis of survival according to American Joint Committee on Cancer (AJCC) stages subdivided as NLR-high and NLR-low revealed a significant worse prognosis for NLR-high subgroups ($p<0.0001$), with a 2.2-fold and 1.5-fold higher risk of death within stages II (HR 2.20; 95%CI 1.20-4.01; $p=0.0103$) and III (HR 1.55; 95%CI 1.01-2.37; $p=0.0459$), respectively. **Conclusions:** High NLR is an independent marker of poor prognosis among pts with localized STS. Inclusion of NLR as a classifier into the AJCC staging of STS may improve estimation of survival.

11050 Poster Session (Board #373), Sun, 8:00 AM-11:30 AM

A pilot trial of irinotecan, temozolomide and bevacizumab (ITB) for treatment of newly diagnosed patients with desmoplastic small round cell tumor (DSRCT). *First Author: Heather D. Magnan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: DSRCT is a rare tumor with a dismal prognosis in the setting of current treatment options. Preclinical data suggested that VEGF-dependent angiogenesis is important for DSRCT tumor biology and that targeting angiogenesis with bevacizumab in combination with irinotecan was more effective than treatment with irinotecan alone. This pilot study was designed to explore the safety and feasibility of adding ITB to the existing "P6- like" regimen used to treat DSRCT. **Methods:** Fifteen patients with newly diagnosed DSRCT were enrolled onto this single-institution study. They began treatment with 2 cycles of irinotecan (20 mg/m2/dose x 10 days) and temozolomide (100 mg/m2/dose x 5 days). Bevacizumab 10 mg/kg q2 weeks was added after sufficient time had passed from initial biopsy or surgery. Patients were then treated with cycles of alkylator based chemotherapy (3 cycles of cyclophosphamide, doxorubicin, vincristine and 3 cycles of ifosfamide, etoposide). An initial surgical resection was performed after cycle 5 and a second resection or second look surgery after cycle 8. Toxicity was graded according to CTCAE v.4.0. Secondary efficacy objectives were assessed using RECIST 1.1 criteria and the Kaplan Meir method. **Results:** 14 of 15 patients completed planned protocol therapy. One patient was taken off study due to complications associated with surgery after cycle 5 of chemotherapy. Stopping rules for unacceptable toxicity were not met. No patients experienced toxicity attributed to bevacizumab, and surgical morbidity was no greater than expected. Grade 3 diarrhea associated with irinotecan was experienced by 2 patients. Expected toxicities with "P6-like" cycles included grade 3/4 hematologic toxicity and admissions for febrile neutropenia in all patients. Response rate to the ITB cycles was 27% (95% CI 8-55%) and to the 5 pre-resection cycles was 73% (95% CI 45-92%). Median time to progression was 18.1 months. Overall survival at 1 year was 100% and 3 years 61% (95% CI 25-84%). **Conclusions:** The combination of ITB is active in patients with DSRCT, and it is feasible to combine these agents with standard chemotherapy without greater than expected toxicity. Clinical trial information: NCT01189643.

11051 Poster Session (Board #374), Sun, 8:00 AM-11:30 AM

Administration of aldoxorubicin and 14 days continuous infusion of ifosfamide/mesna in metastatic or locally advanced sarcomas. *First Author: Frederick C. Eilber, University of California, Los Angeles, Los Angeles, CA*

Background: Aldoxorubicin (A) has demonstrated superior anti-tumor efficacy and lack of cumulative cardiac toxicity in multiple studies. A is doxorubicin (D) with a linker which rapidly binds in vivo to albumin after iv. We studied the combination of A administered on Day 1 with continuous infusion (CI) of ifosfamide/Mesna (I-M) days 1-14, as first line therapy or second line therapy in patients with soft tissue sarcomas (STS) to evaluate efficacy and toxicity. **Methods:** 27 patients have entered the study at 250 mg/m2 (185 mg/m2 D equiv) administered on Day 1. I-M (1 g/m2 of each per day) was given up to 14 days as a CI via an out-patient portable pump. Chemotherapy cycles were repeated at 28 day interval. I-M was limited to a maximum of 6 cycles to avoid cumulative marrow toxicity, but A was continued per investigator decision in responding or SD patients for clinical benefit. Subjects were followed for tumor response (RECIST 1.1) by CT scans and echocardiogram/ECG for cardiac toxicity every 8 weeks along with standard labs. Enrollment continues up to 50 patients. **Results:** Demographics: Leiomyosarc. = 20%, liposarc. = 20%, synovial sarc. = 20%, rhabdosarc. = 8%, others = 32%. Caucasian, 11% Asian, 4% Black; 67% no prior tx, 26% 1 prior tx, 7% >1 prior tx; Median cum. A = 1000 mg/m^2 (740 mg/m^2 D eq.; 185-4070 mg/m^2 D eq.); I = 6.9 g/m^2 (2.1-12.6 g/m^2). Best response: 42% PR, 58% SD. Median PFS not reached. 10 subjects with either PR or SD had surgery to remove accesible tumors. Range of tumor necrosis = 70 to >95%. Grade 3/4 AEs: neutropenia = 78%, febrile neutropenia = 9%, thrombocytopenia = 22%, anemia = 65%, nausea = 4%. Related SAEs = 4 (febrile neutropenia (2), pyrexia, stomatitis). No tx related deaths. No clinically significant cardiac AEs, no decrease in LVEF >20% **Conclusions:** A can be administered for prolonged periods and safely with CI ifosfamide/mesna and achieves high ORR and SD with substantial tumor necrosis. Clinical trial information: NCT02235701.

11052 Poster Session (Board #375), Sun, 8:00 AM-11:30 AM

Post-cross-over activity of regorafenib (RE) in soft tissue sarcoma: Analysis from the REGOSARC trial. *First Author: Nuria Kotecki, Oscar Lambret Center, Lille, France*

Background: Based on the placebo (PBO) controlled phase 2 trial (Mir, Lancet Oncol 2016), RE has shown to be an active drug in patients (pts) with leiomyosarcoma (LMS), synovial sarcoma (SS) and other non-adipocytic sarcoma (OTH), but not in liposarcoma. Pts initially allocated to PBO were allowed to cross-over to RE after progression. We here report the activity of RE after cross-over. **Methods:** From July 2013 to Dec 2014, 138 pts were enrolled in the non-adipocytic sarcoma cohorts (LMS, SS & OTH). After update in Dec 2016, median follow-up was 32 mo (vs 17 mo in the initial publication). Benefit of RE vs PBO in terms of progression-free survival (PFS) and overall survival (OS) from randomization was estimated by hazard ratio (HR) in Cox models. In the PBO arm, intra-patient benefit of RE after cross-over was evaluated by the growth modulation index (GMI), where PFS1=PFS with PBO before cross-over, and PFS2=PFS with RE after cross-over. The impact of timing of RE allocation (delayed after cross-over, vs early at study entry) was evaluated by comparing PFS after cross-over in PBO arm to PFS after randomization in RE arm. **Results:** As detailed in the table, major PFS benefit of RE vs PBO allocated by randomization was confirmed with long follow-up (HR=0.50 [95%CI 0.35-0.71] p<.0001). However, this translates into a smaller and non-significant OS benefit (HR=0.78 [0.54-1.12] p=.18). This finding may partially be explained by the fact that 55 of the 68 pts who progressed in the PBO arm (81%) could receive RE after progression and benefit from RE: 56% of them had a GMI greater than 1.3. Delayed start of RE was associated with a non-significantly shorter PFS compared to earlier treatment (HR=1.21, [0.84-1.73] p=.30). **Conclusions:** Efficacy of RE vs PBO is confirmed with longer follow-up in non-adipocytic sarcoma. PFS of pts receiving RE after cross-over is not significantly shorter than that of pts initially randomized to receive RE. Clinical trial information: NCT01900743.

	RE at randomization		PBO at randomization		RE post cross-over (PBO arm)		RE vs PBO post-randomization		Delayed vs early RE	
	N	PFS (mo)	N	PFS1 (mo)	N	PFS2 (mo)	HR	p	HR	p
LMS	28	3.7	28	1.8	22	2.6	0.60	.059	1.35	.31
SS	13	3.8	14	1.0	13	2.0	0.09	<.0001	1.45	.36
OTH	28	2.9	27	1.0	20	2.8	0.57	.04	1.00	.99
All	69	3.7	69	1.0	55	2.6	0.50	<.0001	1.21	.30

11053 Poster Session (Board #376), Sun, 8:00 AM-11:30 AM

Combination of pembrolizumab and metronomic cyclophosphamide in patients with advanced sarcomas and GIST: A French Sarcoma Group phase II trial. *First Author: Maud Toulmonde, Institut Bergonié, Department of Medical Oncology, Bordeaux, France*

Background: There is a good rationale for immunotherapy in sarcoma. We report results of the first open-label multicentre phase 2 study assessing the anti-PD-1 antibody pembrolizumab in combination with metronomic cyclophosphamide (CP) in patients (pts) with advanced soft tissue sarcomas (STS) and gastro-intestinal stromal tumor (GIST). **Methods:** This trial included 4 cohorts of pts with advanced STS: leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS), other sarcomas (Others), and GIST. All pts received CP 50 mg BID one week on, one week off, and pembrolizumab 200mg IV q21 days. The primary endpoint encompassed non-progression and objective response at 6 months per RECIST evaluation criteria v1.1 for LMS, UPS, and Others, and 6-month non-progression for GIST. Correlative studies of immune biomarkers were planned on pt's tumor and plasma samples. **Results:** Between June 2015 and July 2016, 57 pts were included, and 50 were assessable for efficacy. Three pts experienced tumor shrinkage resulting in a partial response (PR) in one of them. The 6-month non-progression rate was 0%, 0%, 14.3% (95%CI 1.8-42.8), and 11.1% (95%CI 2.8-48.3) in LMS, UPS, Others, and GIST respectively. The most frequent adverse events were grade 1 or 2 fatigue, diarrhea, anemia. The only pt who experienced PR was the only one with a PD-L1-positive staining in more than 10% of immune cells on archived tumor sample. A strong macrophage infiltration was observed in tumor samples, and these macrophages largely expressed the inhibitory enzyme Indoleamine-2,3-dioxygenase-1 (IDO1). Moreover, a significant increase of the kynurenine/tryptophane ratio was observed in pts plasma samples during study treatment (p =0.0007). **Conclusions:** PD-1 inhibition has limited activity in advanced STS and GIST. This primary resistance may be explained by the low percent of PD-L1 positivity in these tumors, and an immune-suppressive tumor microenvironment resulting from macrophage infiltration and IDO1 pathway activation. Further strategies assessing drugs such as CSF1-R inhibitors and/or IDO inhibitors combined with anti-PD-1/PD-L1 in selected sarcoma subtypes are warranted. Clinical trial information: NCT02406781.

11054 Poster Session (Board #377), Sun, 8:00 AM-11:30 AM

SYNFRIZZ: A first-in-human (FIH) study of a radiolabeled monoclonal antibody (Mab) targeting frizzled homolog 10 (FZD10) in patients (pts) with advanced synovial sarcomas (SyS). *First Author: Philippe Alexandre Cassier, Centre Léon-Bérard, Lyon, France*

Background: Advanced SyS are rare tumors with limited curative options. FZD10 is highly expressed in SyS but not in normal adult tissue. OTSA101 is a MAb targeting FZD10, labelled with a radioisotope. **Methods:** We conducted a phase I, FIH study including adult pts with advanced, refractory SyS. In part 1, pts received OTSA101 labelled with In^{111} used as radiotracer to assess biodistribution and tumor uptake. In part 2, pts with significant tumor uptake were randomized to receive OTSA101 labelled with 370MBq of Y^{90} (Arm A) or 1110MBq Y^{90} (Arm B). Primary endpoints were occurrence of unacceptable biodistribution /lack of tumor uptake in part 1 and occurrence of related adverse events (AEs) Grade ≥ 3 during the first 8 weeks following injection of Y^{90}OTSA101 in part 2. Responses were assessed per RECIST 1.1. **Results:** From January 2012 to June 2015, 20 pts (10 females, median age 43, range 21-67) with advanced SyS were enrolled. Ten pts (50%) had sufficient tumor uptake to proceed to part 2 and 8 were randomized (Arm A: 3 and Arm B: 5). Two pts were not randomized due to worsening PS. During part 2, the most common Grade ≥ 3 AEs were haematological, including reversible lymphopenia, thrombocytopenia and neutropenia, and were more common in Arm B. One pt with SD after 12 weeks received a 2nd injection of ^{90}Y-OTSA101, but experienced fatal hemoptysis. No objective response was observed. Best response was SD in 5/8 pts lasting up to 21 weeks for 1 pt. **Conclusions:** This FIH shows that radioimmunotherapy targeting FZD10 is feasible and safe in SyS pts. Tumor uptake was heterogeneous but sufficient to select 50% of pts for ^{90}Y-OTSA101 treatment. Due to limited sample size, further clinical investigations are needed to assess the therapeutic activity of ^{90}Y-OTSA101 with a recommended dose of 1110MBq of ^{90}Y. Clinical trial information: NCT01469975.

11055 Poster Session (Board #378), Sun, 8:00 AM-11:30 AM

Outcome of 212 malignant phyllod tumor patients: A retrospective study from the French Sarcoma Group (GSF-GETO). *First Author: Mathias Neron, Institut du Cancer de Montpellier, Montpellier, France*

Background: The optimal management of malignant phyllod tumors (MPT) is poorly documented. Objective:To study the characteristics and outcome of MPT patients (pts). **Methods:** Retrospective study from the nation-wide French sarcoma network (NetSarc) from 2000 to 2016. Inclusion criteria was central pathological review of MPT. End-points were local recurrence-free survival (LRFS), metastasis-free survival (MFS), and overall survival (OS). **Results:** 212 pts, from 13 centers, were included. Median age was 52.8 years (range: 16.8 - 90.5). All localized MPT pts (96.7%) underwent surgery with 41.4% of mastectomy. The median size was 5.8 cm (range: 1.5 - 30). R1/R2 resection was achieved in 40.1% pts (26.9% 1-2 mm margin, 12.2% 3-7 mm, 20.3% ≥8 mm), with 44.8% of second surgery (SS) for a final mastectomy rate of 72.6%. Presurgical biopsy was performed in 86.3% and associated with R0 resection (p=0.044) and better LRFS (p=0.012). Median follow-up was 4.1 years (range 0-14.8) and revealed 34 (16.6%), 48 (22.9%), 44 (20.8%) events for LRFS, MFS and OS, respectively. The 2-year OS rate was 89%. Prognostic factors found in multivariate analysis are presented in Table 1. Wider margins (≥8mm) were not associated with better outcomes. Adjuvant radiotherapy and chemotherapy were performed in 43.6% and 13.3% respectively and associated with longer LRFS, not significant in multivariate analysis. **Conclusions:** Mastectomy is associated with better local control, but not with MFS and OS. Age, tumor necrosis and metastatic disease are associated with poor prognosis in MPT pts. Our study suggests that margins of 3 mm are necessary and sufficient for the surgical management of MPT and emphasizes the importance of SS to obtain clear margins.

Prognostic factors for each end-point (multivariate analysis).

End Point	Variable		Hazard Ratio	p
LRFS	Mastectomy at first or SS	Yes	1	<0.001
		No	4,85	
	Margins (mm)	0-2 without SS	1	
		0-2 with SS	0,82	0,62
		≥ 3	0,68	0,42
MFS	Age (y)	<50	1	0.038
		≥50	2.14	
	Tumor necrosis	Yes	1.96	0.047
		No	1	
	Margins (mm)	0-2 without SS	1	
		0-2 with SS	0,3	0,005
		≥ 3	0,75	0,43
OS	Metastatic disease at diagnosis	Yes	5.27	0.002
		No	1	
	Metastatic recurrence	Yes	7.29	<0.001
		No	1	
	Margins (mm)	0-2 without SS	1	
		0-2 with SS	0,32	0,005
		≥ 3	0,55	0,099

11056 Poster Session (Board #379), Sun, 8:00 AM-11:30 AM

Effects of temozolomide and bevacizumab in relapsed patients with heavily pretreated uterine leiomyosarcoma. *First Author: Hiroko Matsuura, National Defense Medical College, Tokorozawa, Japan*

Background: Uterine leiomyosarcomas (ULMs) tend to recur regardless of their stage, and there is no satisfactory report for relapsed ULMs. Temozolomide (T) is derivatives of dacarbazin and these agents have been used for treatment of ULMs. ULMs has a plenty of vessels compared to uterine myoma so that bevacizumab (B) was used in ULMs. In the present study, we evaluated the effect of TB in heavily pretreated relapsed ULMs. **Methods:** From 2009 to 2016, total 19 patients (pts) with heavily pretreated ULMs were enrolled. Patients were treated with T (80mg/body/day) and B (2mg/kg; days 1, 8 and 15, q4 weeks). Treatment was continued until disease progression and/or unmanageable toxicities. Response was evaluated with the response evaluation criteria in solid tumors (RECIST) v1.1, and adverse effect (AE) was assessed by common terminology criteria for adverse events (CTCAE) v4.0. **Results:** Seventeen of 19 pts were subjected to response evaluation. Median age of pts was 56.3 years (range: 31-69). Three pts (18%) had complete response (CR), 2 (12%) had partial response, and 7 (41%) had stable disease (SD). The response rate (RR: CR+PR) and clinical benefit rate (CBR: CR+PR+SD) were 29% and 71%. The median progression-free survival was 14.2 months (range: 0-89). Median administration cycle was 9.5 (range: 2-48). AE with grade 3 and more over were observed in 6 pts. There was one dead case from perforation, but toxicity was almost manageable. **Conclusions:** We experienced 3 cases of CR, and two of them had CR for more than two years. Intriguingly, TB could be substantially effective even in relapsed patients with heavily pretreated ULMs. These results warrant further prospective and randomized studies.

11057 Poster Session (Board #380), Sun, 8:00 AM-11:30 AM

Phase 2 multicenter study of the EZH2 inhibitor tazemetostat in adults with synovial sarcoma (NCT02601950). *First Author: Patrick Schoffski, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium*

Background: Synovial sarcoma (SS) accounts for 5-10% of all soft tissue sarcomas (STS). Metastatic and/or locally advanced disease occurs in up to 70% of patients (pts), with reported median overall survival (OS) as short as 22 months. SS18-SSX translocations, a defining molecular feature of SS, generate a fusion protein that competes with native SS18 during SWI/SNF complex assembly disrupting complex function. SWI/SNF complexes containing the fusion protein lack INI1 and cellular INI1 expression levels are reduced to varying degrees in SS. This mechanism of INI1 reduction is distinct to that observed in malignant rhabdoid tumors, epithelioid sarcoma or other INI1 negative tumors. Tazemetostat, a potent and selective EZH2 inhibitor, has demonstrated activity in preclinical SS models with the proposed mechanism of sensitivity being via INI1 reduction inducing compromised SWI/SNF activity and tumor dependence on EZH2. **Methods:** This is a phase 2 multicenter open-label non-randomized study with 5 cohorts of different tumor types with INI1 loss/reduction or evidence of SS18 rearrangement. Adult pts in the SS cohort were treated with tazemetostat (800 mg po BID). Up to 30 pts were enrolled using a 2-stage Green-Dahlberg design. The primary endpoint is complete response, partial response or stable disease (SD) at 16 wks. Success at the end of stage 2 requires $\geq$9 of 30 treated pts meet this criterion. Key secondary endpoints include overall response rate, PFS, OS, safety/tolerability, PK and biomarkers of response. **Results:** In 33 treated SS pts with a median of 2 prior systemic treatments, best response of SD was observed in 11 pts (33%) with 5 pts (15%) having SD lasting $\geq$16 wks. No objective responses were observed. The protocol-defined success criterion at the end of study was not met. Tazemetostat was well-tolerated with grade 1/2 cough (36%), dyspnea (33%) and fatigue (33%) as the most frequently reported adverse events regardless of attribution. **Conclusions:** Tazemetostat was well tolerated with a favorable safety profile. Although there were no objective responses in heavily pretreated pts, the observation of SD in a subset of pts suggests further studies with tazemetostat in combination may be warranted in SS. Clinical trial information: NCT02601950.

11058 Poster Session (Board #381), Sun, 8:00 AM-11:30 AM

Phase 2 multicenter study of the EZH2 inhibitor tazemetostat in adults with INI1 negative epithelioid sarcoma (NCT02601950). *First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Epithelioid sarcoma (ES) is a rare soft tissue sarcoma (STS) typically seen in young adults accounting for $<$ 1% of all STS. While local disease may be indolent, ES can rapidly spread and patients (pts) with distant metastasis are often resistant to systemic treatment with 1 year survival of $<$ 50%. The defining molecular feature of ES is the absence of tumor expression of INI1, a SWI/SNF subunit member involved in chromatin remodeling. Tazemetostat, a potent and selective EZH2 inhibitor, has demonstrated tumor regressions in INI1 negative preclinical malignant rhabdoid tumors (MRT) models and phase 1 clinical activity in MRT and ES pts. The proposed mechanism of tazemetostat sensitivity is INI1 loss inducing compromised SWI/SNF activity and tumor dependence on PRC2 activity (of which EZH2 is the catalytic subunit). Preliminary phase 2 safety and efficacy of tazemetostat in ES pts is reported here. **Methods:** This is a phase 2 multicenter open-label single arm study of tazemetostat (800 mg po BID) in adult pts with ES whose tumors harbor evidence of INI1 loss. Pts enroll into 1 of 5 cohorts of different tumor types with INI1 loss/reduction, up to 30 pts each, using a 2-stage Green-Dahlberg design. For the ES cohort, primary endpoint is disease control rate (DCR) defined as objective response of any duration or stable disease (SD) lasting $\geq$32 wks. Success at stage 2 required DCR in $\geq$5/30 treated pts. Key secondary endpoints include safety/tolerability, ORR, PFS, OS, PK and response biomarkers e.g. H3K27me3. **Results:** In 31 ES pts with a median of 1 prior systemic therapy, stage 2 DCR criteria was surpassed with a RECIST confirmed PR (4 pts) and SD $\geq$32 wks (2 pts) observed to date. 13 pts are still on treatment therefore DCR and ORR will be updated. Tazemetostat was well tolerated with grade 1/2 fatigue (39%), nausea (26%) and vomiting (19%) as the most frequently reported AEs regardless of attribution. **Conclusions:** In the largest prospective clinical trial of ES to date, tazemetostat monotherapy shows promising antitumor activity, including confirmed responses and long-term SD, with favorable safety/tolerability in ES. Enrollment has been expanded to 60 ES pts given the clinical activity described here. Clinical trial information: NCT02601950.

11059 Poster Session (Board #382), Sun, 8:00 AM-11:30 AM

Immunoprofiling in alveolar soft part sarcoma. *First Author: Samer Salah, Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Alveolar Soft Part Sarcoma (ASPS) is a distinctive tumor characterized by a canonical *ASPL-TFE3* fusion. Treatment options are limited. We assessed tumor immune cell infiltrates, and correlated this with patients receiving PD-1 blockade. **Methods:** A retrospective institutional review was performed for 18 cases of ASPS. Immunohistochemistry was performed on paraffin-embedded tissue (PET) for T-lymphocyte markers (CD3/CD4/CD8), and PD-1/PD-L1 (Ventana). Expression was quantified by standard methods: (total cells per high power field: score; 0:0; 1-10:1; 11-50:2; 50-99:3; 100:4). Select cases underwent DNA sequencing analysis using whole exome (WES, $>$ 80X, n = 4) and genome (WGS, $>$ 30X, n = 1) sequencing. Indel analysis was conducted via mutect2 ($>$ 5% variant allele frequency) and mutational signature was performed using deconstructSigs. **Results:** The median age was 27 (15-54). Disease status at diagnosis was: 44% localized; 56% metastatic. The median overall survival was 17 yrs (2.9-31). Four patients (pts) received immunotherapy with PD-1 blockade with 1 complete response (CR), 2 durable partial responses (PR) and 1 stable disease (SD). PET was available in 12 cases. PD-1/PD-L1 expression ($\geq$1) was seen in 50% and 17%, respectively. Composite CD3, CD4 and CD8 infiltration were 2, 1, and 1, respectively. Patients with CR/PR to PD-1 blockade (n = 3) had no clear correlation with PD-1, PD-L1 or lymphocyte markers. Exomic characterization (n = 4) demonstrated no clear excess mutation burden compared to Ewing sarcoma (5.7 vs 6.4 mut/MB). Mutational signatures via COSMIC were identified in the mismatch repair (MMR) pathway in 2 of 4 cases (Pt A: Signature (S) 26; pt B: S6 and S15). Pt B also underwent WGS which confirmed a COSMIC signature in the MMR pathway. Indel analysis did not confirm aberrations in standard MMR or polymerase genes. **Conclusions:** Preliminary findings suggest activity with PD-1 blockade in ASPS; however, this does not appear to correlate with tumour-infiltrating T lymphocytes. Genomic analysis suggests an MMR signature may account for these responses, but standard MMR aberrations were not identified. Further validation is underway.

11060 Poster Session (Board #383), Sun, 8:00 AM-11:30 AM

Trabectedin for advanced soft tissue sarcoma: Ten-year real-life perspective. *First Author: Sivan Shamai, Tel Aviv Medical Center and Sackler School of Medicine, Tel Aviv, Israel*

Background: Trabectedin is a marine - derived chemotherapy, which lately received FDA approval for use in anthracycline resistant advanced soft tissue sarcoma (STS), especially liposarcoma and leiomyosarcoma (L-sarcomas). **Methods:** We report our ten-year real-life experience with trabectedin, 1.5mg/m2/d c.i.v. q3w till progression, regarding safety and efficacy in a cohort of 86 patients (24-83y). Liposarcoma was the diagnosis in 46% , leiomyosarcoma in 43%. **Results:** A total of 703 cycles of Trabectedin were given, with a median of five cycles per patient (range 1-59). Median overall survival (mOS) was 11 months for liposarcoma patients (range 1-63), and 15 months for leiomyosarcoma patients (range 1-35). There was no statistically significant difference in progression free survival (PFS), when stratified according to previous treatment lines given. Trabectedin exhibited a favorable safety profile, with only 22% requiring dose reductions. Grade 3 and more toxicity were noted in 25% of the patients, mostly myelosuppression. There was no treatment related death. **Conclusions:** In contrast to former trials, our retrospective data represents real life experience with Trabectedin, and includes patients with diverse age, histology, performane status, prior treatments and tumor burden. The group includes 10 patients (11.6%) who received Trabectedin as first line (Either due to congestive heart failure or to rapid progression following adjuvant Doxorubicin and Ifosfamide), 10 patients (11.6%) were above age 70, nine (10.5%) had histologies other than liposarcoma or leiomyosarcoma, and 23 (26.7%) had ECOG PS of 2 or higher. Trabectedin is a safe and effective drug in advanced high grade STS. Further research is needed to identify which patients will benefit most.

11061 Poster Session (Board #384), Sun, 8:00 AM-11:30 AM

Trabectedin and radiotherapy in soft-tissue sarcoma (TRASTS) study: An international, prospective, phase I/II trial—A collaborative Spanish (GEIS), Italian (ISG), and French (FSG) groups study. *First Author: Alessandro Gronchi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Myxoid liposarcoma/round cell liposarcoma (ML) exhibits especial sensitivity to trabectedin (T). In prospective series, long-lasting T treatment showed responses in 44% of patients (pts) with ML. ML is also sensitive to radiation therapy (RT) and preclinical data suggested radiosensitizing properties of T. Preoperative short-course of T with concurrent low-dose RT was conducted in a multicenter, European, phase I/II trial. We present here data from the phase I part in pts with centralized diagnosis of locally advanced, resectable ML. **Methods:** Pts received 3 cycles (C) of T in combination with RT (45 Gy) in 25 fractions (1.8Gy/fraction). The phase I had the classic 3+3 design. Dose Levels for T were: -1 (1.1 mg/m^2), 1 (1.3 mg/m^2) and 2 (1.5 mg/m^2). Dose-limiting toxicity (DLT) were defined as grade $\geq$3 events excluding G3/4 neutropenia lasting $<$ 5 days and G3-4 nausea/vomiting due to inadequate prophylaxis. RECIST responses were evaluated preoperatively at week 10. Surgical specimens were processed for histologic changes and residual tumor. **Results:** From February 2015 to May 2016,14 pts (M/F 7/7) with median age 36y (24-71) and median tumor size 12.5 cm were enrolled. 7 pts received T at dose Level 1 and 7 pts at Level 2. One DLT (G3 transaminitis) occurred at Level 1 and another (sepsis due to catheter infection) at Level 2. Overall, grade G 3/4 AEs were: ALT elevation (n = 6, 43%), and GGT elevation, neutropenia, anemia, epithelitis and sepsis (n = 1, 7% each). There were no deaths. One pt developed metastasis after C3 and did not undergo surgery; another one had a sepsis after C1 and received definitive RT. All pts completed RT. 13 pts were evaluable for response: 5 achieved PR (38%), 7 SD (53%), 1 distant PD (8%). 12 pts underwent surgery (7 R0/5 R1). Median viable residual tumor was 5% (0-60) with 9/12 pts (75%) with $\leq$ 10% viable remaining tumor, 3/12 (25%) complete responses. **Conclusions:** T in combination with RT was feasible and well tolerated in the preoperative setting. T dose of 1.5 mg/m^2 is the recommended phase II dose. A high proportion of patients achieved a good pathological response, with 3/12 (25%) complete responses. Clinical trial information: 2014-001549-26.

11062 Poster Session (Board #385), Sun, 8:00 AM-11:30 AM

International single-arm phase II trial of pazopanib in advanced extraskeletal myxoid chondrosarcoma: A Collaborative Spanish (GEIS), Italian (ISG) and French (FSG) Sarcoma Groups study. *First Author: Silvia Stacchiotti, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Extraskeletal myxoid chondrosarcoma (EMC) is an exceedingly rare sarcoma, marked by a specific translocation involving the gene *NR4A3* that can be rearranged with different partners. Preliminary retrospective data suggest that sunitinib is active, but no formal prospective studies are available. We report on a multicentric European prospective, investigator-driven, Phase 2 study on pazopanib (P) in NR4A3+ advanced EMC patients (pts), carried out by the Spanish, Italian and French Sarcoma groups. **Methods:** From June 2014 to November 2016, 24 advanced EMC pts entered this study (median age: 64 yrs - disease extent: metastatic 77%, locally advanced 23% - prior medical treatment: 18 (86%) naive; 2 (9%) 1 line, 1 (5%) $>$ 1 line). Path diagnosis and NR4A3 rearrangement (FISH and/or real-time PCR analysis) were centrally confirmed. Pts received P 800 mg/day (relative dose intensity = 0,82%, 658 mg/day), until progression or toxicity. The primary study end-point was response rate as per RECIST 1.1. Secondary end-points were overall survival, progression-free survival (PFS), clinical benefit rate (CBR) (RECIST CR+PR+SD$\geq$6mos). An exploratory evaluation of the correlation between the rearrangement subtype and the outcome is ongoing. **Results:** 20/24 pts were evaluable for response (1 early death; 3 too early). One patient (5%) had a partial response, 17 (75%) stable disease, 2 (10%) progression as their best RECIST responses. At the time of this analysis, 12 pts were still under treatment, while 12 interrupted P (10 progression, 1 toxicity, 1 other). At a 13-month median follow-up, the median PFS was 13 months (range 1.6-25.1), with 29% pts progression-free at 18 months and a 65% CBR. Median OS was not reached. **Conclusions:** This Phase 2 study is formally negative since the target of at least 3/21 RECIST responses was not reached. However, looking at PFS, P was associated with a prolonged disease stabilization in a significant proportion of pts. This suggests to further explore the use of P in EMC. Clinical trial information: NCT02066285.

11063 Poster Session (Board #386), Sun, 8:00 AM-11:30 AM

Circulating cell free tumor DNA detection as novel biomarkers to monitor desmoid tumors evolution. *First Author: S Bastien Salas, Hopital de la Timone, Marseille, France*

Background: Since desmoid tumors (DT) exhibit an unpredictable clinical course, with stabilization and/or spontaneous regression, an initial "wait-and-see" policy is the new standard of care to select best indications of active treatments in case of significant evolution. Therefore, translational research is crucial to identify predictive factors of progression. Most DT are characterized by *CTNNB1* mutation (CM) in exon 3 (T41A, S45F, S45P). Circulating cell-free tumoral DNA (ctDNA), named "liquid biopsy", has emerged as a new promising non-invasive tool to detect biomarker in several cancers. **Methods:** We present a method of detection of DT-specific CM using a targeted strategy digital droplet PCR (ddPCR) on cell-free DNA (cfDNA) extracted from blood samples of 31 DT patients (pts). T41A, S45P, S45F and their respective CTNNB1 wild-type probe were designed for ddPCR. Furthermore, we analyzed the correlation of cfDNA levels (CTNNB1 wt/ml plasma) and evolution of the tumor. **Results:** Initial DT CM statuswas known for 28 pts and unknown for 3 pts. 24 pts presented a CM (17 pts T41A, 6 pts S45F and 1 pt S45P), 2 pts a mutation of *APC*, 2 pts were wild-type, and 3 pts were undetermined. Among pts with a CM, *CTNNB1* mutants were detected in the cfDNA of 6 patients (19.4%). CM detection was not correlated with the quantity of cfDNA analyzed (p = 0,7263–Mann-Whitney (MW)). Absolute quantification of cfDNA (CTNNB1 wt) normalized by mL of plasma displayed higher levels for patients with progressive DT (p = 0,0009 - MW), this difference of cfDNA quantity was also present between progressive, stable and self-regressive DT (p = 0,0012 - MW). A threshold of 875 *CTNNB1* copies/mL predicted DT progression with a sensibility of 100% ($CI_{95\%}$: 59-100) and a specificity of 76.5% ($CI_{95\%}$: 50.1-93.2). Absolute cfDNA quantity was also higher in patients harboring multiple desmoids (p = 0.0292 - MW). **Conclusions:** The absolute quantification of normalized cfDNA is correlated with evolution of the disease, independently of the initial tumor type of CM. This study opens the perspective of using cfDNA as a genomic biomarker to assess the tumor dynamics at initial diagnosis, and to monitor treatment strategy in case of tumor evolution.

11064 Poster Session (Board #387), Sun, 8:00 AM-11:30 AM

Discordance of histo-pathological diagnosis of patients with soft tissue sarcoma referred to tertiary care center. *First Author: Sameer Rastogi, All India Institute of Medical Sciences, Ghaziabad, India*

Background: Reaching to the correct histo-pathological diagnosis of soft tissue sarcomas (STS) is a great challenge and is cornerstone for treatment planning. Need of expertise for diagnosis is limited by lack of expert pathologists and dedicated sarcoma oncologists in India. Through this study we highlight the pattern of pathological diagnosis and accuracy outside specialist centre. **Methods:** We did retrospective analysis of all patients referred to us with diagnosis of STS in the last 12 months (January 2016 to 2017). According to protocol, all patients had pathology review from our institute. If blocks were available then they were reviewed and if necessary, fresh biopsy was performed. Besides, pathological diagnosis was reviewed in joint clinic, giving clinico-radiological inputs to sarcoma pathologists. For patients diagnosed outside and had discordant report, we divided them into major discrepancy (including change of diagnosis of sarcoma to benign or other histological entity that could potentially change the treatment plan) or minor discrepancy (like mild change in grade or histopathological diagnosis not affecting the treatment plan). **Results:** There were 149 patients registered with median age of 36 years (14-77 years) and 93 patients (62.4%) were males. 85(57%) patients had localized disease. Most common subtypes were synovial sarcoma 16%, liposarcoma 9%, soft tissue ewings sarcoma 9%, MPNST 9%, leiomyosarcoma 8%, pleomorphic undifferentiated sarcoma 8% etc. Of 149 patients, 42 had not been worked up outside and thus comparison was not possible while 4 patients couldn't retrieve blocks and repeat biopsy could not be performed. Of 97 patients (biopsy = 84, FNAC = 13) who had diagnosis from outside, 37% had major discrepancy and 24% had minor discrepancy compared with our biopsy review. Major discrepancy was more in non extremity than extremity STS (p = 0.003). **Conclusions:** Pathological diagnosis of more than half of patients referred from outside was discordant with respect to diagnosis of our centre with major implications on 37%. We believe this is due to lack of sarcoma pathology experts and virtually non-existent multidisciplinary clinics in set up outside tertiary care centres.

11065 Poster Session (Board #388), Sun, 8:00 AM-11:30 AM

Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: Results of a retrospective multi-institutional case series. *First Author: Anna Maria Frezza, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: To report on a multi-institution retrospective study on the activity of anthracycline-based (Ab) and gemcitabine-based (Gb) regimens as well as pazopanib (P) in patients with advanced epithelioid sarcoma (ES) treated within 16 sarcoma reference centres in Europe, US and Japan. **Methods:** Patients with a histologically confirmed diagnosis of locally advanced/metastatic ES were selected. Classic and distal subtypes were defined based on morphology (WHO 2014). INI1 expression is under evaluation.Response was evaluated by RECIST.Progression-free survival (PFS) and overall survival (OS) were computed by Kaplan-Meier method. **Results:** Ninety ES patients were identified (Table 1). They were treated with Ab (72), Gb (30) and P (20); 25 pts received more than one treatment. The median follow-up for Ab, Gb and P groups was 32, 24 and 22 months, respectively. The response rate (RR) for Ab was 25% (95% CI 16%-37%), with a median PFS and OS of 6 and 17 months. The RR for Gb was 23% (95% CI 10% - 42%), with 1 complete response and a median PFS and OS of 5 and 20 months. In the P group, no objective responses were reported, and median PFS and OS were 3 and 9 months. A non-statistically significant trend towards a greater RR in proximal than classic subtype was seen in both Ab (27% vs 22%) and Gb (30% vs 13%) groups. **Conclusions:** This retrospective series, the largest currently available, confirms the activity of Ab and Gb in ES, with a similar RR and PFS in both groups. In this population, the value of P seems limited. These data may serve as a benchmark for trials of novel agents in ES.

Population characteristics.

	Ab (N=72)	Gb (N=30)	P (N=20)
Median age (range)	32 (15-67)	37 (18-76)	34 (15-67)
Gender (%)			
M	51 (70.8)	17 (56.7)	13 (65)
F	21 (29.2)	13 (43.3)	7 (25)
Primary site (%)			
Distal	36 (50)	16 (53.3)	11 (55)
Proximal	36 (50)	14 (46.7)	9 (45)
Histological type (%)			
Classic	39 (54.2)	10 (33.3)	8 (40)
Proximal	33 (45.8)	20 (66.7)	12 (60)
Stage (%)			
Locally advanced	23 (31.9)	5 (16.7)	5 (25)
Metastatic	49 (68.1)	25 (83.3)	15 (75)
Median number of prior lines (range)	0 (0-1)	1 (0-5)	2 (0-4)

11066 Poster Session (Board #389), Sun, 8:00 AM-11:30 AM

Potential therapeutic genomic alterations in desmoplastic small round blue cell tumor. *First Author: Joanne Xiu, Caris Life Sciences, Phoenix, AZ*

Background: Desmoplastic Small Round Blue Cell Tumor (DSRCT) originates from a cell with multilineage potential. A molecular hallmark of DSCRT is the EWS-WT1 reciprocal translocation. Ewing's and DSRCT are treated similarly due to similar oncogene activation pathways and DSRCT has been represented in very limited numbers in sarcoma studies. **Methods:** Thirty-five DSRCT tumors were tested with a multiplatform profiling service (Caris Life Sciences, Phoenix, AZ). Specific tests performed included sequencing (NextGen), protein expression (IHC) and gene amplification (CISH or FISH). Tumor mutational load (TML) was calculated as somatic nonsynonymous missense mutations sequenced with a 592-gene panel. Molecular alterations were compared to 88 Ewing sarcomas (ES). Chi-square tests were used for comparison and statistical significance was determined as $p < 0.05$. **Results:** In the 35 DSRCT tumors, high expression of TOP2A were seen in 63%, TOPO1 in 63%, PTEN in 62%, androgen receptor (AR) in 59%, EGFR in 42% of tumors; low expression of TUBB3 was seen in 44%, MGMT in 45%, TS in 48%, RRM1 in 57% and ERCC1 in 76% of tumors. When compared to ES, no significant difference was seen in protein expressions with the exception of a significantly higher overexpressson of AR in DSRCT (59% vs. 3%, p = 1.7E-10) and TUBB3 (56% vs. 29%, p = 0.03). Tumor expression of PD-L1 (Ab: SP142) was not seen in the 4 DSRCT and 10 ES tested. NextGen revealed a TP53 mutation (7%) and a FOXO3 mutation (L382fs) in DSCRT, while 6 TP53 mutations (13%), 2 APC mutations (L1129S and I1307K), 1 BRCA1(c.301+1G > A) and 1 CTNNB1 (T41A) mutation were identified in ES. Tumor mutational load evaluated in the 3 DSRCT and 11 ES tumors averaged 6 and 5 mutations per megabase, respectively. **Conclusions:** Molecular profiling on 35 DSRCT tumors and comparison with Ewing's sarcoma revealed low immunogenicity (< 10 Mutations/MB) and low frequency of actionable mutations including PD-L1 in both tumor types. High AR expression could present as a potential therapeutic target for DSRCT while taxanes may be more effective in Ewing's sarcoma compared to DSCRT based on TUBB3 expression. Genomic and Molecular assessment may help determine the ideal regimen that will help achieve maximal tumor debulking.

11067 Poster Session (Board #390), Sun, 8:00 AM-11:30 AM

Expression and prognostic significance of PDGF ligands (A, B, C, and D) and PDGFR (A, B, and L) in soft-tissue sarcomas and GIST. *First Author: Tom Lesluyes, Institut Bergonié, Bordeaux, France*

Background: Sarcomas are a variety of rare connective tissue cancers. Doxorubicin and olaratumab (Ab against PDGFRA) improved survival in a recent Phase 1/2 study. Besides PDGFRA mutated gastrointestinal stroma tumor (GIST) and dermatofibrosarcoma protuberans, the role of PDGFR and the according ligands in the biology of sarcoma remain unclear. **Methods:** The expression levels of PDGF (A,B,C,D) and PDGFRs (A,B,L) were studied in a series of 255 sarcoma pts in localized phase using the Agilent 014850 platform. Data are available online (http://atg-sarc.sarcomabcb.org). Histologies were GIST (n = 60), myxoid liposarcoma (MLPS, n = 50), synovial sarcoma (SyS, n = 58), and sarcoma with complex genomics (SCG, n = 87). Expression levels were analyzed and tested for prognostic values for metastasis free survival (MFS) in uni- and multivariate analysis using SPSS 19.0. **Results:** Expression levels (ELs) of *PDGFs* and *PDGFRs* varied across histotypes: *PDGFA* levels were highest in SyS and lowest in MLPS ($p < 0.0001$). *PDGFB* and *C* levels were lower in GIST ($p < 0.0001$), while *PDGFD* ELs were similar across histological subtypes. *PDGFRA* ELs were highest in MLPS, while *PDGFRB* & L ELs were lowest in GIST and SyS ($p < 0.0001$ all). Complex patterns of correlation of expression between ligands and receptors were observed in each individual subtypes. *PDGFA* ELs above median were associated with a marginally higher risk of metastasis . Conversely, *PDGFD* ELs above median was associated with a reduced risk of metastasis in the whole cohort (p = 0.02). The ELs of the 3 receptors were not correlated to MFS. In multivariate analysis using Cox model on the non-GIST sarcoma cohort (histology, grade, depth, with size, *PDGFA*, *PDGFD* as continuous variables): histology, size, grade and PDGFA ELs were independent adverse prognostic factors (PF), while PDGFD ELs was a favorable PF for MFS. In the GIST cohort, testing AFIP score, PDGFA & D ELs as continuous variable, PDGFD ELs was also an independent favorable PF for MFS, in addition to AFIP score. **Conclusions:** The expression of PDGFs and the according receptors varies across sarcoma histological subtypes. PDGFA and D expression levels correlate independently to the risk of metastatic relapse.

11068 Poster Session (Board #391), Sun, 8:00 AM-11:30 AM

Rates of survival throughout the years in soft tissue sarcoma with synchronous metastases: Results of a population-based study. *First Author: Melissa Vos, Erasmus MC Cancer Institute, Department of Medical Oncology and Surgical Oncology, Rotterdam, Netherlands*

Background: Roughly 10% of patients with soft tissue sarcoma (STS) present with synchronous metastases and generally cannot be cured anymore. With the registration of trabectedin, pazopanib and the identification of other agents exerting activity against STS, the treatment of these patients in the Netherlands has changed considerably in the last decade. The aim of this population-based study is to examine whether the overall survival (OS) of patients with STS and synchronous metastases has improved over the years. **Methods:** All patients diagnosed with adult-type STS and synchronous metastases between 1989 and 2014 were queried from the Netherlands Cancer Registry. Trends in OS were assessed by the Kaplan Meier method and log rank test in different timeframes based on year of registration of trabectedin (< 2007 vs. ≥2007) and pazopanib (< 2012 vs. ≥2012). A multivariable Cox regression analysis was performed to identify relevant characteristics prognostic for OS. **Results:** In total, 1,393 patients with adult-type STS and synchronous metastases were identified. Over the whole time period, median OS did not improve significantly (5.8 months in 1989-1994 to 8.1 months in 2010-2014, p = 0.095), but median OS < 2007 compared to ≥2007 did improve significantly (5.8 months to 7.3 months, p = 0.035). This was particularly apparent in the liposarcoma subgroup, where median OS doubled (5.2 months to 11.5 months, p = 0.020). Median OS < 2012 compared to ≥2012 did not increase significantly (6.1 months to 7.6 months, p = 0.062), though there was a relatively short follow-up of 2 years while the survival curve seems to reach a plateau phase. Aside from not receiving (any type of) treatment, elderly age, STS subtype other than lipo- or leiomyosarcoma, high or unknown grade and nodal involvement were significant negative predictors for OS, whereas primary tumor site in the extremity and surgery in an academic center had a favorable effect on OS. **Conclusions:** OS of STS patients with synchronous metastases has not improved significantly over the years, except for the subgroup of liposarcomas after 2007. A longer follow-up period is needed to clarify the impact of pazopanib on OS in patients with metastatic STS.

11069 Poster Session (Board #392), Sun, 8:00 AM-11:30 AM

Clinical utility of routine surveillance CT/MRI imaging in patients with localized soft tissue sarcoma (STS) following curative resection. *First Author: Chiew Woon Lim, National Cancer Centre Singapore, Singapore, Singapore*

Background: Guidelines recommend routine surveillance imaging in patients (pts) following curative resection of STS. However the benefit of such an approach is unclear. We sought to evaluate the utility of a surveillance imaging strategy in pts with localized STS treated with curative intent. **Methods:** Pts with localized non-indolent STS, seen between 2010 – 2016, who had undergone surgery with R0/R1 surgical margins were included. Epidemiology, treatment and relapse data were collected as was the mode of detection. We defined optimal surveillance as CT/ MRI performed at least 6-mthly following surgery; suboptimal surveillance was defined as CT/ MRI imaging performed less frequently than 6mthly. **Results:** Of 294 pts included, 31% (n = 92) vs 34% (n = 100) vs 35% (n = 102) had optimal, suboptimal and no routine CT/ MRI surveillance imaging respectively. At a median follow-up of 27mths (range 0-79), 36% (n = 105) experienced a relapse; 43% (n = 45) local and 57% (n = 60) had metastatic relapse. More relapses were noted in the optimal surveillance group, 57% (n = 52) vs 28% (n = 28) and 25% (n = 25) in the suboptimal and no surveillance groups respectively ($p < 0.001$). Within each cohort, relapses detected directly by routine surveillance imaging vs outside of surveillance imaging were as follows: 35% (n = 32) / 22% (n = 20) in the optimal, 17% (n = 17) / 11% (n = 11) in the suboptimal and 0 / 25% (n = 25) in the no surveillance arms respectively. Comparing the 3 strategies, the proportion of pts who then went on to receive curative resection/ metastacectomy was not significantly different, 38% (n = 20), 57% (n = 16) and 32% (n = 8) of relapses, in the optimal vs suboptimal vs no surveillance cohorts respectively ($p = 0.1$). Notably, routine surveillance imaging directly leading to curative resection occurred only in 15% (n = 14) of pts in the optimal and 9% (n = 9) in the suboptimal surveillance groups. **Conclusions:** While an intensive routine CT/MRI surveillance imaging strategy detected more recurrences, the impact it has on subsequent resection is less certain. Optimal frequency of surveillance imaging remains unclear.

11070 Poster Session (Board #393), Sun, 8:00 AM-11:30 AM

Correlation between a new growth modulation index (GMI)-based Geistra score and efficacy outcomes in patients (PTS) with advanced soft tissue sarcomas (ASTS) treated with trabectedin (T): A Spanish group for research on sarcomas (GEIS-38 study). *First Author: Javier Martinez-Trufero, Hospital Miguel Servet, Zaragoza, Spain*

Background: The GMI is a marker of drug activity and represents an intra-patient comparison of successive time to progression (TTP), defined as the TTP ratio between the second (or later) line (TTPn) of therapy divided by the prior line (TTPn−1). Defining a clinical profile of pts with GMI >1.33 could help to identify pts who can gain greater benefit from T. **Methods:** We retrospectively evaluated the concordance between the GMI and the efficacy outcomes and clinical profiles of 198 pts with ASTS treated with trabectedin 1.5 mg/m² (24-h infusion q3w) as a 2nd or further-line treatment from Jan 2007 to Jun 2016. **Results:** After a median follow-up of 58 months (m; range: 18-172) median overall survival from ASTS diagnosis (MOS) and from T (MT-OS) were 27.5 m (23-32.1) and 10.8 m (8.9-12.7), respectively, while median TTP from T (MT-TTP) and T-1 were 3.4 m (2.8-4) and 3.5 m (2.8-4.2). Overall, 106 pts (53%) had a GMI <1; 22 (11%) a GMI=1-1.33 and 70 pts (35%) a GMI >1.33. A high GMI (<1.33 *vs* >1.33) correlated with favorable efficacy outcomes: MT-OS: 23 *vs* 36 m ($p<0.001$), MT-TTP 2.3 *vs* 8.2 m ($p<0.001$) and clinical benefit (objective response + stable disease) 23% vs 68% ($p=0.001$). The multivariate analysis identified L-type sarcoma (Odds ratio: 1.99, 95% CI 1.06-3.71), metastatic free interval (MFI) from initial diagnosis >8.1 m (2.24, 95%CI 1.19-4.18) and Karnofsky >80 (2.3, 95%CI 1.00-5.28) as factors independently associated to GMI> 1.33. Based on these 3 variables we defined a new GEISTRA score assigning 1 point for each adversely affected variable: non L-Sarcoma, MFI<8.1m or Karnofsky <80. This score showed a strong correlation with MT-TTP ($p<0.001$) and MT-OS ($p<0.001$). **Conclusions:** Based on the high GMI we defined a new GEISTRA score, which is strongly associated with favorable efficacy outcomes in pts with ASTS treated with T. Thus, GEISTRA score could be a potentially useful predictable clinical tool for T benefit.

GEISTRA Score	MT-TTP m (range)	p	MT-OS M (range)	p
0	7.4 (5.8-9)	<0.001	25.7 (11.4-40)	<0.001
1	4.2 (2.7-5.8)		11.3 (8.6-14)	
2	2.5 (1.9-3.1)		6.4 (4.3-8.6)	
3	1.9 (0.7-3.2)		2.5 (0.2-4.8)	

11071 Poster Session (Board #394), Sun, 8:00 AM-11:30 AM

Predictive role of FAS for trabectedin in second lines of advanced soft tissue sarcoma (ASTS): A Spanish group for research on sarcoma (GEIS) study. *First Author: Javier Martin Broto, Virgen del Rocio University Hospital, Institute of Biomedicine Research (IBIS), Seville, Spain*

Background: There are currently several second-line options for the treatment of ASTS as gemcitabine combinations, trabectedin, pazopanib, eribulin or olaratumab plus doxorubicin in cases where anthracyclins are still possible. There is an unmet need for predictive biomarkers which hinders the rational selection of the best sequence in second line. We already published the prognostic value of FAS in first line of ASTS while this study analyzes its predictive role in different second line schemes. **Methods:** Most relevant selection criteria for this study were having received trabectedin in 2nd line or beyond for ASTS, progressive disease after at least one previous line for ASTS and signed CI. A TMA was set up for FAS staining (Cell Signaling) with blocks from diagnostic time. Two expert blinded pathologists reviewed and classified the cases as negative, weak or strong. Kaplan–Meier estimations were used for time-to-event variables and the log-rank test was used to compare groups. **Results:** A series of 198 patients accomplished selection criteria. Metastases at diagnosis occurred in 46 (24%) and median time to metastases was 18.8 months (CI 16,3; 21.3). Previous line to trabectedin consisted of gemcitabine combination 83 (42%), Doxorubicin-based 65 (33%) and others 50 (25%). Median PFS for previous and trabectedin lines were 3.5 (2.8-4.2) and 3.4 (2.8-4) months respectively. FAS positive entailed significantly better PFS for the previous trabectedin line: 4.1 (1.5-6.7) vs 3.0 (2.5-3.5) months, $p = 0.01$ whereas FAS positive was related with worse PFS for the trabectedin line 2.5 (2.2-2.8) vs 3.7 (2.7-4.8) months, $p = 0.028$. These results were more notorious for L-sarcoma cases: 7.0 (3.6-10.5) vs 4.3 (1.9-6.6) months, $p = 0.017$ in previous line and 2.4 (2.2-2.6) vs 6.5 (3.8-9.3) months, $p < 0.001$ in trabectedin. From trabectedin administration, FAS+ had significantly worse OS especially in L-sarcomas: 11.9 (5.2-18.7) vs 21.7 (12.7-30.8) months, $p = 0.002$. **Conclusions:** FAS showed predictive value in PFS and OS for trabectedin administration in ASTS. The different prognostic role of FAS across distinct lines and its relevance in L-sarcomas deserve further attention.

11072 Poster Session (Board #395), Sun, 8:00 AM-11:30 AM

Sensitivity to chemotherapy of low-grade endometrial stromal sarcoma (LGESS) versus high-grade endometrial stromal sarcoma (HGESS). *First Author: Roberta Sanfilippo, Instituto Tumori Milano, Milan, Italy*

Background: LGESS and HGESS are rare uterine neoplasms of endometrial stromal origin. The activity of hormonal therapy in LGESS is reported, whilst no data are available in HGESS. The activity of chemotherapy is unknown in both. We focused on LGESS and HGESS to explore their sensibility to chemotherapy **Methods:** Cases diagnosed with LGHSS and HGESS from 1997 at Istituto Nazionale Tumori, Milan, or within the Italian Rare Cancer Network (RTR), were reviewed. **Results:** We identified 39 patients (pts), 28 with LGESS (median age:43) and 11 (median age: 54) with HGESS. Seventeen LGESS pts received systemic therapy for advanced disease (1-5 lines). Eight received an aromatase inhibitor, with 2 PR, 5 SD and 2 PD; 8 received oral progestins, with 4 PR, 5 SD and 2 PD. Nine patients (6/9 in first line, 1/9 in second line and 1/9 in third line) received antracyclines +/- ifosfamide and were evaluable for response: 2 had a CR, 4 a PR and 3 a SD. Median PFS was 7,6 months. Five patients received high-dose ifosfamide (HDIFX), obtaining 2 PR and 3 SD. Five pts received trabectedin, with 1 PR, 3 SD and 1 PD. All eleven pts with HGESS received systemic therapy for advanced disease (1-5 lines). Three patients received oral progestins, with PD. Ten pts received an antracycline-based combination chemotherapy and were evaluable for response: 5 had SD and 5 had PD. Median PFS was 3 months. Four pts received HDIFX and all progressed. Four pts received gemcitabine-based chemotherapy, obtaining 1 SD and 3 PD. Five pts received trabectedin, obtaining 1 SD and 4 PD. One pt received Pazopanib, with a PR lasting 5 months. **Conclusions:** In this series of endometrial stromal tumor pts treated with medical therapy, chemotherapy with antracycline-based combinations resulted in some objective responses in LGESS, while it was essentially inactive in HGESS. An observational clinical study is ongoing to expand this series.

11073 Poster Session (Board #396), Sun, 8:00 AM-11:30 AM

Rhabdomyosarcoma (RMS) in adults: Histologic subtypes and overall survival with actinomycin-based chemotherapy vs doxorubicin-based chemotherapy. *First Author: Alia Vang, St. Olaf College, Northfield, MN*

Background: RMS typically occurs in children. Vincristine, Actinomycin and Cyclophosphamide (VAC) based chemotherapy is the current standard. Limited data exist on the frequency of the histologic subtypes and optimal chemotherapy regimen for the treatment of adult patients with RMS. **Methods:** We retrospectively identified patients ≥18 years with RMS seen at our institution from 2000-2015. The analysis was performed with JMP statistical software. **Results:** We identified 73 patients, with a median age of 51 (range 18-85 years). The majority of patients were male (40 of 73) and presented with localized disease (59 of 73). Histologic subtypes were as follows: 32% embryonal (E), 27% alveolar (A), 36% pleomorphic (P), and 6% variants (V) (botryoid and spindle cell/sclerosing). The median overall survival (OS) for patients with localized disease was 16.2 months and metastatic disease 9 months. The median OS for patients with localized disease treated with VAC was 20.3 months (4A, 7E, 3P) and VDC (vincristine doxorubicin cyclophosphamide) was 14.1 months (3A, 3E, 2P). For those with localized disease treated with a VAC/actinomycin-based chemotherapy had a median OS of 19.5 months (4A, 9E, 3P) and with a VDC/doxorubicin-based chemotherapy had a median OS of 15.9 months (8A, 5E, 13P, 2V). **Conclusions:** Adult patients with RMS have an even distribution among the histologic subtypes. Given the small, unbalanced number of patients in each histologic subtype treated with VAC/actinomycin-based or VDC/Doxorubicin-based regimens, the overall survival benefit favoring the use of VAC/actinomycin-based is hypothesis generating and confirmatory studies are needed to truly determine the optional regimen for adult patients with RMS.

11074 Poster Session (Board #397), Sun, 8:00 AM-11:30 AM

Prognostic value of microscopic evaluation of organ infiltration and visceral resection margins (VRM) in patients with retroperitoneal sarcomas (RPS). *First Author: Salvatore Lorenzo Renne, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Surgery with gross margin clearance (R0 and R1) is the standard treatment for RPS and visceral resection has been proposed even in the absence of macroscopic visceral infiltration. Formal definition and margin sampling procedures for pathological evaluation are lacking for RPS. This study investigated VRM as well as viscera infiltration and their association with patient survival. **Methods:** Consecutive patients operated on for primary RPS (2009-2014) were extracted from a prospectively maintained database. VRM were sampled for each resected organ and classified as negative and positive. Also, tumor infiltration of resected organs was classified as follow: absence of infiltration, infiltration of perivisceral fat, early infiltration (i.e., renal/adrenal capsule, muscular fascia, contact with muscular tunica of hollow viscera), and infiltration of the viscera. **Results:** In 207 patients VRM were negative in 182 (88%) and positive 25 (12%). Organ infiltration was absent, perivisceral, early, and visceral in 37 (18%), 13 (6%), 17 (8%), and 140 (68%), respectively. Overall survival analysis showed that patients with negative VRM plus organ infiltration (HR = 3.56; 95%CI 1.15-11.00, P = 0.028) and those with positive VRM irrespective of organ infiltration (HR = 7.76; 95%CI 2.18-27.65, P = 0.002) did worse that patients with negative VRM plus no organ infiltration, after adjustment from known prognostic features. **Conclusions:** After liberal multivisceral resection for primary RPS, up to 80% of patients have infiltrated organs at some extent, while VRM are positive in up to 10% of cases. Visceral resection is justified even in the absence of macroscopic infiltration. Systematic evaluation of microscopic involvement of adjacent viscera may stratify prognosis.

11075 Poster Session (Board #398), Sun, 8:00 AM-11:30 AM

NY-ESO-1 antigen expression as a prognostic factor for soft tissue sarcomas. *First Author: Yuriy Komarov, N. N. Petrov Research Institute of Oncology, St. Petersburg, Russia*

Background: While a number of antigens are known to be expressed in soft tissue sarcomas, little is known about the prognosis of patients with such tumors. Recent data have demonstrated immunologic activity in sarcoma patients expressing the NY-ESO antigen, found positive in 20-80% cases. MAGE A3 has also recently attracted attention with regard to soft tissue sarcomas. In our study we aimed to assess any association between antigen expression and prognosis. **Methods:** In a case-control study we retrospectively collected data from a prospective database of all 137 patients with sarcomas receiving first line therapy in the Petrov Research Institute of Oncology in Saint-Petersburg. All cases were morphologically verified, with mRNA expression of NY-ESO-1, MAGE A3, PDGFR A, PDGFR B, beta-tubullin and top2alpha additionally being tested by quantitative real-time PCR in a subset of patients. The log-rank test was applied to compare Kaplan-Mayer estimates of progression-free (PFS) and overall survival (OS) by univariate analysis. Hazard ratios were derived after adjustment for age, gender, several covariates for type of chemotherapy and disease stage with two-sided probability at a significance level of 0.05. **Results:** The positive rate for expression of NY-ESO was 20% (11/43).Only NY-ESO was significantly associated with PFS ($p < 0,001$), with a median durations of 10, 4 and 7 months for positive, negative and not tested for NY-ESO expression, respectively. The adjusted hazard ratio (HR) for NY-ESO positive patients was 2.2 (95%CI, 1.2;4.2) compared with their negative counterparts, The HR for patients not tested for NY-ESO was 2.0 (95%CI, 1.3;3.0). Among other covariates, only a combination of drugs was associated with a lower risk of progression (HR, 0.7 95%CI, 0.4;0.98) , as compared to those receiving a single chemotherapy agent. **Conclusions:** This first report showing prognostic significance of NY-ESO expression in soft tissue sarcoma patients, suggests that research should be focused on targeting this antigen. Participation in clinical trials for patients with positive NY-ESO expression is highly recommended, because of poor survival regardless of the type of standard treatment.

11076 Poster Session (Board #399), Sun, 8:00 AM-11:30 AM

The incidence of other malignancies before and after sarcoma diagnosis: A population-based study. *First Author: Winette T.A. Van Der Graaf, Institute of Cancer Research and The Royal Marsden NHS Trust Foundation, London, United Kingdom*

Background: Sarcomas encompass a group of rare and heterogeneous mesenchymal malignancies with mostly unknown origin. Both exogenous risk factors, in particular radiotherapy, as well as genetic risk factors have been described. Second tumors next to sarcomas suggest associated risk factors. In the current study, we investigate the incidence of sarcomas and other malignancies by using population-based data from the Netherlands Cancer Registry. **Methods:** In 29,638 patients diagnosed with sarcoma between 1989 and 2015, with a median age of 59 years, we quantified the risk of other malignancies *after* sarcoma diagnosis using standardized incidence ratios (SIRs). In assessing associations with malignancies *before* sarcoma diagnosis, we focussed on previous radiotherapy. Skin carcinomas, with the exception of melanomas, were excluded. **Results:** In total, 3,381 (11.4%) sarcoma patients, median age 71years, had a *previous* malignancy (at a median age of 66 years). The most frequent sarcomas associated with prior tumors were angiosarcoma (34.5%) and gastrointestinal stromal tumours (20.6%). In the angiosarcoma group, 78.6% of patients had received prior radiotherapy for their previous tumors. Subsequent tumors (diagnosed in patients with median age of 69.5 years) *after* sarcoma diagnoses were detected in 2,523 patients with median age of 63 years (SIR 1.13; 95%CI: 1.09–1.18). Risks appear notably elevated for breast cancer (SIR 1.19; 95%CI: 1.06–1.34), lung cancer (SIR 1.15; 95%CI: 1.04–1.27), cancers of the urinary tract system (SIR 1.33; 95%CI: 1.14–1.53) and hematological cancers (SIR 1.31; 95%CI: 1.13–1.51). Median time until diagnosis of subsequent cancer was 52.7 months. **Conclusions:** Sarcoma patients have a markedly increased risk on another malignancy, either before or after the sarcoma diagnosis. Further research into genetic and exogenous risk factors may help to explain the associations.

11077 Poster Session (Board #400), Sun, 8:00 AM-11:30 AM

When to treat Kaposi's Sarcoma? Paclitaxel survival benefit on classic versus AIDS/HIV-related subtypes. *First Author: Eduardo Eyzaguirre, Universidad Científica del Sur, Lima, Peru*

Background: Kaposi's Sarcoma (KS) is a angioproliferative disease related to AIDS/HIV (AIDS-KS) or not (Classic, CKS). Treatment options are limited in low-income countries where taxanes represent a cost-effective alternative. Our aim was to compare overall response (ORR) of paclitaxel and progression free survival (PFS) and overall survival (OS) between KS subtypes. **Methods:** We reviewed 203 medical records from pts diagnosed between 2002-2014 at the Instituto Nacional de Enfermedades Neoplasicas (Peru). Survival differences were calculated by log-rank test in the univariate analysis and Cox regression analysis for prognostic factors. **Results:** From 203 pts, 85 had CKS and 118 AIDS-CK. Mean age was 67 and 36years in CKS and AIDS-KS, respectively. Most pts were males (84.7%), coinfections as tuberculosis (11.9%) were more frequent in AIDS-CK. In CKS pts, 80% debuted with localized elevated lesions at lower limbs, 16% were resected, 48% received RT and 29% paclitaxel. Among AIDS-KS, 37% had poor risk, 22% were diagnosed concurrently to HIV infection. 76.9% had generalized lesions with origin at lower limbs, 50.5% had +ve nodes and 19% visceral disease. 25.8% had Zubrod $>$ 2 and mean neutrophil to lymphocyte ratio (NLR) was 3.5, CD4 count was lower in pts with recently diagnosis of AIDS/HIV (166 vs 268, p = 0.039) and no differences were noted on viral load (mean 233 411). 77.1% of AIDS-KS pts received ART and 56.8% paclitaxel. In AIDS-KS ORR was 77%(CR:52%, PR:22%) versus 86% in CKS (CR:43%, PR:43%). At 4.3year median follow-up, 3-year PFS and OS was 71% and 75% in AIDS-CK, while CKS had 78% and 79%, respectively. Paclitaxel was associated with better survival among AIDS-KS patients (PFS HR:0.41, 95%CI:0.2-0.7, p = 0.004 and OS HR: 0.37, 95%CI:0.1-0.7, p = 0.007), patients with Zubrod$\leq$2 had more survival benefit. There was not survival benefit in CKS pts. At multivariate analysis, ART and paclitaxel were associated with favorable PFS and OS, while higher NLR and poorer status performance to worse outcomes in AIDS-KS pts. **Conclusions:** Paclitaxel is an effective alternative treatment for AIDS-KS, there was not survival benefit in CKS patients. Poorer status performance and higher NLR were associated to worse prognosis.

11078 Poster Session (Board #401), Sun, 8:00 AM-11:30 AM

A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-CSF1R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). *First Author: Kamalesh Kumar Sankhala, Sarcoma Oncology Center, Santa Monica, CA*

Background: TGCTis a proliferative, neoplastic joint disease that presents as single nodule (local) or multiple nodules (diffuse D-TGCT). Localized overexpression of colony stimulating factor 1 (CSF1) leads to recruitment of cells expressing the CSF1 receptor (CSF1R), formation of a tumor and inflammation of joints and tendons. Cabira is a monoclonal antibody that inhibits the interaction of the CSF1 and IL-34 ligands with their shared receptor CSF1R. **Methods:** This Ph 1/2 study is evaluating the safety and efficacy of cabira monotherapy administered IV Q 2wk for 6 mo in patients (pts) with D-TGCT. Eligible pts have inoperable D-TGCT or tumor for which resection would cause unacceptable morbidity. Response is evaluated by MRI, pt reported outcomes, and Ogilvie-Harris (O-H) score (which combines pain, synovitis, range of motion and functional capacity on a scale of 0-12). **Results:** As of 15 Dec 2016, 22 pts received $\geq$ 1 dose of cabira at 1, 2 or 4mg/kg. Dose-related exposure increase and significant reduction in target peripheral monocytes were observed. No dose limiting toxicity was identified. 4 mg/kg was chosen for Ph2 based on efficacy, tolerability, and PK. AEs $\geq$ Gr 2 ($>$ 10%) were CK elevation 46%, rash and other skin disorders 36%, fatigue 23%, and periorbital/peripheral/face edema 18% each. Gr 3 AEs in $\geq$ 2 pt were CK elevation (n = 8) and periorbital edema (n = 2). Four drug-related SAEs were reported in 3 pts; hypertension, fever, CRP elevation, and myocarditis. AEs of CK elevation were asymptomatic, improved to $<$ 2X ULN after protocol mandated drug discontinuation and are a known on-target effect of CSF1R inhibition. An amendment was made during Phase 2 to allow dosing with higher CK levels Activity at 4 mg/kg was: 1PR and 1 CK discontinuation in 3 pts in Ph1; 4 PRs in 7 evaluable pts with 6 additional ongoing in Ph2. Positive functional status improvements by O-H score were noted in objective responders (from 2 to 7). **Conclusions:** The initial demonstration of objective and functional activity supports further development of cabiralizumab in pts with D-TGCT. Updated data from the ongoing Ph2 will be presented. NCT02471716. Clinical trial information: NCT02471716.

TPS11079 Poster Session (Board #402a), Sun, 8:00 AM-11:30 AM

A bi-shRNA^{furin} and GMCSF engineered autologous tumor cell immunotherapy vs. gemcitabine + docetaxel for Ewing sarcoma and with cryoablation in Ewing family tumors. *First Author: Peter Meade Anderson, Cleveland Clinic, Cleveland, OH*

Background: Vigil, an immuno-stimulatory autologous cellular therapy, uses patient tumor cells transfected with a plasmid encoding genes for GM-CSF and furin (to down regulate TGFβ 1&2). A Phase I study in relapsed Ewing's sarcoma. (N = 16) had one 9 month partial response and a two-year survival rate of 44% [1]. Rapid, durable systemic immune activation was seen in the majority of patients using an IFNɣ ELISPOT assay [2]. We seek to extend these early findings in a randomized Phase 2 study (NCT02511132). **Methods:** Following surgery (for Vigil manufacture), patients are randomized 1:1 to Vigil (1 x 10^7cells/ml by monthly intradermal injection), or to chemotherapy with gemcitabine 675mg/m2 IV D1 and D8 and docetaxel 75 mg/m2 IV D8 every 21 days. Key eligibility criteria include: Age $>$ 2, histologically documented metastatic Ewing's, refractory or intolerant to $\geq$2 prior lines of chemotherapy, and availability of at least 4 doses of manufactured Vigil. Patients with bone only disease are ineligible. The primary objective is to compare the overall survival of patients treated with Vigil vs. chemotherapy. The sample size of 62 patients assumes a one-year survival rate of 25% in the chemotherapy group vs. 60% in the Vigil group, corresponding to a hazard ratio of 0.383 favoring Vigil. **Results:** As of January 2017, thirteen patients have been randomized at 10 centers in the U.S. The design allows for reduction in disease burden prior to surgery using modalities like SBRT and interventional radiology. Toxicity of Vigil has been low compared to chemotherapy. Time to disease progression is being assessed in patients who crossover to Vigil after progressing on chemotherapy. Systemic control of metastatic lesions using cryoablation is also being assessed in other patients (e.g. DSRCT liver metastases) using a separate IND. **Conclusions:** Although associated with systemic immune activation, additional means to reduce disease burden such as SBRT and cryoablation can possibly improve patient health and augment Vigil efficacy. References: 1.Ghisoli M, Barve M, et al. Mol Ther. 2016 Apr 25 2. Oh J, Barve M, et al. Gynecologic Oncology 2016; 143: 504–510. Clinical trial information: NCT02511132.

TPS11080 Poster Session (Board #402b), Sun, 8:00 AM-11:30 AM

A randomized, double-blind, placebo-controlled, phase III study of crenolanib in advanced or metastatic GIST patients bearing a D842V mutation in *PDGFRA*: The CrenoGIST study. *First Author: Jean-Yves Blay, Centre Léon-Bérard, Lyon, France*

Background: Activating mutations in the kinase domain of PDGFRA account for 10-15% of GIST. The most common PDGFRA mutation reported is D842V, which is known to confer resistance to imatinib and sunitinib. Currently, there is no approved treatment for GIST patients carrying such mutation. Cassier PA et al. showed that patients with D842V mutated GIST had a short median progression free survival (PFS) of 2.8 months with first line imatinib and 2.1 months with second line (2012 Clin Cancer Res). Crenolanib is a highly selective PDGFRA and FLT3 inhibitor with nanomolar activity against PDGFRα D842V mutation. In a previous dose-finding study, crenolanib showed a 31% clinical benefit rate with 2 pts achieving PR and 3 pts maintaining SD (total evaluable: 16 pts) in heavily pretreated GIST patients harboring the *PDGFRA D842V* mutation. In this study, 35% patients stayed on study for at least 7 months despite 80% patients having progressed after prior imatinib (15 pts), sunitinib (7 pts), dasatinib (5 pts), sorafenib (4 pts), nilotinib (2 pts), and regorafenib (2 pts). Therefore, a phase III trial has been initiated to further confirm the clinical activity of crenolanib in patients with *PDGFRA D842V*mutation. **Methods:** This randomized phase III study will enroll adult subjects with histologically or cytologically confirmed advanced or metastatic GIST with a *PDGFRA D842V* mutation. Prior treatment with TKI is allowed. Approximately 120 subjects will be randomized in a 2:1 ratio to receive either crenolanib 100 mg or matching placebo orally 3 times daily in combination with best supportive care. Randomization will be stratified by prior tyrosine kinase inhibitor exposure and ECOG performance status. The primary objective is PFS; key secondary objectives include OS. A formal interim analysis is planned after approximately 50 subjects have met the primary outcome. This study is already opened in the US, France, Norway, and Poland, and will soon be opened in Germany, Italy, Spain, UK and Asia. NCT02847429; EudraCT: 2015-000287-34 Clinical trial information: NCT02847429.

TPS11081 Poster Session (Board #403a), Sun, 8:00 AM-11:30 AM

Tappas: An adaptive enrichment phase 3 trial of TRC105 and pazopanib versus pazopanib alone in patients with advanced angiosarcoma (AAS). *First Author: Robin Lewis Jones, Royal Marsden Hospital, The Institute of Cancer Research, London, United Kingdom*

Background: AAS is an aggressive soft tissue sarcoma (STS) of endothelial cell origin with an expected median overall survival of 8-12 months. Pazopanib (P) is approved for treatment of advanced STS following progression on chemotherapy. In a retrospective study of 40 AAS patients treated with single agent P the median PFS was 3.1 months and median OS 9.9 months with no complete responses. Endoglin is an essential angiogenic receptor expressed on AAS that is upregulated following VEGF inhibition, and TRC105, an endoglin antibody, given with P produced durable complete responses in AAS patients with median PFS of 5.6 months in refractory patients including those receiving prior P. The TAPPAS trial is the first randomized Phase 3 trial performed in AAS, and was initiated following protocol assistance from the EMA and Special Protocol Assessment from the FDA. **Methods:** TAPPAS is a randomized multicenter study of TRC105/P vs P alone in the United States and Europe that is actively enrolling cutaneous and non-cutaneous AAS patients and incorporates an adaptive enrichment design. Key inclusion criteria: 0, 1 or 2 prior lines of therapy, ECOG ≤ 1. Primary endpoint is PFS and secondary endpoints include ORR and OS. The initial sample size of 124 patients, followed until 95 PFS events, provides more than 80% power to detect a hazard ratio of 0.55. At the time of interim analysis, projected to occur upon the occurrence of 40 events in approximately 70 patients, the result will be classified as belonging to either the favorable, promising, enrichment or unfavorable zones, based on conditional power. The sample size and PFS events will be unchanged in the favorable and unfavorable zones, and will be increased to a total of 200 patients followed for 170 PFS events in the promising zone. The trial will enroll 100 additional patients, with cutaneous disease only, in the enrichment zone and will follow them until 110 events are observed in the total cutaneous population. An independent DMC will follow the trial for safety and futility. The adaptive design requires the enrollment of fewer patients, preserves type-1 error, and protects power to detect a clinically meaningful survival benefit. (NCT 02979899). Clinical trial information: NCT02979899.

TPS11082 Poster Session (Board #403b), Sun, 8:00 AM-11:30 AM

Phase 2 trial of the novel multi-receptor tyrosine kinase inhibitor sitravatinib in well-differentiated/dedifferentiated liposarcoma. *First Author: Matthew Ingham, New York-Presbyterian Hospital, Columbia University School of Medicine, New York, NY*

Background: Well-differentiated/dedifferentiated liposarcoma (WD/DD LPS) is a sarcoma subtype of adipocytic origin characterized by amplification of cyclin dependent kinase 4 (CDK4) and MDM2. WD/DD LPS is resistant to chemotherapy and success with CDK4 inhibitors is limited. We recently characterized the landscape of activated receptor tyrosine kinases (RTKs) and intracellular signaling pathways finding marked heterogeneity by sarcoma subtype [Patwardhan et al. Oncotarget 2016;7(4)]. In WD/DD LPS cell lines, phosphorylated (p) IGF1-R, MET and PDGFRb are strongly expressed. Selective siRNA knockdown of expression of 1 or more of these RTKs inhibited growth of WD/DD LPS cell lines. Sitravatinib (S) is a novel inhibitor of a broad panel of related RTKs. We showed that S abrogates expression of p-RTKs, including IGF1-R, MET and PDGFRb, at low nanomolar concentrations and potently inhibits proliferation of WD/DD LPS cell lines, where anti-proliferative effects of S were superior to other RTK inhibitors including imatinib, crizotinib and pazopanib. S suppressed tumor growth *in vivo* in WD/DD LPS. A phase 1 trial of S in solid tumors showed clinical activity in WD/DD LPS. Recommended phase 2 dose was 150 mg/day. As there are no approved RTK inhibitors for adipocytic sarcomas, and based on these findings, we initiated a phase 2 trial of S in WD/DD LPS. **Methods:** This is a single-arm open-label multi-center Simon 2 stage phase II trial of S in 29 patients (pts) with advanced WD/DD LPS who failed 1 prior therapy and show disease progression before enrollment. Pts receive S 150 mg orally daily continuously. Primary endpoint is the progression free rate at 12 weeks (PFR_{12}) versus historical controls. The design has power of 85% to show improvement in PFR_{12} from 20% (inactive) to 40% (active) with $\alpha = 0.10$. Secondary endpoints are ORR, PFS and safety. A subset of pts undergo baseline and on-treatment biopsies and reverse phase protein array used to measure changes in expression of p-RTKs and signaling pathway proteins with confirmation by immunoblot. Genomic landscape of these tumors will be analyzed by next generation sequencing. The study opened in 1/2017. Clinical trial information: NCT02978859.

11500 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

TCR repertoire sequencing of 254 resected non-small cell lung cancers to reveal TCR clonality in normal tissues compared to tumor tissues. *First Author: Alexandre Reuben, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The mechanisms underlying resistance to immune checkpoint blockade are poorly understood. Major efforts have been made to understand how mutations, through generation of neoantigens, may alter tumor immunogenicity and anti-tumor responses, particularly through T cell responses. However, the T cell repertoire and its interaction with cancers bearing specific molecular alterations have not been systemically studied. **Methods:** We delineated the landscapes in the T cell receptor (TCR) repertoire, immune infiltration (immunohistochemistry using multiple immune markers), genome (exome sequencing), epigenome (methylation array) and transcriptome (mRNA gene expression array) of 254 resected non-small cell lung cancers (NSCLC), matched normal lung tissues and peripheral blood mononuclear cells (PBMC). We report herein the preliminary analyses of TCR sequencing of NSCLC tumors and matched normal lung tissues. **Results:** We observed that: 1) Smaller tumors (smaller than median) had a higher T cell infiltrate ($p = 0.0016$) and higher entropy than larger tumors ($p = 0.0098$); 2) Tumors from ever/current smokers had higher T cell clonality than former/never-smokers ($p = 0.005$); 3) TCR clonality was positively correlated with mutational burden ($p = 0.0026$); 4) Compared to tumors, normal lung tissues demonstrated significantly less T cell infiltration ($p = 2.1x10^{-11}$), but a significantly higher clonality ($p = 3.9x10^{-7}$). Finally, many T cell clones, including major clones were shared between normal lung tissues and matched NSCLC tumors. **Conclusions:** Our preliminary data demonstrate the distinct immune microenvironment in different NSCLC tumors may be associated with particular clinicopathological features. The higher TCR clonality in normal lung tissues and overlap of T cell clones between normal lung and NSCLC tumors implies a significant proportion of tumor infiltrating T cells may be a function of constant exposure to mutagens rather than an anti-tumor response. Analysis of the peripheral TCR repertoire, the molecular landscape of these tumors and the association with immune profiling is underway.

11501 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Immune and molecular determinants of response to neoadjuvant chemotherapy in inflammatory breast cancer. *First Author: Sangeetha Meda Reddy, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Inflammatory breast cancer (IBC) is the most aggressive form of primary breast cancer and has poor responses to standard of care neoadjuvant chemotherapy (NAC). Given there is a limited understanding of the immune microenvironment of IBC, this study aims to characterize the immune and molecular profiles of stage III and IV IBC and to identify biomarkers of response to treatment and targets for future therapies. **Methods:** IBC patients with available pre-treatment tumor samples and with intent to take to mastectomy were identified in the IBC tumor registry and tissue bank. Tumor infiltrating lymphocyte (TIL) infiltration in the tumor stroma was quantified on H&E slides per consensus guidelines ($n = 91$). On a subset of patients with available samples, deeper immune profiling was performed, including quantification of CD8 T cells by immunohistochemistry (IHC) ($n = 33$), PD-L1 tumor expression by IHC ($n = 14$), myeloid cells by multiplex IHC ($n = 15$), T cell clonality by T cell receptor sequencing ($n = 22$), and total mutational load (TML) by whole exome sequencing ($n = 20$). **Results:** Mean TIL were higher in tumors from patients that achieved a pathological complete response (pCR) to NAC than from those that did not (13.79 vs 7.24%, $p = 0.019$) and in patients with stage III compared to stage IV disease (11.90 vs 4.79%, $p < 0.001$). Though no statistically significant differences in CD8 infiltrate by response, stage, or receptor status were seen, the presence of a more clonal T cell population was predictive of pCR (13.27 vs 5.70% top 5 clone frequency, $p = 0.042$ among stage III patients). Myeloid cell staining revealed that tryptase staining, indicative of mast cells, was inversely associated with pCR (28.26 vs 108.0 counts/mm2, $p = 0.011$). Three of fourteen patient tumors displayed low PD-L1 tumor positivity (range 1-2%, 1+-2+) with the others being negative. Genomic profiling showed no statistically significant differences in TML by stage, receptor status, response, or immune infiltrate. **Conclusions:** Higher TIL, more clonal T cells, and lower mast cell infiltration are predictive of response to NAC in IBC. Comprehensive immune characterization of a larger cohort of pre- and post-treatment samples is currently underway.

11503 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Cancer-associated macrophage-like cells as prognostic indicators of overall survival in a variety of solid malignancies. *First Author: Daniel Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: Cancer Associated Macrophage-Like cells (CAMLs) are a recently described circulating stromal cell subtype commonly found in the peripheral blood of patients in all stages of solid malignancies and in a variety of cancer subtypes. However, while their biological association to cancer is being studied, their clinical utilization as it relates to cancer prognosis has not been evaluated. **Methods:** A two year prospective study was undertaken to evaluate the relationship of CAMLs and overall survival (OS) in 6 solid tumor types. The single blind multi-institutional study consisted of 269 stage I-IV patients; breast ($n = 57$), esophageal ($n = 21$), prostate ($n = 43$), pancreatic ($n = 59$), lung ($n = 54$), and renal cell ($n = 35$), in treatment ($n = 134$) and untreated baseline ($n = 135$). 7.5mL of whole blood was filtered by CellSieve microfiltration assay and CAMLs enumerated, as previously described. Patients were grouped by CAML number (< 6 or ≥ 6) and by size (< 49 or ≥ 50 μm) to evaluate hazard ratios (HR) by censored univariate & multivariate analysis. **Results:** CAMLs were identified in 93% of samples, averaging 8.2 CAMLs/7.5mL blood sample, and found in all 6 cancers at baseline and during treatment. Average CAML number was associated with disease stage and CAML positivity was 4.4 & 80% (Stage I), 4.7 & 93% (Stage II), 9.3 & 98% (Stage 3), 12.1 & 97% (Stage IV). Univariate analysis of patients ($n = 269$) stratified by ≥ 6 CAMLs had reduced OS (HR = 1.8, 95%CI 1.1-2.9, $p = 0.03$). Further, CAML size also had reduced OS in patients with ≥ 50 μm CAMLs (HR = 2.7, 95%CI 1.8-4.0, $p < 0.0001$). **Conclusions:** Our data suggests that in solid malignancies, CAML number and size appear to clinically correlate with OS in early and late stage disease. Given these results relating CAMLs with OS, further analysis is warranted to determine if CAMLs can serve as a clinically-relevant blood-based marker.

11504 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Interferon-gamma (INFG), an important marker of response to immune checkpoint blockade (ICB) in non-small cell lung cancer (NSCLC) and melanoma patients. *First Author: Niki Karachaliou, Hospital Universitari Sagrat Cor - Grupo Quirónsalud- Oncology Department, Barcelona, Spain*

Background: PD-L1 can be induced by oncogenic signals or up-regulated via INFG in a STAT1- and NFκB-dependent manner. STAT3 opposes STAT1-mediated anti-tumor immune responses. I kappa B kinase epsilon (IKBKE) is an interferon signaling inducer. We explored whether INFG expression in pre-treatment tumors is associated with to the efficacy of ICB in NSCLC and melanoma patients. The role of inflammation-associated transcription factors STAT3, IKBKE and STAT1 was also examined. **Methods:** Total RNA from 17 NSCLC and 21 melanoma patients, was analyzed by qRT-PCR. INFG, STAT3, IKBKE, STAT1 and PD-L1 mRNA were examined. PD-L1 protein expression in tumor and immune cells was evaluated (Ventana SP142 assay). Progression free survival (PFS) and overall survival (OS) were estimated. **Results:** 17 previously treated NSCLC patients received nivolumab; 71% lung adenocarcinoma, 71% male, 53% smokers, 35% KRAS mutant, 88% EGFR wild-type (wt). 21 previously treated melanoma patients received pembrolizumab; 67% male, 67% BRAF wt. PFS to nivolumab was significantly longer in NSCLC patients with high vs. low INFG expression (5.12 vs. 2mo, $p = 0.0124$). PFS to pembrolizumab was significantly longer in melanoma patients with high vs. low INFG expression (4.99 vs. 1.86mo, $p = 0.0099$). Significantly longer OS was observed for melanoma patients with high vs. low INFG expression (not reached vs. 3.10mo $p = 0.0183$). There was a trend for longer OS for NSCLC patients with high vs. low INFG expression (10.15 vs. 4.86mo, $p = 0.0687$). The other gene levels and PD-L1 protein levels in tumor and immune cells did not affect the outcome to ICB. IKBKE was positively correlated with INFG and PD-L1 expression (NSCLC Spearman's $\rho = 0.58$ and 0.65; melanoma Spearman's $\rho = 0.61$ and 0.59), and STAT3 expression was loosely anticorrelated with PD-L1 expression (NSCLC Spearman's $\rho = -0.21$; melanoma Pearson's $\rho = -0.01$). **Conclusions:** INFG is an important marker for qRT-PCR mediated prediction of response to ICB in NSCLC and melanoma patients. Further research is warranted in order to validate that INFG is more accurate than PD-L1.

11505 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Increased CD73 and reduced IFNG signature expression in relation to response rates to anti-PD-1(L1) therapies in EGFR-mutant NSCLC. *First Author: Katie Streicher, MedImmune, Translational Medicine (currently with EMD Serono), Gaithersburg, MD*

Background: Anti-PD-1(L1) therapies appear to be less efficacious in NSCLC patients whose tumors have EGFR activating mutations, but the underlying mechanism is poorly understood. We investigated the relationship between **Methods:** Flow cytometry and/or quantitative PCR were used to evaluate genes and proteins in five NSCLC EGFR mt cell lines and 6 wt lines. Anti-EGFR TKIs gefitinib and osimertinib were used at concentrations ranging from 0.001-100uM; EGF was used at 50 ng/mL. CP1108/NCT01693562 was a non-randomized phase 1/2 trial evaluating durvalumab (10 mg/kg Q2W) in advanced NSCLC. As of 24OCT16, 304 previously treated patients in CP1108 were enrolled. RNA sequencing was conducted on available tumor specimens from 97 patients in CP1108. CP1108 and TCGA were separated by EGFR status for genomic comparisons. **Results:** Median CD73 expression was increased 10-fold in EGFR mt NSCLC cell lines (n = 5) compared to wt cell lines (n = 6). EGF induced CD73 protein levels 5-40-fold in 3/6 EGFR wt lines. There was dose-dependent inhibition of CD73 expression (45-70 fold maximum) following treatment with gefitinib or osimertinib in 3/5 mt cell lines and 4/6 wt lines, suggesting a causal relationship between the EGFR pathway and CD73 expression. Consistent with these observations, EGFR mutant tumors had $\geq$2 fold increased expression of CD73 compared to wt ($p < 0.05$) in TCGA and CP1108 NSCLC adenocarcinoma patients. These EGFR mutants had significantly lower levels of IFNg signature, previously reported to be associated with enhanced benefit from durvalumab. **Conclusions:** Our findings identify a novel relationship in NSCLC between EGFR pathway activation, expression of the immunosuppressive molecule CD73 and reduced expression of IFNg mRNA signature. These results prompt the hypothesis that overexpression of CD73 in EGFR-mt NSCLC may explain, at least in part, the reduced benefit from anti-PD-1(L1) in this subset of NSCLC, and suggest evaluating anti-CD73 in combination with EGFR TKIs or anti-PD-L1 in EGFR-mt NSCLC.

11506 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Genomic profiling of resistant tumor samples following progression on EGF816, a third generation, mutant-selective EGFR tyrosine kinase inhibitor (TKI), in advanced non-small cell lung cancer (NSCLC). *First Author: Daniel Shao-Weng Tan, National Cancer Centre Singapore, Singapore, Singapore*

Background: Up to 60% of patients (pts) with NSCLC harboring an activating EGFR mutation (mut) and treated with a 1st generation EGFR TKI develop a secondary gatekeeper T790M mut. EGF816 is an irreversible EGFR TKI that is highly potent against activating mut (L858R, ex19del) and T790M mut, while sparing wild-type EGFR. As previously reported, in a Phase I dose escalation study, the overall response rate to EGF816 in pts with advanced EGFR T790M mut NSCLC was 47% and the disease control rate was 87%. However, pts ultimately develop disease progression. Tumor biopsies were obtained from pts who had progressed on EGF816 to identify mechanisms of resistance. **Methods:** Pts with NSCLC with locally or centrally confirmed T790M status were enrolled in this multicenter, dose escalation study to determine the safety, tolerability and antitumor activity of EGF816 (NCT02108964). EGF816 was administered at 7 dose levels ranging from of 75-350 mg QD. Following disease progression, a tumor sample was obtained and was analyzed by the Foundation Medicine next-generation sequencing (NGS) T7 panel, which interrogates 395 cancer-related genes for base substitutions, insertion-deletions, and copy number changes, as well as introns of 31 genes involved in rearrangements. **Results:** Tumor samples taken following disease progression on EGF816 were analyzed from 9 pts. Of the 8 pts whose tumors were T790M+ at baseline, this was detected in only 3 pts' post-EGF816 progression samples. One patient developed an EGFR C797S mut and concurrent deletion in mTOR. Other identified alterations include BRAF fusions (n = 2) and c-MET amplification (n = 1). Only one patient was found to have concurrent TP53 mutation and RB1 truncating mutation. Individual patient response data, including duration of response, will be presented along with detailed genomic parameters. **Conclusions:** NGS analysis of tumors that developed resistance to EGF816 revealed multiple potential mechanisms of resistance. These data are hypothesis-generating and could lead to rational combination studies with EGF816 to improve the depth and/or duration of response to EGF816. Clinical trial information: NCT02108964.

11507 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Genetic variations within the vitamin C transporter genes to predict outcome in metastatic colorectal cancer patients treated with first-line FOLFIRI and bevacizumab: Data from FIRE-3 trial. *First Author: Martin D. Berger, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Vitamin C is involved in many critical metabolic processes. Beside its major role as an antioxidant and free radical scavenger vitamin C exerts a regulatory influence on angiogenesis. Additionally, epidemiologic studies show an association between vitamin C levels and incidence of cancer.We therefore hypothesize that variations in genes encoding for vitamin C transporter proteins may predict outcome in patients (pts) with metastatic colorectal cancer (mCRC) treated with FOLFIRI and bevacizumab (bev). **Methods:** Theimpact of 3 functional SNPs within the SVCT1, SVCT2 and Glut1 genes on outcome was evaluated in 292 pts with mCRC treated with first-line FOLFIRI/bev in the randomized phase III FIRE-3 trial. 294 pts receiving FOLFIRI and cetuximab (cet) (FIRE-3) served as a negative control. Genomic DNA was extracted from formalin fixed paraffin embedded tissue and SNPs were analyzed by PCR-based direct sequencing. **Results:** Baseline characteristics in the FOLFIRI/bev arm were as follows: female/male 99/193; median age = 65y andmedian PFS/OS = 10.1/24.2 months (mts). The SVCT1 rs11242462 SNP showed significant association with PFS. T allele carriers had a longer median PFS compared to those with a C/C genotype (10.7 vs 9.7 mts) in both univariate (HR 0.77, p = 0.046) and multivariate analysis (HR 0.73, p = 0.028). The effect on outcome was most significant among KRAS mutant pts. Here, T allele carriers showed a markedly prolonged PFS and OS compared to pts with a C/C genotype (12.5 vs 7.0 mts, HR 0.50, p = 0.018 and 32.8 vs 14.7 mts, HR 0.45, p = 0.009). These associations remained significant in multivariate analyses (p = 0.009 and p = 0.021, respectively). However, the favorable impact on outcome was not observed among T allele carriers treated with FOLFIRI/cet. **Conclusions:** Our results provide the first evidence that the SVCT1 polymorphism rs11242462 might serve as a predictive marker in pts with mCRC treated with FOLFIRI/bev in the first-line setting. Targeting vitamin C transporter proteins might be a promising approach to further improve treatment options against mCRC and to overcome resistance to anti-angiogenic therapy.

11508 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Dissecting primary resistance to anti-EGFRs in *RAS* and *BRAF* wt metastatic colorectal cancer (mCRC): A case-control study. *First Author: Chiara Cremolini, Unit of Medical Oncology 2, Azienda Ospedaliera-Universitaria Pisana, the Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy*

Background: Almost half of *RAS* and *BRAF*wt mCRC patients do not respond to anti-EGFRs. Different molecular alterations suggested as predictors of resistance have not been validated. **Methods:** We conducted a case-control study to prospectively demonstrate the negative predictive impact of *HER-2* amplification or mutations (mut), *MET* amplification, *NTRK/ROS1/ALK/RET* rearrangements, and mut activating MAPKs or PI3K/Akt axis. Patients with *RAS* and *BRAF*wt mCRC clearly resistant (cases) or clearly sensitive (controls) to anti-EGFRs were selected. Hypothesizing a prevalence of candidate alterations of 0% and 15% among controls and cases, 47 cases and 47 controls were needed to be able to reject the null hypothesis of equally prevalent alterations, with a- and b- error 0.05 and 0.20. Since hypermutated tumors may hardly rely on a single pathway for their growth, we also evaluated the impact of microsatellite instability. **Results:** 47 cases and 47 controls were included. Primary endpoint was met: mentioned alterations were reported in 20 (42.6%) cases and 1 (2.1%) control ($p<0.001$). MSI-high was significantly more frequent among resistant than sensitive tumos (15% vs 0%, $p<0.001$). **Conclusions:** This is the first prospective demonstration that the combined assessment of these rare alterations allows to better select patients for anti-EGFRs, while opening the way to other tailored therapies.

Molecular alteration	Cases (Resistant patients) N=47	Controls (Sensitive patients) N=47
***HER-2* amplification**	7*	0
***HER-2* mut**	1 (G776V, exon 20)	0
***MET* amplification**	5*	0
***NTRK* rearrangements**	2 (*SCYL3-NTRK1* and *TPM3-NTRK1*)	0
***ALK* rearrangements**	0	0
***ROS1* rearrangements**	0	0
***RET* rearrangements**	1 (*CCDC6-RET*)	0
***PIK3CA* exon 20 mut**	1 (A1035V)	1 (H1047R)
***AKT1* mut**	1 (R25C, exon 2)	0
***PTEN* mut**	3 (L247S, R233stop and del P248, exon 7)	0
Total n. of patients with candidate alterations	20	**1**
Microsatellite instability (MSI-high)	7	0
RAS* mut at low allele fraction *	3 (*KRAS* G12V, exon 2, 6%; *NRAS* Q61R, exon 3, 10%; *KRAS* Q61H, exon 3, 12%)	0
New *RAS* mut	3 (2 *KRAS* L19F, exon 2; *KRAS* T50I, exon 3)	0

* in 1 case *HER-2* and *MET*co-amplification was found; ** by Hotspot Cancer Panel v2, (Life Technologies), previously found wt by pyrosequencing

11509 Poster Discussion Session; Displayed in Poster Session (Board #209), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

***RAS* mutations concordance in circulating tumor DNA (ctDNA) and tissue in metastatic colorectal cancer (mCRC): RASANC, an AGEO prospective multicenter study.** *First Author: Jean-Baptiste Bachet, Hopital Universitaire Pitie-Salpetriere, Paris, France*

Background: *RAS* mutational status is required to prescribe anti-EGFR antibodies in mCRC. In comparison to molecular testing from tumor tissue, the characterization of *RAS* mutations in ctDNA is a promising and credible way to shorten the workflow. This study reports for the first time the performance of plasma testing in a large prospective series. **Methods:** Blood samples were prospectively collected before 1st line chemotherapy in mCRC patients. ctDNA was centrally assessed by NGS using the colon lung cancer V2 Ampliseq panel and by methylation digital PCR assay (WIF or NPY). Tumor tissue testing was done according to routine practice in each center. We expect a minimal kappa coefficient of 0.7 to reflect concordance. In order to have a precision of $\pm$ 0.07 with an estimated 5% of non-exploitable data 425 pts had to be included. Results were analyzed separately in the whole study population and in the subgroup of pts with ctDNA evidenced either by the presence of at least 1 mutation or by the presence of 1 methylated biomarker. **Results:** From 07/2015 to 12/2016, 425 patients were included, and 406 plasma samples were available for analysis. A *RAS* mutation was detected in 183 plasma samples (45.1%) As compared to tumor mutational status the kappa coefficient was 0.68 (95%CI: 0.61-0.75) with a concordance of 83.7%. Primary tumor removal, metachronous status, absence of liver metastases and peritoneal carcinomatosis were significantly associated with mutant *RAS* tumor and negative plasma status. In the subgroup of 324 samples for which ctDNA was evidenced, kappa coefficient was 0.85 (95%CI: 0.80-0.91) with a concordance of 92.9%. 23 pts had discordant results: *RAS* mutation in tumor tissue and not in ctDNA (15 pts, 4.6%), *RAS* mutation detected in ctDNA but not in tumor tissue (8 pts, 2.5%). Rectal tumor, absence of liver metastases, peritoneal carcinomatosis and tumor tissue cellularity $<$ 10% were associated with discordant cases. **Conclusions:** We confirm, in this large prospective multicenter study, the high concordance rate for RAS status assessment between blood and tumor samples. This result argues for the use of blood testing in daily practice for pts with detectable ctDNA. Clinical trial information: NCT02502656.

11510 Poster Discussion Session; Displayed in Poster Session (Board #210), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Evaluation of clinical outcomes by analysis of mutations in tumor tissue and circulating plasma DNA using next-generation sequencing (NGS) from STEAM, a prospective, randomized, multicenter study in metastatic colorectal cancer (mCRC). *First Author: John J. Lee, Roche Sequencing Solutions, Pleasanton, CA*

Background: STEAM (NCT01765582) assessed the efficacy and safety of concurrent (c) and sequential (s) FOLFOXIRI-bevacizumab (BEV) vs FOLFOX-BEV for first-line treatment of mCRC. **Methods:** The AVENIO ctDNA Expanded Kit (Research Use Only) was used to assess somatic mutations in 77 cancer-related genes by NGS in tissue, and both pre- and post-induction plasma samples (n = 182, 150 and 118 respectively) from STEAM. Four mutation classes including single-nucleotide variants (SNVs), indels, copy number amplifications (CNAs) and fusions were identified. SNVs and indels were called in tissue and plasma at allele frequencies of 5% and 0.25% respectively. **Results:** Overall concordance of mutations in pre-induction plasma with tissue was 83%. Concordance for the seven most mutated genes ranged from 91.5%-100%. In pts with matched samples (n = 118), RAS WT pts showed significantly longer progression-free survival (PFS) in both cFOLFOXIRI-BEV (A) and sFOLFOXIRI-BEV (B) arms versus FOLFOX-BEV (C), using genotyping of either tissue or plasma. This was not seen in RAS MUT pts. In contrast, TP53 WT showed no significant treatment differences while TP53 MUT showed longer PFS for cFOLFOXIRI-BEV versus FOLFOX-BEV. A list of mutation frequencies for all samples, as well as hierarchical clustering analysis of tissue mutations will be presented. **Conclusions:** The AVENIO ctDNA Expanded Kit identified mutations in 77 cancer-related genes, in both plasma and tissue, with high overall concordance. Compared to FOLFOX-BEV, longer PFS was observed for c- or s- FOLFOXIRI-BEV in RAS WT pts and for cFOLFOXIRI-BEV in TP53 MUT pts, irrespective of sample type. These results are hypothesis generating and require further clinical validation. Clinical trial information: NCT01765582.

	Tissue			Pre-Induction Plasma		
		HR	p-val		HR	p-val
A v C	RAS WT (n = 55)	0.39	0.038	RAS WT (n = 65)	0.38	0.023
B v C		0.32	0.015		0.39	0.014
A v C	RAS MUT (n = 63)	0.47	0.105	RAS MUT (n = 53)	0.50	0.155
B v C		1.01	0.980		1.11	0.793
A v C	TP53 WT (n = 43)	0.44	0.168	TP53 WT (n = 47)	0.48	0.166
B v C		1.00	0.997		0.97	0.933
A v C	TP53 MUT (n = 75)	0.40	0.016	TP53 MUT (n = 71)	0.36	0.010
B v C		0.56	0.089		0.51	0.063

11511 Poster Discussion Session; Displayed in Poster Session (Board #211), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Genomic analysis of circulating tumor DNA in 442 patients with carcinoma of unknown primary: Implications for targeted therapeutics. *First Author: Shumei Kato, Moores Cancer Center, La Jolla, CA*

Background: Carcinoma of unknown primary (CUP) is a rare, difficult-to-treat malignancy. To further understand the genomic landscape of CUP, next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) from patient plasma was performed. To our knowledge, this is the largest cohort of patients with CUP interrogated by liquid biopsy. **Methods:** We evaluated the molecular alterations of 442 patients with CUP using clinical-grade NGS of ctDNA isolated from patient plasma. The test detects single nucleotide variants in 54-70 genes, as well as copy number amplifications, fusions and indels in selected genes. **Results:** Eighty percent of patients (353/442) had ctDNA alterations with 66% (290/442) harboring at least one characterized alteration; 43.9% (194/442) $\geq$ 2 characterized alterations. *TP53*-associated genes were most commonly altered (37.8% [167/442]) followed by genes involved in the MAPK pathway (31.2% [138/442]), PI3K signaling (18.1% [80/442]) and the cell cycle machinery (10.4% [46/442]). Among patients harboring at least one characterized alteration, most (87.9% [255/290]) had distinct genomic profiles, and 99.7% (289/290) had alterations theoretically targetable with either an FDA-approved or investigational agent. The mean number of potentially actionable alterations per patient was 1.7 (range, 0 to 10). Illustrative patients who had dynamic changes in ctDNA content during the course of therapy and responding patients matched on the basis of ctDNA to targeted therapies or immunotherapy will be presented. **Conclusions:** Evaluation of ctDNA was feasible among individuals with CUP. Most patients harbored a unique somatic profile. The majority of patients had potentially actionable alterations. Serial ctDNA showed dynamic changes in molecular alterations in response to therapy, and several patients have attained responses to targeted or immune therapies chosen on the basis of ctDNA findings. The current report suggests that non-invasive liquid biopsies merit investigation in next generation clinical trials.

11512 Poster Discussion Session; Displayed in Poster Session (Board #212), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Genomic profiling of squamous malignancies across anatomic sites. *First Author: Christine H. Chung, Moffitt Cancer Center, Tampa, FL*

Background: Primary squamous cell carcinomas (SCCs) have diverse etiologies, but can share genomic features. We reviewed the genomic profiles of a series of SCC cases of differing anatomic origin. **Methods:** Hybrid-capture based genomic profiling of 182 or 236 or 315 genes was performed on 4783 squamous malignancies in the course of clinical care, with baits for HPV6, 11, 16, and 18, and assessment of tumor mutation burden (TMB; mutations/Mb) and microsatellite instability. **Results:** Sites of origin were head and neck (HNSCC, n = 1300), cervical (cSCC; n = 318), anal (aSCC, n = 248), esophageal (n = 242), lung (lSCC, n = 2386), and cutaneous (sSCC, n = 289) SCC cases. For HNSCC, cSCC, and aSCC (collectively termed HCA SCC), 395 (30%), 215 (68%), and 211 (83%) were HPV positive, respectively. For HCA SCC, the most common GA were in *TP53* (45%), *CDKN2A* (29%), *PIK3CA* (24%), *TERT* (21%), and *FAT1* (14%). The most frequent GA differentially associated with HPV status were in *PIK3CA* (34.9% versus 16.0%), *CYLD* (11.4% versus 1.4%) and *PTEN* (14.8% versus 6.1%) for HPV+ cases, and *TP53* (3.8% versus 76.5%), *CDKN2A* ()1.4% versus 49.8%), and *TERT* (4.3% versus 33.0%) for HPV- cases. Mean TMB for HPV+ and HPV- cases were 6.6 (STDEV 7.3) and 13.7 (STDEV 29.7), respectively. TMB of all SCC cases was significantly different ($p < 10^{-12}$) when stratified by HPV status. For lSCC and eSCC, the most common GA were found in *TP53* (86%) *CDKN2A* (40%), and *PIK3CA* (26%) and mean TMB was 11.6 with HPV found in 3.1% of cases. In sSCC, the most common GA were in *TP53* (85.5%), *CDKN2A* (54.3%), and *TERT*(44.0%), and mean TMB was 59.5 with HPV in 3.1% of cases. Subsets of SCC cases had defining and targetable GA including bi-allelic deletion of *SMARCB1* ($<$ 0.3%), amplification of *PD-L1* (~2%), and various kinase fusions. Cases demonstrating radiologic response to immunotherapy and matched targeted therapies, as well as subsequent development of multiple mechanisms of acquired resistance, will be presented. **Conclusions:** HPV driven SCC have similar genomic profiles regardless of of site origin, and have a significantly lower median TMB than HPV negative SCC. Early consistency of responses of SCC to matched therapies may strengthen the case for site independent genomic predictors of therapy response.

11513 Poster Discussion Session; Displayed in Poster Session (Board #213), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Whole exome analysis of patients (pts) with metastatic GIST (mGIST) demonstrating exceptional survival with imatinib (IM) therapy compared to those with short term benefit. *First Author: Eytan Ben Ami, Dana-Farber Cancer Institute, Boston, MA*

Background: Most patients with mGIST initially benefit from IM therapy with durable disease control (DC), i.e. objective responses and stable disease, with median duration of approximately two years. We reported exceptional long-term benefit (LTB) with DC and overall survival (OS) >14 years in a subset of mGIST pts treated with IM. We aimed to characterize tumor and normal genomes of exceptional LTB pts treated with IM and compare with short-term benefit (STB) pts. **Methods:** Among 87 mGIST pts enrolled between July 2000 and June 2001 in the B2222 trial of IM and followed prospectively at the Dana Farber Cancer Institute, we identified 10 LTB (>14 years of DC) pts, and 6 STB (<2 years of DC) pts on IM. Targeted genotyping (*KIT/PDGFRA*)was performed in all tumors (n=16). Whole exome sequencing (WES) was performed on archival FFPE tumor samples from LTB and STB pts prior to any IM treatment. We compared WES results from LTB with STB pts to identify unique features of long-term DC and OS with IM. **Results:** *KIT* mutation in LTB pts were as follows: exon 11(6 pts), exon 9 (3 pts), and SDH-deficient with *KIT/PDGFRA* wild type (1 pt). In STB pts, mutated *KIT*was found 4 pts (exon 11) and 2 pts (exon 9). WES was successful in six LTB (five exon 11, one exon 9) and three STB (two exon 11, one exon 9) pts. A total of 1211 somatic mutations were observed (546 missense, 37 nonsense, 256 silent, 285 indels, 36 splice mutations). The mean somatic mutational burden was 3.42 mutations/Mb (range 1.18-4.93) and 3.34 mutations/Mb (range 1.06-6.68) among LTB and STB, respectively. Genes mutated in LTB but not in STB were MUC7 (4 pts), H1F0 (3 pts), ZKSCAN1 (3 pts), SLC24A1 (3 pts) and USP4 (2 pts). **Conclusions:** KRAB domain containing zinc finger (KRAB-ZNF) gene expression signatures have been associated with prediction of response to IM, and a possible role in response modulation to tyrosine kinase inhibitors in GIST. We found variants in ZKSCAN1, a gene encoding a transcriptional regulator of the KRAB subfamily of zinc finger, to be present in LTB but not in STB. KRAB-ZNF family of genes may be linked to LTB and exceptional survival with IM in mGIST; functional analyses will be important to test such hypotheses.

11514 Poster Discussion Session; Displayed in Poster Session (Board #214), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Molecular signatures and responses to targeted therapies in over 300 relapsed and therapy-refractory young adult (AYA) and childhood cancers. *First Author: Erin Haag Breese, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: Contemporary chemotherapy-based regimens provide cures for most pediatric & AYA cancers. However, for patients with relapsed/refractory malignancies, outcomes are poor & imply a distinct and aggressive biology. Identifying common themes in the molecular architecture & oncogenic mechanisms in these patients is a critical priority for drug development. We hypothesized that the molecular signature of cancers in these patients would be independent of histology. We also assessed the response to molecular alteration (MA)-targeted therapies. **Methods:** IRB-approved analysis of MAs in 306 relapsed/refractory pediatric & AYA malignancies (116 hematologic malignancies, 68 sarcomas, 46 neuroblastomas, 36 CNS, 14 liver, 9 renal, 17 other) was performed. DNA was analyzed for MAs (Foundation Medicine, Cambridge, MA; Univ of Washington, Seattle, WA); additional MAs were identified by cytogenetic & fluorescent *in situ* hybridization analyses. **Results:** Median age was 8 years (range birth - 44 yrs). MAs were identified in 90.1% of patients & included a median of 2 mutations (range 0-18) in 133 cancer-related genes. In contrast to genomic analyses of *de novo* malignancies in children, a high frequency of TP53 MAs was identified (20.4% of patients) and was associated with inferior survival. MAs were identified in targetable pathways including cell cycle regulation (32.6%), DNA repair (7.2%), epigenetic (28.6%), RAS/RAF/MEK (24%), tyrosine kinase (TK; 18.4%), PI3K/AKT/mTOR (11.8%), and NOTCH/WNT (8.9%). A higher number of MAs was associated with inferior survival. Patients with alterations in epigenetic & TK pathways also had inferior outcomes. MAs were frequently independent of histology & the spectrum of mutations was similar to adult cancers. Exceptional responses were observed with MA-based assignment of therapies (epigenetic, NTRK, RAS/RAF/MEK & ALK). **Conclusions:** Relapsed/refractory pediatric & AYA cancers have frequent MAs independent of histology. The spectrum of MAs is distinct from *de novo* disease & potentially reflects tumor evolution & resistance mechanisms. These findings support MA-guided approaches to new drug development paired with adult trials.

11515 Poster Discussion Session; Displayed in Poster Session (Board #215), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

SHIVA: Randomized phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer—Overall survival (OS) analysis. *First Author: Sylvain Dureau, Institut Curie, Paris, France*

Background: The SHIVA trial is a multicentric randomized phase II trial comparing molecularly targeted therapy among 11 drugs based on tumor molecular profiling versus conventional therapy in patients with any type of cancer that is refractory to standard of care (NCT01771458). Only patients who had a druggable molecular alteration (DMA) identified on a mandatory tumor sample from a metastatic site using targeted sequencing, CGH and IHC were randomized. Cross-over was allowed at disease progression. The trial did not show any difference for its primary endpoint (PFS) *[Le Tourneau et al., Lancet Oncol 2015]*. We report here the OS of randomized and non-randomized patients. **Methods:** OS was estimated in the 4 following groups: 1) randomized patients, 2) patients for whom a DMA was identified but who were not subsequently randomized because they did not meet the randomization criteria (PS of 0 or 1, adequate organ function), 3) non-randomized patients because of the absence of DMA, and 4) non-randomized patients because no genomic analyses were performed. Since 70% of patients randomized into the standard arm eventually crossed over to the targeted therapy arm, all randomized patients were analyzed in group 1. The groups were compared in terms of patient characteristics using student and $\chi 2$ tests. OS was estimated using the Kaplan Meier method. **Results:** Among 741 patients included in SHIVA, 8 patients were included twice. Follow-up data were available for 680 out of the 733 patients. 197, 78, 222 and 183 patients belonged to groups 1 to 4, respectively. Median OS of the whole cohort was 7.9 months [95% CI: 7.0–9.1].As compared to non-randomized patients due to the absence of identified DMA, non-randomized patients with a DMA had a significantly worse prognosis: HR = 2.3 [95% CI: 1.7–3.0] ($p > 0.0001$) whereas randomized patients had a non-significant trend toward a better prognosis: HR = 0.85 [95% CI: 0.7–1.1] ($p = 0.18$). **Conclusions:** A statistically significant difference in OS was only observed in patients with a DMA who were not randomized. However, our analysis does not allow showing an intrinsic prognostic value of the DMA on OS.

LBA11516 Poster Discussion Session; Displayed in Poster Session (Board #216), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Performance of a high-intensity 508-gene circulating-tumor DNA (ctDNA) assay in patients with metastatic breast, lung, and prostate cancer. *First Author: Pedram Razavi, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 AM (EDT) on Saturday, June 3, 2017, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2017, issue of the *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

11517 Poster Discussion Session; Displayed in Poster Session (Board #217), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Characterization of tumor mutation load (TML) in solid tumors. *First Author: Mohamed E. Salem, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Rapid advances in immunotherapy have created a need for biomarkers to improve patient treatment selection. TML is proposed as a potential predictive biomarker due to its association with tumor immunogenicity. **Methods:** TML was assessed in 8020 tumors from 14 different cancers using somatic nonsynonymous missense mutations sequenced with a 592-gene panel. High TML was set at $\geq$ 17 mutations per megabase (mt/MB) based on an established concordance ($>$ 99%) with MSI-High in colorectal cancer (CRC). **Results:** Mean TML was highest in melanoma (Mel; 21 mt/MB), NSCLC (11 mt/MB), and bladder cancer (BLC; 11 mt/MB), whereas prostate cancer (PC), pancreas adenocarcinoma (PA), and renal cell carcinoma (RCC) had the lowest levels (all 6 mt/MB). High TML was seen most frequently in Mel (36%), NSCLC (15%), BLC (15%), and anal cancer (SCCA; 9%); and least frequently in PA (1.6%) and RCC (0.5%). Primary NSCLC carried lower TML than its brain metastases (11 vs. 16 mt/MB, $p < 0.001$). Older age was associated with higher TML in Mel ($p = 0.001$), CRC ($p = 0.009$), breast cancer (BC; $p = 0.01$), and NSCLC ($p = 0.02$). Higher TML was seen in males than in females for Mel ($p = 0.002$) and NSCLC ($p < 0.001$). Presence of mutations in oncogenic driver genes such as EGFR, ALK, ROS1 RET fusions, cMET exon 14 skipping correlated with lower TML in NSCLC (6.9 vs. 12 mt/MB, $p < 0.001$), as did BRAF and NRAS mutations in Mel (17 vs. 26, $p = 0.003$). Conversely, mutations in tumor suppressor genes such as ARID1A (CRC, NSCLC, and BLC) and NF1 (BC, CRC, Mel, BLC, and NSCLC) were associated with higher TML ($p < 0.05$). MSI-high was correlated with high TML in CRC and gastric cancers ($p < 0.05$). **Conclusions:** TML varied significantly among different cancers. High TML was associated with older age, absence of oncogenic mutations and presence of tumor suppressor gene mutations. Future studies will assess the impact of TML on clinical outcome and establish its role in selecting patients for immunotherapy.

	N = 8020	Mean TML	High TML %	PD-L1 %	TML ≥ 17 & PD-L1 %
Mel	399	21	37	23	9
NSCLC	2185	11	15	15	3
BLC	173	11	15	24	3
CRC	1768	10	6	3	1
right	390	12	10	6	2
Left	611	9	3	2	1
SCLC	99	10	5	5	3
SBA	95	9	7	11	2
SCCA	42	9	10	31	5
Gastroesophageal Ca	454	8	5	12	1
HCC	91	7	2	6	0
BC	1143	7	2	6	0
TNBC	401	7	2	11	0
Non-TNBC	702	7	4	6	0
Biliary Tract Ca	512	7	4	7	1
PC	260	6	2	1	0
RCC	192	6	0.5	16	0
PA	607	6	1.6	9	1

11518 Poster Discussion Session; Displayed in Poster Session (Board #218), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Changes in computer extracted features of vessel tortuosity on CT scans post-treatment in responders compared to non-responders for non-small cell lung cancer on immunotherapy. *First Author: Vamsidhar Velcheti, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Background: Immune-checkpoint blockade treatments demonstrate promising clinical efficacy in patients with non-small cell lung cancer (NSCLC). Nivolumab is a PD-1 inhibitor that is FDA approved for treatment of patients with chemotherapy refractory advanced NSCLC. The current standard clinical approach to evaluating tumor response is sub-optimal in defining clinical benefit from immunotherapy drugs. We sought to evaluate whether computer extracted measurements of vessel tortuosity significantly and differentially change post treatment between NSCLC patients who do and do not respond to immunotherapy. **Methods:** A total of 50 NSCLC patients including pre- and post- treatment CT scans were included in this study. The patients were either responders or non-responders to Nivolumab. Patients who did not receive Nivolumab after 2 cycles due to lack of response or progression as per RECIST were classified as 'non-responders'. A total of 35 tortuosity features of the vessels around the lung nodules were investigated. In the training cohort (N = 25), the features were ranked based on the degree of change between pre- and post- treatment CT. The top 4 features were used for training a Support Vector Machine (SVM) classifier to identify which patients did and did not respond to immunotherapy on a validation cohort of N = 25 patients. **Results:** The top features identified were the ones associated with the curvature of the vessel branches. The AUC for the SVM classifier was 0.75 for the training and 0.79 for the test set. **Conclusions:** Changes in specific vessel tortuosity features between baseline and post-treatment CT scans following nivolumab were different between NSCLC patients who did and did not respond. Multi-site validation of the vessel tortuosity features is needed to establish it as a predictive biomarker for NSCLC patients treated with immunotherapy.

11519 Poster Discussion Session; Displayed in Poster Session (Board #219), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Change in metabolic tumor activity on ^{18}F-FDG PET after a single dose of cetuximab to predict for treatment benefit, PFS, and OS in patients with advanced colorectal cancer. *First Author: Erik Jacobus Van Helden, Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: Despite RAS selection, one third of patients with metastatic RAS wild-type colorectal cancer (mCRC) do not benefit from anti-EGFR inhibitors. Therefore, an additional or more accurate predictive biomarker is needed to identify patients with primary resistant mCRC. **Methods:** In the IMPACT-CRC trial (NCT02117466) patients with chemotherapy refractory mCRC received 500 mg/m^2 cetuximab every 2 weeks. Before the first dose and just before the second dose, patients underwent a ^{18}F-FDG PET/CT (FDG PET). PET scans were quantitatively assessed by manual tumor delineation of $\leq$ 5 lesions, 2 per organ. Outcome is reported in total lesion glycolysis (TLG), defined as metabolic tumor volume times mean standard uptake value of the tumor. An optimal threshold to assess metabolic response was defined as decrease in TLG $\geq$15%. Quantitative data were correlated with CT evaluation after 8 weeks of treatment according to RECIST v1.1. **Results:** Out of 35 patients, 1 was excluded due to an infusion reaction. Median age was 64 years, 74% was male, 4 patients had a BRAF mutated tumor and 9 patients had right-sided primary tumors. 62% of patients had stable disease or partial response on CT after 8 weeks. At the time of this analysis, 88% of patients had progressive disease and 71% had died. Of the patients with right-sided tumors 11% had treatment benefit, compared to 80% in the left-sided group ($p = 0.001$). None of the 9 metabolic non-responders had treatment benefit, whereas 83% of the metabolic responders had treatment benefit according to RECIST v1.1. After adjustment for age, WHO score, BRAF mutation, sex and primary tumor site, FDG PET response remained correlated with PFS and OS ($p = 0.002$ and $p = 0.014$). **Conclusions:** Early evaluation of metabolic response after 1 dose of cetuximab is highly and independently predictive for treatment benefit with a 100% negative predictive value. Implementation of early FDG-PET evaluation in daily clinical practice can prevent unnecessary toxicity, costs of ineffective treatment and allows timely treatment adjustment for patients with mCRC undergoing anti-EGFR treatment. Clinical trial information: NCT02117466.

11520 Poster Discussion Session; Displayed in Poster Session (Board #220), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

ACRIN 6698 trial: Quantitative diffusion-weighted MRI to predict pathologic response in neoadjuvant chemotherapy treatment of breast cancer. *First Author: Savannah C. Partridge, University of Washington Seattle Cancer Care Alliance, Seattle, WA*

Background: Diffusion-weighted (DW) MRI is a non-contrast technique that can reflect treatment-induced alterations in tumor microstructure and cellularity. ACRIN 6698 was performed as a sub-study of the I-SPY 2 TRIAL to evaluate quantitative DW MRI for early assessment of breast cancer response to neoadjuvant chemotherapy (NAC) in a multisite, multiplatform trial. **Methods:** The IRB-approved trial was performed at ten institutions. Of 406 enrolled breast cancer patients, 272 were randomized to treatment (12 weekly cycles paclitaxel+/-experimental agent, followed by AC) and underwent breast DW MRI at four time points: pre-NAC (T1), early-NAC after 3 cycles paclitaxel (T2), mid-NAC between paclitaxel and AC (T3) and post-NAC (T4). Tumor apparent diffusion coefficient (ADC) was measured at each time point and compared for patients with and without complete pathologic response (pCR) by Wilcoxon signed rank test. Exploratory analyses were performed across subtypes defined by hormone receptor (HR) and HER2 expression. Performance for predicting pCR was assessed by calculating the area under the ROC curve (AUC). **Results:** Of 272 treated patients, 227 comprised the final cohort (14 were excluded for missing MRI exams, 31 for poor image quality). Median patient age was 48 (range, 25-77) years, and 71/227 (31.3%) achieved pCR. Subtype groups were HR+/HER2+ (n = 38), HR+/HER2- (n = 95), HR-/HER2+ (n = 20), and HR-/HER2- (n = 74). For the full cohort (all subtypes and treatments), both ADC and change in ADC from T1 were significantly predictive of pCR at T3 (AUC = 0.63, 95% CI 0.55-0.71; AUC = 0.62, 95% CI 0.53-0.70, respectively), and also at T4. ADC measures were not predictive of pCR at either T1or T2. Stratifying by subtype showed change in ADC at T3 was more predictive in HR-/HER2+ (AUC = 0.86) and HR+/HER2- (AUC = 0.75) tumors than HR-/HER2- and HR+/HER2+ tumors (AUC = 0.59 and 0.56, respectively). **Conclusions:** DW MRI reflects cytotoxic effects of chemotherapy, and mid-treatment ADC was a predictive marker of pCR. The predictive value of ADC varied across biologic subtypes. Further work is needed to determine the comparative predictive value of ADC to other imaging metrics. Clinical trial information: NCT01564368.

11521 Poster Session (Board #221), Sat, 1:15 PM-4:45 PM

Inter-tumor validation, through advanced MRI and circulating biomarkers, of plasma Tie2 as the vascular response biomarker for bevacizumab. *First Author: Gordon C. Jayson, CRUK Manchester Institute, Manchester, United Kingdom*

Background: VEGF inhibitor (VEGFi) use is compromised by lack of predictive/ response biomarkers. Previously, we identified plasma Tie2 (pTie2) as a vascular response biomarker (VRB) for bevacizumab (bev) in ovarian cancer (OC). Here, we applied dynamic contrast-enhanced MRI (DCE-MRI) and circulating biomarkers in colorectal cancer (CRC), to validate pTie2 as the first tumor VRB. **Methods:** Seventy patients were recruited, with untreated, mCRC and ≥1 lesion of 3-10cm diameter for DCE-MRI. Patients received bev 10mg/kg for 2 weeks to elicit a biomarker response and then FOLFOX6/bev until progressive disease (PD) Thirteen circulating and 6 imaging biomarkers were measured before and during treatment and at PD. Unsupervised correlation analysis identified bev-induced biomarker correlations. Biomarkers were evaluated by clustered parameter-time course studies to determine their epithelial or vascular origin. Clinical significance was determined by relating the biomarker data to tumor 3D volumetric change assessed by MRI and PFS. The emergent vascular biomarker signal was modelled with epithelial biomarkers to assess the independent contribution of the vascular compartment to PD. **Results:** Bev induced significant correlations between pTie2, Ang2 and K^{trans}. Cluster analysis of Tie2 concentration-time course curves showed that pTie2 reflected tumor K^{trans}but not CK18, an epithelial antigen, i.e. changes in pTie2 reflected tumor vascular biology Patients who had the greatest area under the pTie2-time curve had tumors with high $K^{trans}$and/or low pVEGFR2, pre-treatment. They also had the greatest reduction in tumor volume and longest PFS. Fusion of pTie2 and CK18 data significantly improved modelling of PD. **Conclusions:** Bev impacts tumor vasculature causing proportional changes in pTie2. Information from pTie2 adds clinical value to that derived from the epithelial compartment. Thus (i) pTie2 is the first vascular response biomarker for bev and probably all VEGFi and (ii) demonstration of separate vascular and epithelial compartments in ovarian and CRC validates the vascular compartment as a target. This work identifies the first assay that could optimise use of VEGFi. Clinical trial information: 2009-011377-33.

11522 Poster Session (Board #222), Sat, 1:15 PM-4:45 PM

Effect of mast cells on efficacy of anti-angiogenic therapy by secreting matrix-degrading granzyme b. *First Author: Mark Wroblewski, Department of Hematology and Oncology with Sections BMT and Pneumology, University Medical Center Hamburg-Eppendorf; Department of Tumor Biology, University Medical Center Hamburg-Eppendorf, University Hospital Hamburg-Eppendorf, Hamburg, Germany*

Background: Resistance towards anti-angiogenic therapy (AAT) still represents a substantial clinical challenge. As mast cell (MC) density is known to correlate with tumor angiogenesis, we analyzed if inhibition of MC holds potential to increase efficacy of AAT in mice and cancer patients. **Methods:** C57BL/6J (WT), NSG or MC-deficient $Kit^{W\text{-}sh}$(Wsh) mice were subcutaneously injected with Panc02, EL4 or BxPC3 cells with or without bone marrow-derived MC. Tumors were treated with 20 mg/kg of anti-VEGFR2 antibodies (DC101) or 25 mg/kg cromoglicic acid. Tissue microarrays from n = 299 breast cancer patients from the GeparQuinto Phase 3 clinical trial were stained for MC and MC numbers were correlated with clinical data. **Results:** We observed that absence of MC reduced tumor growth and increased the efficacy of AAT in different tumor models. Intriguingly, AAT only initially reduced microvessel proliferation but this was abrogated over time as a result of MC-mediated resistance. We show that MC secrete increased amounts of granzyme b upon therapy, which mobilizes alternative pro-angiogenic factors from the tumor matrix. These factors act beside the targeted VEGFA-VEGFR2-axis and reinduce angiogenesis despite the presence of AAT. Importantly, MC-mediated resistance could be overcome using the FDA-approved MC inhibitor cromoglicic acid. In line with our preclinical data, high intratumoral MC density correlated with disease progression in HR+ breast cancer patients when Bevacizumab was added to standard neodjuvant chemotherapy (HR 8.45, p = 0.006). Accordingly, Kaplan-Meier curves indicated that disease free survival of patients with high tumoral MC density was numerically shorter in the whole cohort and significantly shorter in the HR+ cohort upon addition of AAT to chemotherapy (p = 0.168 and p = 0.004, respectively). **Conclusions:** Here we unravel a novel resistance mechanism, by which MC hamper efficacy of AAT in mice and cancer patients. In preclinical models this effect could be overcome by combining AAT with an FDA-approved MC inhibitor indicating high clinical relevance. Thus, combination of FDA-approved MC inhibitors with AAT might be a suitable approach to increase efficacy of AAT in the clinic.

11523 Poster Session (Board #223), Sat, 1:15 PM-4:45 PM

VEGFR2 cytoplasmic expression (VEGFR2ce) in relation to survival in metastatic breast cancer (MBC) patients (pts) treated with bevacizumab (Bev). *First Author: Roseana Melo Borba, A.C. Camargo Cancer Center, São Paulo, Brazil*

Background: Bev is a monoclonal antibody that binds to VEGFA that demonstrated improved progression free survival (PFS) in MBC clinical trials. VEGFR2, NOTCH1, Integrin a1b2 and ILK are angiogenesis-related proteins possibly related with Bev efficacy. The correlation of these proteins expression and Bev survival variables was evaluated. **Methods:** We retrospectively analyzed 1st line chemotherapy in two HER2 negative MBC cohorts. Pts were treated between May-07 and July-14. Cohort 1 (C1) was treated with paclitaxel and Cohort 2 (C2) with paclitaxel and Bev. Expression of biomarkers was determined by immunohistochemistry. Tumor samples were arranged on a tissue microarray. Survival curves were calculated by Kaplan-Meier method and log-rank test. Cox model was used in multivariate analysis. **Results:** C1 had 42 pts. Median age was 63y. Tumor subtypes were divided in luminal (92.9%) and triple negative (TN) (7.1%). Visceral metastasis (mets) were present in 71.4%. Median follow-up (mFUP) time was 32.1m. mPFS was 8.0m and mOS was 33.5m. C2 had 29 pts. Median age was 57y. Luminal 79.3%; TN 20.7%; Visceral mets 79.3%; mFUP 38m. mPFS was 10.5m and mOS was 47m. In C2, high VEGFR2ce was correlated with improved PFS (high VEGFR2 16.5m x low VEGFR2 6.8m, p = 0.025). Breast cancer subtype, metastasis pattern and VEGFR2 expression were included in the multivariate analysis for PFS. VEGFR2 remained as independent factor (HR 0.35; IC95% 0.14 – 0.85, p = 0.021). In C1, VEGFR2 was not correlated with improved PFS (high VEGFR2 8.6m x low VEGFR2 8.0m, p = 0.24). Other markers were not associated with PFS. **Conclusions:** High VEGFR2ce was associated with increased PFS in patients treated with Bev. In MBC VEGFR2 may have a role as a predictive tool on benefit of antiangiogenic therapy.

11524 Poster Session (Board #224), Sat, 1:15 PM-4:45 PM

Circulating tumor cell status and benefit of radiotherapy in stage I breast cancer. *First Author: Chelain Rae Goodman, Northwestern Memorial Hospital, Chicago, IL*

Background: Circulating tumor cell (CTC) status has been shown to be prognostic of decreased survival in non-metastatic breast cancer. While up to 20-30% of patients with early breast cancer have detectable CTCs, less is known regarding the role of CTC-status in guiding clinical management. **Methods:** An observational cohort study was performed on women with stage I breast cancer evaluated for CTCs from the 2004-2014 National Cancer Database. Logistic regression was used to explore clinicopathological associations with CTC-status. Kaplan-Meier and multivariable Cox proportional-hazards survival analyses were used to estimate associations of CTC-status with overall survival using a propensity score-adjusted and inverse probability-weighted matched cohort. **Results:** Of the stage I breast cancer women evaluated for CTCs, 23.1% (325/1,407) were CTC-positive. Age, histology, receptor status, and nodal stage were associated with CTC-status. CTC-status was an effect modifier of the radiotherapy-survival association: CTC-positive women who did not receive radiotherapy had an increased hazard of death compared to CTC-negative women who also did not receive radiotherapy (four-year survival: 85.7% vs. 93.3%, HR = 2.92, CI = 1.43-5.98, P = 0.003). CTC-positive patients treated with radiotherapy did not have decreased survival compared to CTC-negative patients not treated with radiotherapy (HR = 0.67, CI = 0.28-1.65, P = 0.40). From the matched cohort analysis, CTC-positive women who did not receive radiation had a 4.82-fold increased hazard of death compared to CTC-positive women treated with radiotherapy (four-year survival: 83.2% vs. 96.6%; CI = 2.62-8.85, P < 0.001). **Conclusions:** Treatment with adjuvant radiotherapy was associated with improved survival in CTC-positive women with stage I breast cancer. If prospectively validated, CTC-status may be valuable as a predictor of benefit of radiotherapy in early stage breast cancer.

11525 Poster Session (Board #225), Sat, 1:15 PM-4:45 PM

CD4+ T cells in PBMC to predict the outcome of anti-PD-1 therapy. *First Author: Hiroshi Kagamu, Niigata University, Niigata, Japan*

Background: Antibody blockade of programmed death 1 (PD-1), has led to durable responses and significant prolongation of overall survival in metastatic cancers including non-small cell lung cancer (NSCLC). However, in clinical trials, response rates were as low as 20 %, and approximately 50 % of the patients did not achieve benefits to prolong progression free survival. These results bring us a hypothesis that there are subgroups with distinct pre-existing anti-tumor immunity resulting in different responses to anti-PD-1 therapy. We reported that effector T cells, which are capable of mediating antitumor reactivity, are primed in LNs draining growing tumors and that these T cells exclusively belong to the T cells that down-regulated CD62L ($CD62L^{low}$) subpopulation. In the absence of purified tumor antigenic proteins or peptides on many tumors, the expression of the homing molecule CD62L on T cells may serve as a surrogate marker for identifying tumor-specific immune cells. **Methods:** We analyzed the peripheral blood mononuclear cells (PBMC) of 50 consecutive NSCLC patients who were planned to be treated with anti-PD-1 Ab, Nivolumab after obtaining written informed consent. The patients received Nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks. Tumor response was assessed with the use of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, at week 8 and every 8 weeks thereafter. **Results:** The NSCLC patients who achieved partial response (PR) or stable disease (SD) had significantly ($p = 4.1x10^{-7}$) more $CD62L^{low}$ $CD4^+$ T cells in PBMC than progressive disease (PD) patients. The percentages of $CD62L^{low}$ in $CD4^+$ T cells provided sensitivity 92.9 %, and specificity 96.7 % to predict the patients who had PD. Moreover, SD patients had significantly ($p = 0.0067$) less regulatory T cell subpopulation than PR patients, thus, it was possible to predict PR from SD. **Conclusions:** These results show that the major differences in pre-existing immunity among PR, SD, and PD patients to anti-PD-1 Ab existed in $CD4^+$ T cell balance between primed effector and regulatory T cells. Further characterization of $CD62L^{low}$ $CD4^+$ T cells including mRNA microarray, checkpoint molecules, and chemokine receptors is going on.

11526 Poster Session (Board #226), Sat, 1:15 PM-4:45 PM

Cell-free DNA (cfDNA) mutations from clonal hematopoiesis: Implications for interpretation of liquid biopsy tests. *First Author: Pedram Razavi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A large fraction of cfDNA fragments are derived from hematopoietic sources. Somatic alterations in cfDNA can be tumor-derived but also could represent somatic changes associated with clonal hematopoiesis. We performed deep sequencing of both plasma cfDNA and matched white blood cell (WBC) genomic DNA (gDNA) to determine the contribution of clonal hematopoiesis to the variants observed in cfDNA. Four cohorts were investigated: metastatic breast (BC), non-small cell lung (NSCLC), castration-resistant prostate cancer (CRPC), and non-cancer participants (pts). **Methods:** Metastatic cancer pts with *de novo* or progressive disease were prospectively enrolled. Non-cancer pts were blood bank donors. Plasma cfDNA and matched WBC gDNA were sequenced using a targeted 508-gene panel (2 Mb) to $>$ 60,000X raw depth. Variant calling used a novel pipeline that employed molecular barcoding for error suppression followed by *de novo* assembly and graph-based variant calling. **Results:** Of 151 metastatic cancer pts (48 BC, 49 NSCLC, 54 CRPC), median age was 64 (30-87) with 53% female and 33% treatment naive. Of 47 non-cancer pts, median age was 61 (20-78) with 51% female. Analysis of cfDNA identified 1072 variants (AF $>$ 0.1%, $>$ 2 mutant reads, passing bioinformatic quality filters) which were also detected in WBC gDNA as non-germline ($<$ 35% allele frequency [AF]) non-synonymous variants. For these cfDNA variants, AF ranged from 0.1-14.4% and correlated with AF in WBC gDNA ($r^2 = 0.47$, $p < 0.001$). Mutated genes were consistent with clonal hematopoiesis, with the most frequently mutated genes being DNMT3A, TET2, PPM1D, and TP53 (215, 77, 45, and 36 variants, respectively). For both cancer and non-cancer pts (age $>$ 45), median number of overlapping variants was 5 per pt (range 0-22). The number of WBC gDNA and cfDNA variants per individual was positively associated with age ($p < 0.001$) in both cancer and non-cancer pts (interaction $p = 0.08$). **Conclusions:** Somatic cfDNA variants are frequently derived from clonal hematopoiesis and increase with age. Accurate assessment of somatic alterations in cfDNA should account for this phenomenon to distinguish between tumor-derived and WBC-derived variants.

11527 Poster Session (Board #227), Sat, 1:15 PM-4:45 PM

Circulating tumor DNA profiling to reveal heterogeneity of EGFR-TKI resistance mechanisms in lung adenocarcinoma patients. *First Author: Rongrong Chen, Geneplus-Beijing, Beijing, China*

Background: EGFR-TKI therapy has significantly improved prognosis of NSCLC patients with *EGFR* sensitive mutation. However, almost all patients ultimately develop PD while receiving TKI treatment. Circulating tumor DNA (ctDNA) is promising as a minimally-invasive liquid biopsy for comprehensive analysis of molecular abnormalities. **Methods:** A total of 254 advanced lung adenocarcinoma patients with signs of EGFR-TKI resistance were enrolled in the study. ctDNA was analyzed using next-generation sequencing based ER-Seq method, which enables simultaneously assess single-nucleotide variants, insertions/deletions, rearrangements, and somatic copy-number alterations across 59 genes. **Results:** ctDNA profiling was possible for all patients, 172 patients had $\geq$ 1 ctDNA alteration(s). Median number of plasma somatic mutations was 2, predominantly located in *EGFR* and *TP53*, with *MET*, *ERBB2* and *PIK3CA* followed. Of that, 30.6% of mutations detected in ctDNA were at a frequency below 1%. In exploring the mechanisms of TKI-resistance, we found TKI-sensitizing mutations were not detected in plasma of 138 patients (54.3%). Known mechanisms such as *EGFR* T790M/C797S mutation, activating mutations of *PI3K-AKT-mTOR* signaling, amplification of *MET*, activating mutation / amplification of *ERBB2*, activating mutation of *KRAS*, *BRAF* or mutations in *EGFR* EX20 other than T790M/C797S were identified in 59, 16, 8, 7, 3, 2, and 2 patients respectively. T790M/C797S was detected in 50.8% of patients with plasma positive for TKI-sensitizing mutations. Of note, C797S was only detected in patients treated with AZD9291. *EGFR* amplification were identified in 15 patients, though whether it would result in TKI-resistance was still controversial. Co-occurrence of resistance mechanisms were observed in 22 patients including 13 patients without TKI-sensitizing mutations. **Conclusions:** There was a high frequency of inter and intra-patient heterogeneity of resistance mechanisms after EGFR TKI therapy. ctDNA can be used as a 'liquid biopsy' to facilitate the broad exploration of potential resistance mechanisms.

11528 Poster Session (Board #228), Sat, 1:15 PM-4:45 PM

Association of circulating tumor DNA clearance during treatment with improved progression-free survival in advanced non-small cell lung cancer patients. *First Author: Shun Lu, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China*

Background: Currently, response assessment of patients with non-small cell lung cancer (NSCLC) primarily relies on imaging scans, which do not reflect biological processes at the molecular level. We utilized circulating tumor DNA (ctDNA) coupled with capture-based ultra deep next generation sequencing to conduct dynamic monitoring of treatment response, thus evaluating the ability of ctDNA as a tumor clonal response biomarker. **Methods:** We performed capture-based sequencing on longitudinal plasma samples, including baseline and a minimum of 2 evaluation points, obtained from 88 patients with advanced NSCLC using a ctDNA panel, spanning 160KB of human genome and consisting of critical exons and introns from 168 genes. This real world study comprises a highly heterogeneous cohort with a mixture of prior treatment exposure. **Results:** At baseline, treatment-naïve patients often harbor solo driver mutation; in contrast, patients with prior treatments are more likely to harbor concurrent driver mutations. Patients who received molecular targeted therapy according to the baseline sequencing results have a longer progression-free survival (PFS) ($p = 0.0001$), demonstrating the value of ctDNA in directing treatment. During subsequent evaluations, we observed 74% concordance rate between molecular and radiographic responses. Furthermore, our data revealed that during follow-up, patients with at least one time of undetectable ctDNA are associated with a longer PFS ($p = 5.52e^{-6}$), regardless the type of treatment commenced. Among 44 patients who had at least one time of undetectable ctDNA, 39 achieved partial response or stable disease as their best response. Collectively, this phenomenon reflects clonal response, thus demonstrating the biological nature underlying the clinical response assessed by imaging modalities. **Conclusions:** This real world study demonstrates that patients with at least one time of ctDNA clearance during subsequent evaluation are associated with a longer PFS. Our study warrants further investigations to explore the value of ctDNA clearance as a surrogate endpoint of efficacy and as a risk stratification factor.

11529 Poster Session (Board #229), Sat, 1:15 PM-4:45 PM

Early detection of competing resistance mutations using plasma next-generation sequencing (NGS) in patients (pts) with *EGFR*-mutant NSCLC treated with osimertinib. *First Author: Nicolas Marie Guibert, Dana-Farber Cancer Institute, Boston, MA*

Background: In pts with *EGFR*+ NSCLC, genotyping of plasma cell-free DNA (cfDNA) has become a routine option for non-invasive detection of *EGFR*T790M. We hypothesized that serial NGS of cfDNA would allow early detection of co-existent resistance mutations during osimertinib treatment. **Methods:** Serial plasma samples were collected from pts with advanced *EGFR*+ NSCLC and T790M+ acquired resistance treated with osimertinib. Up to 4 specimens were analyzed, blinded to tumor genotype: baseline, initial 2 follow-ups, and progression. Plasma NGS was performed using enhanced tagged amplicon sequencing of hotspots and coding regions from 36 genes. Diagnostic accuracy was compared to tumor genotype (including NGS when available) and droplet digital PCR (ddPCR) of cfDNA. **Results:** 94 specimens from 26 pts underwent plasma NGS. Studying 26 baseline specimens, plasma NGS was more sensitive than ddPCR for known *EGFR* driver mutations (100% vs 88.5%). In 8 pts with pretreatment tumor NGS, 5 of 6 TP53 mutations were detected; one plasma positive/tissue negative result was seen across 36 genes, a *PIK3CA* mutation (0.6% AF) which was confirmed using ddPCR (99.6% specificity). Quantitative concordance of AF compared to ddPCR was high (R = 0.94). 21 pts had detectable *EGFR* driver mutations at resistance. Among 6 pts with maintained T790M, 4 acquired C797S and 2 of these additionally acquired low level *KRAS* mutations (G13D, Q61K). Among 15 pts with loss of T790M, 7 had competing non-*EGFR* alterations identified: *MET* amp, *PIK3CA* E545K, *BRAF* V600E (n = 2), *HER2* amp, *KRAS* G12S, and *FGFR1* amp. Resistance mutations detected at AF $>$ 0.3% were confirmed with ddPCR. In 3 pts, a competing resistance mutation (1 *KRAS*, 2 *BRAF*) could be detected in plasma NGS pretreatment and reemerged as putative drivers at time of resistance. **Conclusions:** In this retrospective blinded validation, tagged amplicon-based plasma NGS was more sensitive than ddPCR with high specificity and quantitative concordance. In a subset of cases, serial plasma NGS can detect emergence of competing resistance mutations, creating an opportunity for the study of osimertinib-based targeted therapy combinations.

11530 Poster Session (Board #230), Sat, 1:15 PM-4:45 PM

Prevalence and heterogeneity of androgen receptor splice variants and intra-AR structural variation in patient with castration-resistant prostate cancer. *First Author: Luc Yves Dirix, Department of Oncology, GZA Hospitals Sint-Augustinus, Antwerp, Belgium*

Background: Androgen receptor splice variant 7 (AR-V7) is linked to *a priori* resistance to abiraterone acetate and enzalutamide. However, AR-V7 negativity does not necessarily indicate responsiveness and up to 20% of AR-V7 positive patients do demonstrate moderate response to these second-line endocrine therapies. **Methods:** Peripheral blood samples from patients with CRPC (n = 30) starting a new line of systemic therapy were subjected to comprehensive profiling of AR. AR splice variant (ARV) profiling for eight isoforms was performed by targeted RNA-Seq on CellSearch-enriched circulating tumour cells. Low-pass whole-genome and targeted sequencing of the entire AR gene in plasma-derived circulating cell-free DNA allowed the assessment of copy number status and structural rearrangements, respectively. ARV expression, structural variation, copy number alterations and ligand-binding domain mutations were combined and correlated to clinicopathologic parameters. **Results:** Twenty-five out of 30 patients (83%) demonstrated an aberration in AR. Twenty out of 30 patients (66.7%) demonstrated AR amplifications. Interestingly, 15/30 patients had intra-AR structural variants, of whom 14 expressed ARVs. In the context of endocrine treatment, 15/26 (57.7%) patients were ARV-positive with 13/15 patients having less than 6 months benefit from their therapy (Fisher's exact test, p = 0.0115). ARV expression was heterogeneous with 10/15 ARV-positive patients expressing several ARV. Notably, AR-V7 was most frequently detected, however AR-V3 was 3.5x more abundant (Wilcox signed rank, p = 0.0029). In 17 patients, a baseline AR profile was available and demonstrated how having any ARV was associated with progression-free survival (HR: 4.53, 95%CI: 1.424–14.41; p = 0.0105). In the poor response group, 6/17 (35.2%) were AR-V7 negative, of whom 4 carried other AR aberrations. **Conclusions:** Comprehensive AR profiling on liquid biopsies is feasible and provides new insights into the mechanisms driving endocrine resistance. Clinical validation, by means of a non-interventional, prospective and multicentric study, is essential and currently ongoing.

11531 Poster Session (Board #231), Sat, 1:15 PM-4:45 PM

Prognostic impact of *PD-1*, *PD-L1,* and *CD8* genes expression in peripheral blood in gastric cancer. *First Author: Shuhei Ito, Kyushu University, Fukuoka, Japan*

Background: Programmed death 1 (PD-1)/PD-1 ligand (PD-L1) blocking agents to gastric cancer (GC) in the clinical setting show significant therapeutic promise. However, since these agents are enormously expensive and potentially toxic, it is crucial to identify predictive biomarkers for detecting the best candidate who would benefit from these agents by less invasive and simpler method, such as liquid biopsy. **Methods:** Expression levels of genes coding for *PD-1*, *PD-L1* and *CD8* (CD8+ T cells are closely associated with cellular immune responses to tumors) were assessed in peripheral blood (PB) samples using quantitative RT-PCR. Samples were obtained from 407 GC patients (392 patients with neoadjuvant chemotherapy [NAC] and 15 patients without NAC) before surgery and 23 PB from normal controls (NC). Flow cytometric analysis was performed to identify PD-1-expressed cells in PB mononuclear cells. **Results:** *PD-1*, *PD-L1* and *CD8* mRNA levels of GC patients were significantly higher than those of NC: 4.2-, 3.0- and 6.1-fold increases, respectively ($P < 0.0001$, $P = 0.0001$ and $P < 0.0001$). *PD-1* mRNA levels were significantly lower in GC patients with NAC than in GC patients without NAC ($P < 0.01$). GC patients with low *PD-1*, high *PD-L1* and low *CD8* mRNA levels had significantly poorer overall survival (OS) than those with high *PD-1*, low *PD-L1* and high *CD8* mRNA levels, respectively ($P < 0.05$, $P < 0.05$ and $P < 0.05$). Multivariate analysis showed that *PD-1* low/*PD-L1* high mRNA levels was independent risk factors for OS (OR 2.15, 95%CI 1.29-3.45, $P < 0.01$). Flow cytometric analysis demonstrated the proportion of CD3 (T cell marker)-positive cells in the PD-1-positive fraction were 95.4 $\pm$ 6.9% in GC patients. Thus, most PD-1 protein expression occurred on T cells. Taken together, *PD-1*, *PD-L1* and *CD8* mRNAs in PB were overexpressed in GC patients, and *PD-1* mRNA levels which was mostly expressed on T cells in protein levels in PB were decreased in GC patients with NAC. Furthermore, relative levels of *PD-1*, *PD-L1* and *CD8* were associated with prognosis, respectively. **Conclusions:** Preoperative *PD-1*, *PD-L1* and *CD8* mRNA levels in PB may reflect antitumor immune response, and *PD-1* low/*PD-L1* high mRNA levels in PB are markers of poor prognosis in GC patients.

11532 Poster Session (Board #232), Sat, 1:15 PM-4:45 PM

Evaluation of liquid biopsies for molecular profiling in patients with advanced non-small cell lung cancer (NSCLC) in the relapse treatment setting. *First Author: Jordi Remon, Medical Oncology Department, Gustave Roussy, Villejuif, France*

Background: Molecular profiling is limited by access to sufficient tumor tissue for comprehensive analysis and due to tumor heterogeneity, the complete range of tumor DNA abnormalities may not be represented nor accurately reflect the clinical evolution of disease. Circulating tumor DNA (ctDNA) can be used as a minimally-invasive liquid biopsy for the detection, quantification and monitoring of molecular abnormalities for personalized treatment strategies. **Methods:** In a prospectively designed program, to date, we have recruited 227 advanced NSCLC patients having received prior therapy, with unknown molecular profile at time of blood collection. Blood collections (10ml K2-EDTA) were performed to assess molecular profile prior to or at time of relapse. Repeat samples were performed on patients initiated on treatment and followed for up to 18months. Patient samples were analyzed with InVision (enhanced tagged-amplicon sequencing) using a 34 gene panel. Interim analysis performed with full descriptive summary statistical analyses to be presented at conference. **Results:** ctDNA profiling detected somatic mutations in 182pts (80.2%), predominantly located in *TP53 (46%), EGFR* (28%), *KRAS (11%)* and STK11 (7%, half of which had concurrent KRAS). Of note, clinically actionable mutations were detected: T790M (25pts, median 1.4% AF), ERBB2 (8 pts), MET (8pts) and BRAF (4pts) providing eligibility for new therapy options. 20pts including 12 EGFR/T790M+ve were evaluated for ctDNA monitoring up to 18 months (median 10m); correlation between dynamic change in mutation allele fraction and clinical response was observed, especially predictive of relapse to treatment. 10 patients demonstrated SD/PR response to osimertinib treatment with T790M detection at low allele fraction (7/10 $<$ 1% AF with 1pt at 0.08% AF). **Conclusions:** ctDNA can be used as a non-invasive 'liquid biopsy' for molecular profiling of NSCLC patients to detect clinically relevant and actionable mutations when tissue biopsy is unavailable. Liquid biopsies can be repeated as needed where tissue is not feasible, providing real-time information to support personalised treatment.

11533 Poster Session (Board #233), Sat, 1:15 PM-4:45 PM

Prospective characterization of circulating tumor cells using a nanotechnology-based capture system in oligometastatic patients undergoing definitive radiation therapy. *First Author: Daniel Paul Lindsay, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Circulating tumor cells (CTCs) can provide prognostic information in select patients with advanced cancers. We have developed a sensitive and specific CTC capture system (Oncosensor) which may predict clinical outcomes in patients undergoing definitive radiation for head and neck cancers. There is increasing interest in utilizing potentially curative metastasis-directed therapy for patients with oligometastatic solid-tumor malignancies. There is currently no biomarker to predict the success of this approach in most patients. The purpose of this prospective study is to investigate the potential utility of CTCs as a predictive biomarker for patients with oligometastatic cancer undergoing potentially curative therapy. **Methods:** Eligible patients had a metastatic solid-tumor malignancy with 3 or fewer metastases. All sites of disease were treated with definitive radiation or surgery. Concurrent chemotherapy was allowed. Peripheral blood (7 ml) was collected prior to starting, first week, mid-point, end RT, and every 4 to 12 weeks post RT. CTCs were quantified using the Oncosensor platform. We then assessed correlations between CTCs (baseline, end treatment, and changes during treatment) and clinical outcomes using multivariate analysis. **Results:** Baseline CTCs were detected in 20/20 enrolled patients with a mean baseline of 32/ml which decreased to a mean of 14/ml at the end of treatment. There was no association between pretreatment CTCs and clinical outcomes ($p = 0.81$). There was a significant association between post-RT CTCs and PFS ($p = 0.039$, HR 1.07 per CTC). Our data also suggest that post-treatment CTC monitoring may be able to detect early disease recurrence. Among the 4 patients with documented clinical failures and post-treatment CTC monitoring, all 4 had increases in CTCs with or prior to clinical or radiographic disease progression, with 1.6 to 7.3 fold increase at the time of progression compared to the prior time point. **Conclusions:** Our pilot data suggest CTCs may provide a predictive biomarker for patients with oligometastatic disease and could potentially provide a novel marker of disease recurrence.

11534 Poster Session (Board #234), Sat, 1:15 PM-4:45 PM

Bim and soluble PD-L1 (sPD-L1) as predictive biomarkers of response to anti-PD-1 therapy in patients with melanoma and lung carcinoma. *First Author: Roxana Stefania Dronca, Mayo Clinic, Rochester, MN*

Background: To date, there are no validated blood-based biomarkers of predicting response to PD-1 blockade. We previously reported that Bim is a downstream signaling molecule of the PD-1 pathway, and that measurement of Bim levels in circulating T-cells may predict and monitor responses to anti–PD-1 therapy in melanoma. We have identified the existence of sPD-L1 in cancer patients and showed that the sPD-L1 is biologically active and capable of triggering apoptosis in activated T-cells. Here we evaluated T cell Bim and sPD-L1 in the peripheral blood (PB) as biomarkers of response in a cohort of patients with metastatic melanoma and lung cancer undergoing anti-PD1 therapy. **Methods:** 60 pts treated with anti-PD-1 had PB collected at baseline and at radiographic tumor evaluation. Frequencies of Bim^+ T cells and Bim median fluorescence intensity (MFI) were measured by flow cytometry in gated tumor-reactive $CD11a^{high}PD1^+$ $CD8^+$ T cells. We also measured levels of sPD-L1 at baseline and serially during treatment with sPD-L1 ELISA. Baseline Bim and sPD-L1 levels and percent change in Bim levels in patients (pts) who had a radiographic response (CR/PR) were compared to those who had progressive disease (PD) at 12 wks. **Results:** Similarly to previously reported preliminary data, pts with objective response (CR/PR, 15/60) after 4 cycles of anti-PD1 therapy had higher frequency of Bim T cells at baseline compared to pts with PD (16/60) (mean 43% vs. 30%, $P = 0.0484$). The frequencies of Bim+ T cells decreased significantly after the first 3 months of treatment in responders compared with progressors (mean -16% vs. + 40% $P = 0.0111$). High baseline sPD-L1 were associated with progression on anti-PD1 therapy (mean 2.8 ng/mL vs. 0.7 ng/mL, $p = 0.07$, $n = 13$) and the levels increased by the first tumor assessment in patients resistant to anti-PD-1. **Conclusions:** Measurements of Bim and sPD-L1 levels may help to select patients who are likely to benefit from anti-PD1 monotherapy versus combinatorial strategies, and provide a new non-invasive way to monitor response to anti-PD-1 blockade. A larger validation study is underway.

11535 Poster Session (Board #235), Sat, 1:15 PM-4:45 PM

Monitoring of circulating tumor DNA in non-small cell lung cancer patients treated with EGFR-inhibitors. *First Author: Remy B Verheijen, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Epidermal growth factor receptor (EGFR) inhibitors such as erlotinib and gefitinib are routinely used in the treatment of non-small cell lung cancer (NSCLC). Monitoring of EGFR mutations in circulating tumor DNA (ctDNA) derived from plasma has been proposed as an alternative for repeated tumor biopsies. Our aim was to investigate the dynamics of ctDNA in a cohort of NSCLC patients and explore the roles of EGFR driver and resistance mutations in predicting disease progression and progression free survival (PFS). **Methods:** NSCLC patients treated with either erlotinib or gefitinib as first-line anti-EGFR therapy were included. Clinical data was collected retrospectively from medical records. Plasma samples collected as part of routine care were analyzed. First DNA was isolated from plasma using the QIAsymphony SP (Qiagen). Then EGFR driver (L858R and exon 19 deletions) and resistance (T790M) mutations were quantified using the X100 Droplet Digital PCR and analyzed using QuantaSoft software (Bio-Rad). The dynamics of ctDNA mutations over time and the relationship between copy numbers and progression free survival were explored. **Results:** 68 NSCLC patients and 249 plasma samples (1-13 per patient) were included in the analysis. In 33 patients, the T790M mutation was detected. The median (range) T790M concentration in these samples was of 7.3 (5.1 - 3688.7) copies/mL. In 30 patients, the L858R or exon 19 deletion driver mutations were found in median concentrations of 11.7 (5.1 – 12393.3) and 27.9 (5.9 – 2896.7) copies/mL, respectively. Using local polynomial regression, the copies/mL of EGFR driver mutations increased several weeks prior to progression on standard response evaluation. In Kaplan-Meier analysis, patients with a detectable T790M mutation during the first 8 weeks of treatment had a shorter PFS (7.6 versus 14.4 months, $p < 0.01$, log-rank test). **Conclusions:** Early detection of the T790M mutation in plasma ctDNA is related to poor PFS. Furthermore, an increase in the copies/mL of the EGFR driver mutation over time may predict clinical progression.

11536 Poster Session (Board #236), Sat, 1:15 PM-4:45 PM

Liquid biopsy in the clinic: A prospective study of plasma circulating tumor DNA (ctDNA) next generation sequencing (NGS) in patients with advanced non-small cell lung cancers to match targeted therapy. *First Author: Joshua K. Sabari, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Liquid biopsy for plasma ctDNA NGS is a rapidly evolving science. Plasma ctDNA assays are commercially available and are increasingly adopted in the community with a paucity of evidence-based guidance. We set out to study the optimal timing and utility of plasma ctDNA NGS in clinic. **Methods:** Pts with advanced NSCLC who were driver unknown, defined as not having prior tissue NGS or clinical concern for tumor heterogeneity that may affect treatment decisions, were eligible. Peripheral blood was collected in a Streck tube (10mL), DNA extracted, and subjected to a bias-corrected hybrid-capture 21 gene targeted NGS assay in a CLIA lab with unique reads at 3000x and sensitive detection at variant allele frequency above 0.1% (ResolutionBio *Bellevue, WA*). Pts also had concurrent tissue NGS via MSK IMPACT. Clinical endpoints included detection of oncogenic drivers in plasma, ability to match pts to targeted therapy, concordance and turnaround time of plasma and tissue NGS. **Results:** Forty-one pts were prospectively accrued. Plasma ctDNA detected an oncogenic driver in 39% (16/41) of pts, of whom 17% (7/41) were matched to targeted therapy; including pts matched to clinical trials for *HER2* exon 20 insertionYVMA, *BRAF* L597Q and *MET* exon14. Mean turnaround time for plasma was 7 days (4-12) and 28 days (20-43) for tissue. Plasma ctDNA was detected in 56% (23/41) of pts; detection was 40% (8/20) if blood was drawn on active therapy and 71% (15/21) if drawn off therapy, either at diagnosis or progression (Odds ratio 0.28, 95% CI 0.06 - 1.16; $p = 0.06$). All pts had concurrent tissue NGS; of the 10 samples resulted, there was 100% driver concordance between tissue and plasma in pts drawn off therapy. **Conclusions:** In pts who were driver unknown or who had clinical concern for tumor heterogeneity, plasma ctDNA NGS identified a variety of oncogenic drivers with a short turnaround time and matched them to targeted therapy. Plasma ctDNA detection was more frequent at diagnosis of metastatic disease or at progression. A positive finding of an oncogenic driver in plasma is highly specific, but a negative finding may still require tissue biopsy.

11537 Poster Session (Board #237), Sat, 1:15 PM-4:45 PM

Association of circulating tumor DNA (ctDNA) tumor mutational burden (TMB) with DNA repair mutations and response to anti-PD-1/PD-L1 therapy in non-small cell lung cancer (NSCLC). *First Author: Andrew A. Davis, Northwestern University, Chicago, IL*

Background: Identifying optimal biomarkers for response to anti-PD-1/PD-L1 therapies in NSCLC is critical. TMB is a potential biomarker of genomic instability and neoantigen binding sites to activated effector T cells. The goal of this study was to derive a measure of ctDNA TMB and to examine the association between TMB and clinical variables, DNA repair mutations, and response to checkpoint blockade. **Methods:** We retrospectively examined 136 patients with NSCLC who had undergone ctDNA next-generation sequencing (NGS) in our institution. The ctDNA testing, performed by Guardant360, is not currently clinically indicated for TMB. We derived ctDNA TMB using coding base substitutions and indel alterations both including and excluding potentially functional variants, but excluded rearrangements, fusions, and copy number variants. In addition, survival data were obtained for 17 patients who were treated with anti-PD-1/PD-L1 therapy and had ctDNA before first line therapy or within 90 days of therapy initiation. **Results:** ctDNA TMB was associated with the number of direct and indirect DNA repair gene mutations (t-test, $p < 0.05$). Smoking was also associated with higher TMB when including functional variants (chi-square test, $p = 0.034$). Driver mutations (EGFR, KRAS) and prior radiation therapy were not correlated with TMB. Lower ctDNA TMB (below the median, 15 mutations/MBp) was associated with longer PFS and OS (Kaplan-Meier log-rank test, $p < 0.05$). **Conclusions:** ctDNA TMB was derived and was significantly associated with greater number of DNA repair mutations. Smoking predicted higher TMB score. However, in a small subset of patients, lower ctDNA TMB predicted response to checkpoint blockade. Potential reasons include the small sample size, the possibility of ctDNA reflecting tumor burden, and the limited length of DNA sequenced (~78,000-138,000 bp). Larger, prospective studies are necessary to validate these findings.

11538 Poster Session (Board #238), Sat, 1:15 PM-4:45 PM

Association of early reduction in circulating tumor DNA (ctDNA) with improved progression-free survival (PFS) and overall survival (OS) of patients (pts) with urothelial bladder cancer (UBC) treated with durvalumab (D). *First Author: Michael Kuziora, MedImmune, Gaithersburg, MD*

Background: Mutation variant allele frequencies (VAFs) in ctDNA indicate the frequency of cancer clones harboring the specific variant in the primary lesion and metastases, thus providing a surrogate for tumor burden. We previously reported that early reduction in VAF in ctDNA was associated with improved survival on durvalumab in NSCLC subjects. Here we replicated this association in UBC pts treated with durvalumab. **Methods:** CP1108/NCT01693562 was a nonrandomized phase 1/2 trial evaluating D in pts with advanced UBC or other solid tumors. By 24OCT2016, 103 UBC pts received 10 mg/kg Q2W of D with median 8.4 mos follow up. A panel of 70 genes was assayed for DNA variants using the Guardant360 cancer panel in plasma ctDNA from 33 UBC pts pre-treatment and 29 pts pre and 6 wks on-treatment. The mean VAF pre or on treatment of patient single nucleotide variants (SNVs) and insertion/deletions was correlated with clinical outcomes. Objective response rate (ORR) was calculated according to RECIST v1.1 and a Cox proportional hazard ratio (HR) was calculated adjusting for baseline ECOG, sex, age, and smoking status. **Results:** Complete and partial responders (CR/PRs) showed a significant decrease ($\Delta = -2.4\%$, $p = 0.02$) in ctDNA mean VAF post-treatment with D (i.e. reduction in tumor burden) compared to an increase in mean VAF (i.e. increase in tumor burden) in progressive disease (PD) pts ($\Delta = +2.7\%$, $p = 0.31$). This correlation was also observed in total mutation count in CR/PR ($\Delta = -4.6$, $p = 0.003$) compared to PD pts ($\Delta = +2.8$, $p = 0.44$). Pts with a decrease in ctDNA VAF at week 6 had longer median PFS (9.3 mos, 95%CI = [3.0, not reached(NR)] and OS (median NR, 95% CI = [20.3,NR]) compared to those with an increase in VAF (median PFS = 1.4 mos, 95%CI = [1.3,NR];HR = 0.29; $p = 0.05$ and median OS = 8.2 mos, 95% CI = [2.3,NR]; HR = 0.12; adjusted $p = 0.04$). DCR was 85%/14% for pts with a decrease/increase in VAF ($p = 0.002$). **Conclusions:** CtDNA VAFs were reduced in responders but not non-responders after six wks of D. A decrease in VAFs 6 wks following treatment with D correlated with longer PFS and OS, suggesting utility as an early indicator of clinical benefit. Clinical trial information: NCT01693562.

11539 Poster Session (Board #239), Sat, 1:15 PM-4:45 PM

CK19 combined with contrast-enhanced ultrasound: A prediction model for non-sentinel lymph node involvement in early breast cancer. *First Author: Xingfei Yu, Zhejiang Cancer Hospital, Hangzhou, China*

Background: According to Z0011 and AMAROS trials, patients with breast cancer stage cT1~2cN0 and sentinel lymphnode (SLN) 1~2 involvement can avoid axillary lymphnode dissection (ALND). But the risk of non-sentinel lymphnode (nSLN) involvement in those early stage patients is still unclear and it is difficult to predicting the risk before surgery. Our previous study showed CK19 mRNA in peripheral blood had predicative value of nSLN involvement. Also, contrast-enhanced ultrasound (CEUS) is a new effective method exmaming axillary lymph node. We aim to establish a prediction model for nSLN involvement in early breast cancer using CK19 combined with CEUS score. **Methods:** We identified 119 cases diagnosed early breast cancer (stage cT1~2cN0 and 1~2 SLNs involvement as in Z0011 and AMAROS trials) from Oct 2015 to Nov 2016 in Zhejiang Cancer Hospital. The CK19 mRNA of peripheral blood by RT-PCR and CEUS score of axillary lymph nodes were acquired before surgery. We used logistic regression analysis for filtering out valuable predictive clinical parameters and establishing formulas to calculate the probability of nSLN involvement. Our model was compared with Memorial Sloan Kettering Cancer Center (MSKCC) nomogram, which is one of the most reliable and validated methods for predicting of nSLN. **Results:** The histological grade, CK19 and CEUS score were screened by logistic regression analysis into the formula to calculate the probability of nSLN involvement. The sensitivity, specificity, total accuracy of this model was 89.13%, 80.82% and 84.03%, respectively. The false negative rate was 10.87%. The model had high quality of consistency (Kappa 0.675, $p < 0.01$) and goodness of fit (likelihood-ratio test, -2log liklihood = 84.607). The area under curve (AUC) of ROC was significantly higher ($P < 0.01$) in our model (0.914, 95%CI, 0.863~0.965) than in MSKCC nomogram (0.563, 95%CI, 0.459~0.667). **Conclusions:** The prediction model based on CK19 and CEUS score has satisfying sensitivity, specificity and accuracy, more effective than MSKCC nomogram. It is a valuable model of evaluating the risk of nSLN involvement in early breast cancer before surgery, picking out the patients who can truly avoid ALND.

11540 Poster Session (Board #240), Sat, 1:15 PM-4:45 PM

Evaluation of liquid biopsies for molecular profiling in untreated patients with stage III/IV non-small cell lung cancer (NSCLC). *First Author: Benjamin Besse, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Molecular profiling is limited by tumour heterogeneity and access to sufficient tissue for comprehensive analysis. Circulating tumour DNA (ctDNA) can be used as a minimally-invasive liquid biopsy for mutation detection, quantification and monitoring for personalised treatment strategies. **Methods:** We recruited 110 patients into a prospectively-designed study for Stage III/IV NSCLC patients intended to initiate 1stline platinum-based chemotherapy. Blood collections (10ml K2-EDTA) were performed prior to treatment and analysed by InVision (enhanced tagged-amplicon sequencing) using a 34-gene panel. Tissue biopsies, when available, were analysed by NGS (Ion-Torrent, Sanger) for concordance analysis. To evaluate correlation with outcome, repeat blood collections were performed in selected patients. **Results:** 110 NSCLC pts were included (61% male, 14% never-smoker, and 70% adenocarcinoma). ctDNA profiling detected mutations in 83 pts (79%). TP53 (44%), KRAS (17%), STK11 (18%; 11/19 with KRAS/STK11) and EGFR (10%) were the commonest abnormalities detected. Additionally, MET (6%), ERBB2 (6%), PIKC3A (6%) and BRAF (4%) mutations and EGFR, MET, ERBB2 amplifications were detected in 2% of patients, respectively. 20% of the mutations detected in ctDNA were observed at $< 0.5\%$ allele fraction, with 6% between 0.03%-0.25% AF. Tissue was available in 44 pts; somatic mutations were detected in 73%. Tissue & liquid concordance was 92.3%. 10 pts (23%) reported as tissue negative had a positive liquid biopsy. 33 advanced NSCLC patients were evaluated for longitudinal serial ctDNA monitoring up to cycle 4 of chemotherapy; the ratio of mutated molecules between D1 and D42 was significantly correlated with change in RECIST 1.1 measurement at D42 (p-value = 0.002625 CI 95% 0.298, 0.875). **Conclusions:** ctDNA can be used as a 'liquid biopsy' for molecular profiling of NSCLC patients to detect clinically relevant and actionable mutations when tissue biopsy is unavailable. Liquid biopsies can be used longitudinally and may provide an early surrogate for response evaluation by radiographic RECIST.

11541 Poster Session (Board #241), Sat, 1:15 PM-4:45 PM

Predictive impact of PD-L1-expressing circulating tumor cells in NSCLC patients treated with nivolumab. *First Author: Ryota Shibaki, Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan*

Background: PD-L1 expression on tumor tissue is associated with response to PD-1 blockade in NSCLC. Here, we conducted a serial evaluation of PD-1-expressing circulating tumor cells (CTCs) as a potential real-time diagnostic modality in NSCLC patients treated with nivolumab. **Methods:** Advanced NSCLC patients after failure of at least one prior chemotherapy regimen received nivolumab monotherapy (3mg/kg, q2W) until progressive disease (PD) or unacceptable toxicity. Peripheral whole blood (3 mL) was collected for CTC evaluation at baseline and at week 4. CTCs were detected using microcavity array system (Hitachi Chemical Co., Ltd, Chikusei, Japan). PD-L1 expression was immunohistochemically examined on both tumor tissues and CTCs. This study was registered at UMIN (ID: 000024414). **Results:** Thirty patients were registered in the study between January 2016 and September 2016 at Wakayama Medical University Hospital and 29 were included in the analysis. Demographics of the patients were as follows: median age 70 (range, 49 to 86); male 73 %; stage IV, 100 %; squamous/non-squamous, 27/73 %. At baseline, CTCs were detected in all patients (median, 15; range, 1 to 90) and PD-L1-expressing CTCs were detected in 87% of patients. Tumor proportion score (TPS) of PD-L1 expression on CTCs ranged from 6% to 100%, indicating intrapatient heterogeneity. Matched tumor tissues were available from 14 patients and 7 showed the PD-L1 TPS $\geq$ 50%. No positive correlation was observed on PD-L1 expression between tumor tissues and CTCs based on TPS (R2 = 0.0035). Overall response rate was 25% (7/29), and disease control rate was 54% (15/29). Total CTC count was significantly decreased after nivolumab treatment at week 4 ($p < 0.05$), but no significant change was observed in PD-L1 TPS on CTC. Patients harboring CTCs with PD-L1 TPS 50% or more at baseline were significantly more likely to achieve non-PD than those harboring CTCs with TPS less than 50% ($p < 0.05$). **Conclusions:** This is the first report on a serial monitoring of PD-L1 expression on CTCs in patients treated with nivolumab. PD-L1-expressing CTCs are suggested to hold potential for predicting clinical benefit. Clinical trial information: 000024414.

11542 Poster Session (Board #242), Sat, 1:15 PM-4:45 PM

Dynamics of soluble programmed death-ligand 1 (soluble PDL1) during chemotherapy and its prognostic implication in cancer patients. *First Author: Hyerim Ha, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea*

Background: The soluble form Programmed Death-Ligand 1(sPDL1) is suggested to have immunosuppressive activity and under investigation as candidate biomarker for immuno-oncology drug development. In this study, we measured the serum sPDL1 at pre-and post-chemotherapy and evaluated its prognostic implication and dynamics during chemotherapy in biliary tract cancer (BTC) patients. **Methods:** From 90 advanced BTC patients (training cohort 42 patients, validation cohort 48 patients) who were candidates for palliative 1st-line chemotherapy, blood was collected at pre-and post-chemotherapy. sPDL1 was measured using an enzyme-linked immunosorbent assay. Response to chemotherapy, overall survival (OS) and other prognostic factors including neutrophil-lymphocyte ratio (NLR) were also obtained. **Results:** OS of all patients was 11.5 months (95% CI; 9.7-16.2). The best response was CR in 7 patients (7.8%), PR 20 patients (22.2%), SD 52 patients (57.8%) and PD 11 patients (12.2%). Median sPDL1 at pre-chemotherapy was 0.97 ng/mL (range 0.6-1.9). Patients with high pre-chemo sPDL1 ($\geq$ 1.30 ng/mL) showed worse OS than patients with low pre-chemo sPDL1 (9.1 vs. 12.5 months, p =0.003). In multivariate analysis, high pre-chemo sPDL1 (HR 1.96, 95% CI; 1.2-3.9, p = 0.011) and pre-chemo NLR (HR 1.82, 95% CI; 1.1-3.0, p = 0.020) were independent poor prognostic factors for OS. Post-chemotherapy sPDL1 and its changes compared with pre-chemotherapy were not significantly different across tumor response groups. However, at the time of disease progression, sPDL1 was increased significantly compared with pre-chemo sPDL1 (1.59 ng/mL vs 0.72 ng/mL, p = 0.003). In PR group, sPDL1 at pre-chemo, post-chemo, and PD was 1.19, 0.98, and 2.77 ng/mL, respectively. In SD group, sPDL1 at pre-chemo, post-chemo, and PD was 1.16, 1.19, and 1.83 ng/mL, respectively. In PD group, sPDL1 at pre-chemo and PD was 0.62, and 1.04 ng/mL. **Conclusions:** sPDL1 at pre-chemotherapy confers the prognostic value for OS in BTC patients under palliative chemotherapy. The dynamics of sPDL1 during chemotherapy correlates with disease progression.

11543 Poster Session (Board #243), Sat, 1:15 PM-4:45 PM

Assessing tumor heterogeneity using circulating tumor DNA to predict and monitor therapeutic response in metastatic breast cancer. *First Author: Fei Ma, Department of Medical Oncology, National Caner Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Within metastatic breast cancer (mBC), tumor heterogeneity limited efficacy and duration of response to treatment. In this study, circulating tumor DNA (ctDNA) was used to evaluate tumor heterogeneity as a prognostic factor and monitor therapeutic response in patients with mBC. **Methods:** We collected plasma samples from 37 *HER2*-positive mBC patients treated with pyrotinib. Target-capture deep sequencing was performed to detect somatic mutations in plasma ctDNA. Clonal population structures were identified based on variations from ctDNA using Bayesian cluster with PyClone. Molecular tumor burden index (mTBI) was calculated with the mean variant allele frequency of mutations in trunk clonal population. **Results:** Mutations in *TP53* and genes of PI3K/Akt/mTOR pathway were associated with drug resistance for pyrotinib. The result showed that patients with resistant mutations occurring as a truncal event, who receiving monotherapy of pyrotinib, presented worse therapeutic effect (HR, 4.52; P = 0.03). The median PFS of patients with versus without resistant mutations in trunk clonal population was 7.8 weeks (95% CI 7.4 to 26.8 weeks) versus 31.6 weeks (95% CI 15.7 to 60 weeks), respectively. Patients with high heterogeneity (clonal population $\geq$3) had a significantly worse PFS (HR, 2.79; 95% CI 1.23 to 6.34; P = 0.014). The median PFS among patients with high versus low heterogeneity was 30.0 weeks (95% CI 13.9 to 53.5 weeks) versus 60.0 weeks (95% CI 31.4 to 84 weeks), respectively. Longitudinal monitoring of 21 patients during treatment showed positive correlation between mTBI in ctDNA and tumor size evaluated by CT imaging ($P < 0.0001$). Monitoring the mTBI in serial ctDNA increased sensitivity for prediction of progressive disease in 6 of 21 patients, with a mean time of 12.7 weeks earlier than using CT scan. ROC curve analysis showed an area under the curve value was 0.97 ($p < 0.0001$). **Conclusions:** Assessing tumor heterogeneity in ctDNA provides genetic predictors of treatment outcome. Molecular tumor burden in ctDNA is a potential indicator of therapeutic response. These observations might be supplements for the current therapeutic response evaluation.

11544 Poster Session (Board #244), Sat, 1:15 PM-4:45 PM

Early TKI-pharmokinetics and circulating tumor DNA (ctDNA) to predict outcome in patients with EGFR-mutated non-small cell lung cancer (NSCLC). *First Author: Frederic Bigot, Department of Medical Oncology, Paris Descartes University, Hopital Européen Georges Pompidou, AP-HP, Paris, France*

Background: Erlotinib (E) and gefitinib (G) are indicated as first-line therapy of *EGFR*-mutated NSCLC patients (pts). Many studies highlighted TKI pharmacokinetic (PK) impact on toxicities. However, data about the relationship between PK and efficacy are sparse. Recently, ctDNA has been shown to be a strong prognostic factor for metastatic NSCLC pts undergoing specific treatment. Thus, we underwent an observational study to determine plasma drug concentration and ctDNA impact on outcomes in NSCLC pts treated with E or G. Then, we explored the correlation between PK and ctDNA in order to improve management of pts treated with *EGFR*-TKI. **Methods:** We analyzed consecutive pts with *EGFR*-mutated NSCLC treated with TKI in Cochin and European Georges Pompidou hospitals (APHP, Paris) from April 2010 to March 2016. Plasma samples were collected 2 to 6 weeks after TKI initiation. Steady state trough concentration (Cssmin) was assessed by high performance chromatography. CtDNA was analyzed using Next-Generation Sequencing (Ampliseq ColonLungV2 panel, BPER method). Therapeutic ranges obtained from previous studies were between 1200 to 2000 ng/mL and $>$ 200 ng/mL for E and G, respectively. **Results:** Out of 77 pts, 56 had Cssmin analysis, 40 ctDNA analysis and 31 both. Median age was 70 years (range: 31-90), 49 were treated with E, 24 with G. Median follow-up was 19 months. Whatever *EGFR* TKI, pts with Cssmin into therapeutic ranges had longer PFS than pts over or under-exposed (median: 17.5 vs 7.5 months, p = 0.002). Those with early indetectable ctDNA had significantly better PFS (median 13 vs 5.8 months, p = 0.01) and OS (median: 21.4 vs 14.3 months, p = 0.02). No correlation was found between ctDNA and Cssmin. Occurrence of toxicity $>$ grade 2 in pts treated with E was associated with higher plasma concentration (mean 1991 vs 1184 ng/mL, $p < 0.01$). **Conclusions:** Early Cssmin and ctDNA assessment appear as markers to predict outcomes. Our observational study is the proof of concept that pts undergoing *EGFR*-TKI therapy could be monitored with Cssmin and ctDNA to define optimal personalized treatment strategies. A prospective study is planned to evaluate dose adaptation of TKI based on those 2 tools.

11545 Poster Session (Board #245), Sat, 1:15 PM-4:45 PM

Progastrin: A new specific early cancer screening biomarker. *First Author: Alexandre Prieur, ECS-Screening, Lausanne, Switzerland*

Background: One in two people will be diagnosed with cancer during his/her lifetime. Because we are lacking effective screening tests, most cancers are detected in late stages, when survival rates are very low. Here, we show the development of the first early cancer screening test for multiple cancers using progastrin (PG) as biomarker. The gene coding for PG is a target gene of the Wnt oncogenic pathway that is activated in almost all type of cancers, at the earliest stages of development. We showed that the neutralization of PG by a specific humanized antibody could be used for colorectal cancer treatment. Moreover, as PG is secreted by cancer cells, we can specifically detect it in the blood of persons having a cancer at early stage. **Methods:** Antibodies directed against PG were produced and selected for target specificity and affinity. ELISA is the most reliable assay to detect biomarker on the blood. Hence, selected antibodies were used to set up an ELISA sandwich to detect PG in the blood of patients with various types of cancers and at various stages. **Results:** We first set up a prototype ELISA using polyclonal antibodies. We validated our test using 223 blood samples from patients with polyps and colorectal cancers at various stages for which we observed an increased levels of PG. Then, we showed the presence of PG in the blood of 212 patients with other types of cancer, including liver, pancreatic and breast cancers, confirming that PG could be used as a biomarker for multiple types of cancers. Next, we set up our industrial ELISA using polyclonal and monoclonal antibodies called DECODE Lab and tested 245 new blood samples from patients with various types of cancer including early stages. Strikingly, using our test we were able to detect breast (AUC = 0.9638; sensitivity 70%), colorectal (AUC = 0.9635; sensitivity 73%), melanoma (AUC = 0.9882; sensitivity 87%) and cervix utery (AUC = 0.9827; sensitivity 84%) all stages combined with a high specificity of 97.5%. Finally, for early stage patients with melanoma and breast cancer, we had a sensitivity of 68% and 81% respectively. **Conclusions:** Taken together, the results presented here show that PG is a reliable biomarker for early cancer screening. The ELISA test that we developed is very efficient and now available for the clinic.

11546 Poster Session (Board #246), Sat, 1:15 PM-4:45 PM

Biomarker modulation in patients treated with TRC105 in combination with anti-VEGF therapy. *First Author: Yingmiao Liu, Duke University Medical Center, Durham, NC*

Background: TRC105, an endoglin-targeting monoclonal antibody with anti-angiogenic and anti-tumor activity, is being evaluated in multiple diseases. Here we report on pharmacodynamic and prognostic biomarkers in patients (pts) treated with both TRC105 and anti-VEGF agents. **Methods:** Plasma samples were collected from pts on three phase 2 trials combining TRC105 with an anti-VEGF agent: axitinib in metastatic renal cell carcinoma (mRCC), pazopanib in advanced soft tissue sarcoma, and bevacizumab in glioblastoma (GBM). Baseline and on-treatment levels of 22 soluble protein biomarkers were assessed. **Results:** Soluble endoglin markedly increased after TRC105 treatment in all pts ($p< 0.001$) as previously reported. BMP9 (a ligand for endoglin) and TGFβR3 (a type III TGFβ receptor) decreased in sarcoma pts at Cycle 2 Day 1 (C2D1) and generally remained below baseline throughout the course of treatment (BMP9, $p= 0.004$; TGFβR3, $p= 0.003$). Although TGFβR3 was decreased at C2D1 in mRCC (p = 0.030), no clear patterns were observed over time. Overall BMP9 levels did not change in response to therapy in either mRCC or GBM. Osteopontin (OPN) levels, a downstream effector of TGFβ signaling, were increased in sarcoma pts [$p=$ 0.002 at C2D15, $p< 0.001$ at C4D1 and end of study (EOS)]; however, in mRCC ($p= 0.010$) and GBM ($p= 0.003$), OPN was only elevated at EOS. Increases in PlGF and VEGFD, and decreases in VEGFR2 were observed across all studies, as previously noted for VEGF inhibitors. In the mRCC trial, 5 of 18 pts exhibited a ≥30% tumor reduction. Lower OPN ($p= 0.026$) and higher TGFβR3 ($p= 0.003$) levels at baseline correlated with radiographic response to treatment. In the sarcoma trial, 6 of 19 pts responded (CHOI criteria) in which lower baseline levels of ICAM1 ($p= 0.018$) and TSP2 ($p=$ 0.042) correlated with stable disease. **Conclusions:** In these trials, increases of soluble endoglin in response to TRC105 were observed, independent of the presence of any specific VEGF inhibitor. Differential regulation of BMP9, TGFβR3, and OPN suggests potential disease-specific modulation of key TGFβ signaling molecules in response to dual therapy. Baseline levels of OPN and TGFβR3 showed potential prognostic value in mRCC. Confirmation in larger trials is needed.

11547 Poster Session (Board #247), Sat, 1:15 PM-4:45 PM

Pre-treatment hematological markers as a predictive biomarker for survival in patients with non-small cell lung cancer treated with nivolumab. *First Author: Pradnya Dinkar Patil, Cleveland Clinic, Cleveland, OH*

Background: The absolute neutrophil count (ANC), absolute monocyte count (AMC) and neutrophil to lymphocyte ratio (NLR) are known markers of inflammation. We evaluated whether ANC, AMC and NLR are prognostic for overall survival (OS) and evaluated change in NLR as a predictive marker of response per RECIST in non -small cell lung cancer (NSCLC) patients treated with nivolumab. **Methods:** A total of 115 patients with NSCLC treated with nivolumab were included. ANC, AMC and NLR were examined at initiation of nivolumab therapy and after two cycles. The prognostic role of ANC, AMC and NLR on OS and changes in NLR ratio in responders was assessed using Cox regression model. **Results:** ANC > 6, AMC > 0.5 and NLR > 2.8 at baseline were independently associated with shorter OS (Hazard ratio (HR) 1.17 (1.08-1.27), p = .00001; HR 4.53 (1.99-10.31), p = 0.04 and HR 1.09 (1.04-1.13), p = 0.0002 . Responders had a decrease in NLR by (median (range) -0.93 (-14.7-52.95), p = 0.03) whereas non-responders had an increase in NLR by (median (range) 0.85 (-8.6-132.9), p = 0.03). **Conclusions:** ANC, AMC andNLR are independent prognostic factors in NSCLC patients treated with nivolumab. Changes in NLR can be an early biomarker for response with nivolumab in NSCLC patients.

Baseline Characteristics	N (%) or Median (Range)
Factor	
Male	42 (46%)
Female	49 (54%)
Age	67 (45-90)
Histology	56 (62%)
Adenocarcinoma	25 (27%)
Squamous Cell	10 (11%)
Other	
Pre-treatment ANC	5.5 (0.5-20.6)
< 6	62 (54%)
≥6	52 (45%)
ANC:ALC Ratio	5.61 (0.38-34.83)
≤ 2.8	20 (18%)
> 2.8	93 (82%)
Pre-Treatment AMC (K/μL)	0.72 (< 0.01-2.18)
≤0.5	24 (21%)
> 0.5-0.8	49 (43%)
≥ 0.8	41 (36%)
Best Response	31 (36%)
PR	17 (20%)
Stable	37 (44%)
Progression	
No. Deaths	31 (30%)
Median OS in Months (95% CI)	11.1 (9.3-N/A)
Overall Survival from Nivolumab	
	HR (95% C.I); P value
Pre-Treatment ANC	1.17 (1.08-1.27); 0.0001
Pre-Treatment ANC:ALC ratio	1.09 (1.04-1.13); 0.0002
Pre-Treatment AMC	4.53 (1.99-10.31); 0.04

11548 Poster Session (Board #248), Sat, 1:15 PM-4:45 PM

Exosomal Del-1 as a potent diagnostic marker for breast cancer: A prospective cohort study. *First Author: Soo Jung Lee, Department of Oncology/ Hematology, Kyungpook National University Medical Center, Kyungpook National University School of Medicine, Daegu, South Korea*

Background: The authors recently reported exosomal Del-1 as a diagnostic marker for breast cancer (Moon PG *et al*, Clin Cancer Res. 2016). Therefore, the current study aimed to confirm the diagnostic role of exosomal Del-1 in a prospective cohort with breast cancer by comparing plasma exosomal Del-1 levels before and after curative surgery. **Methods:** To identify the optimal time of sampling after surgery, blood samples were serially collected at day 1, 3, 5, and 7 after surgery from 22 patients with breast cancer. Thereafter, one hundred fourteen breast cancer patients who underwent curative surgery were prospectively enrolled and then their exosomal Del-1 levels before and after surgery were compared using ELISA with both anti-Del-1 and anti-CD63 antibodies. **Results:** Among 22 patients for identifying the optimal sampling time, all the exosomal Del-1 levels were normalized at post-operative day (POD) 1 (0.5 or less), and therefore POD 3 or later was accepted for the sampling time for 114 prospective patient cohort.At diagnosis, exosomal Del-1 levels of 110 (96.5%) patients were higher (> 0.5) and 109 (99.1%) patients showed a normalization of Del-1 after surgery including four patients with the borderline Del-1 (between 0.4 and 0.5). During the mean follow-up duration of 21.8 (range, 5.9 – 58.4) months, nine (7.9%) patients experienced relapses (4 loco-regional and 5 distant), where 3 out of 6 in high group (> 0.5), 2 out of 4 in borderline group, and 4 out of 105 in normalized group (≤0.4). In particular, patients who relapsed in higher Del-1 group showed earlier relapse compared to the relapsed patients in lower Del-1 group. **Conclusions:** As the current prospective cohort study demonstrated a normalization of exosomal Del-1 after curative surgery, exosomal Del-1 can be confirmed as a potent diagnostic biomarker for breast cancer. Plus, a high Del-1 level after surgery seems related with early relapse suggesting a potential prognostic marker by identifying the existence of residual tumor.

11549 Poster Session (Board #249), Sat, 1:15 PM-4:45 PM

Cerebrospinal fluid circulating tumor cells (CSF CTC) for real-time patient monitoring and response to treatment. *First Author: Rachna Malani, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The validated CellSearch system (Janssen Diagnostics, LLC), utilizing an immunomagnetic CTC selection method based on EPCAM antibody conjugated ferroparticles, is an FDA-approved methodology for enumerating CTC from blood in pts with breast, prostate and colon cancers. The CellSearch system has been used to evaluate CSF CTC of pts with leptomeningeal metastasis (LM) and has demonstrated potential as a diagnostic marker and response to cancer treatment. We explored the use of CSF CTC enumeration in the follow-up of pts with LM from HER2+ cancers receiving intrathecal (IT) therapy, aimed at characterizing changes over time as a potential biomarker of treatment response. **Methods:** CSF from pts participating in an IRB-approved phase I/II dose escalation trial of IT trastuzumab for LM in HER2+ cancer (NCT01325207) was evaluated by CellSearch system. 3 ml CSF from a ventricular reservoir was collected for CSF CTC enumeration at pre-treatment Day 1 of each cycle and correlated with CSF cytology from the same sample, and with clinical and radiographic response. LM progression was defined as clinical, CSF cytologic or radiographic worsening. **Results:** 15 pts with HER2+ LM (14 breast, 1 colon) were enrolled; 13 were women. At baseline 7 pts had positive CSF cytology, the other patients had a diagnosis by MRI. Of the 15 pts, 10 had greater than 1 cycle of treatment to be evaluable; 5 pts progressed during cycle 1 (Table). Mean CSF CTC at baseline was 82 per 3ml (range 0-200); 2 pts had no detectable CSF CTCs. A numerical decrease in CSF CTC was observed in 5 pts after cycle 1 and remained low (mean =9.5, range 0-92) while disease was stable. 3 pts (pts.3, 4 and 7) demonstrated a rise in CSF CTCs roughly 1 month prior to disease progression. **Conclusions:** Changes in CSF CTCs enumeration in response to treatment may allow quantitative surveillance of treatment response. CSF CTCs may serve as a platform to assess treatment response or as an early biomarker of LM progression and should be further investigated. Clinical trial information: NCT01325207.

CTC enumeration by patient.

Number of Cycles	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	200	146	22	5	10	1	0	0	81	139	3	200	166	7	200
2	15	1	8	4	4	2	0	0	111	200					
3	200		10	1		1	0	0							
4			2	8		0	0								
5			3	11		0	0								
7			17	32		0	0								
8			0	58			0								
9			57				0								
15							4								

11550 Poster Session (Board #250), Sat, 1:15 PM-4:45 PM

Correlation of cell-free circulating DNA, RNA, and PD-L1 from plasma with clinical response in patients with metastatic lung and breast cancers. *First Author: Luis E. Raez, Memorial Cancer Institute, Pembroke Pines, FL*

Background: There is an unmet need to evaluate tumor response by other means than radiology tests. Changes in gene expression, allele-fractions of mutations, PDL-1 expression and levels of cell free DNA [DNA] or RNA [RNA] in plasma might be useful for monitoring disease state and predicting outcome to anti-tumoral therapy. **Methods:** We measured serial levels of plasma DNA/RNA in metastatic patients (pts) with NSCLC and breast cancers undergoing treatment and correlated them with response (CR/PR/SD/PD) seen by CT scans. We also monitored PD-L1 expression in NSCLC pts treated with immunotherapy. DNA/RNA were extracted from plasma. RNA was reverse transcribed with random primers to cDNA. Levels of DNA/RNA were determined by RT-qPCR. **Results:** 52 pts were enrolled (28 breast/24 NSCLC). Breast group: 39% (11/28) were Caucasian (NHW) and 36% (10/28) Hispanic (H). 20 pts completed first two cycles of therapy: 2 pts had PR and showed no change (NC) or decrease (DEC) in levels of DNA/RNA. 11pts achieved SD, 9 had NC levels of DNA/RNA. Pts with PD: 5/6 underwent significant increase (INC) in DNA/RNA levels. Overall, among breast pts, there was an 84% (16/19) agreement between response and levels of DNA/RNA. These were correlated with one another ($r = 0.7002$, $p < 0.0001$). NSCLC group: 71% (16/24) were NHW and 25% (6/24) H. Non-SQCC were 87% (21/24). 20 pts had CT scans. One pt had PR with DEC levels of DNA/RNA. 10 pts achieved SD, all showed DEC or NC levels of DNA/RNA. 8 pts had PD, 6 of them had INC in DNA/RNA levels even 7 weeks prior to PD. Among NSCLC pts, there was a 90% (17/19) agreement in response and levels of DNA/RNA. These were correlated with one another ($r = 0.6231$, $p < 0.0001$). In 5 pts PD-L1 expression remained stable when CT scans showed SD or PR. **Conclusions:** There is a strong correlation between clinical responses with changes in plasma levels of DNA/RNA in pts with NSCLC (90%) and breast cancer (84%). Some of these were documented weeks before imaging was done. cfRNA is as effective as cfDNA as predictive tool for response. Plasma PDL-1 expression is a new tool to monitor immunotherapy response.

11551 Poster Session (Board #251), Sat, 1:15 PM-4:45 PM

Liquid biopsies of plasma exosomal nucleic acids, plasma cell-free DNA, and survival of patients with advanced cancers. *First Author: Lino Moehrmann, Department of Translational Oncology, National Center for Tumor Diseases (NCT) Heidelberg and German Cancer Research Center (DKFZ), Heidelberg, Germany*

Background: Blood-based liquid biopsies offer easy accessible genomic material for molecular diagnostics in cancer. Commonly used cell-free DNA (cfDNA) originates from dying cells. In contrast exosomal nucleic acid (exoNA) originates from living cells, which can better reflect underlying cancer biology. **Methods:** We isolated exoNA (EXO52) and cfDNA (QIAamp Circulating Nucleic Acid kit) from plasma of patients with progressing advanced cancers and tested for $BRAF^{V600}$, $KRAS^{G12/G13}$, and $EGFR^{exon19del/L858R}$ mutations using next-generation sequencing (EXO1000), droplet digital PCR (ddPCR, QX200) and BEAMing digital PCR. The results were compared to clinical testing of archival tumor tissue and correlated with survival. **Results:** Of the 43 patients (colorectal cancer, 20; melanoma, 8; non-small cell lung cancer, 6; ovarian cancer, 2; papillary thyroid cancer, 2; other cancers, 5) 41 had a mutation in the tumor tissue (20 [47%] *BRAF* mutation, 17 [40%] *KRAS* mutation and 4 [9%] EGFR mutation). Mutation testing of plasma exoNA from all 43 patients detected 39 (95%) of 41 mutations present in tumor tissue with 100% specificity. Mutation testing of plasma cfDNA from 39 patients using ddPCR detected 33 (89%) of 37 mutations present in tumor and testing of plasma cfDNA from 37 patients using BEAMing detected 34 (97%) of 35 mutations present in tumor tissue; however, both cfDNA methods reported an additional *KRAS* mutation not present in tumor tissue. Patients with high mutation allele frequency (MAF, > median) had shorter median survival compared to patients with low MAF (< median) when using exoNA (5.9 vs. 11.8 months, $P = 0.006$), but not cfDNA ddPCR (6.0 vs. 7.4 months, $P = 0.06$) or cfDNA BEAMing (6.5 vs. 7.4 month, $P = 0.07$). High MAF in exoNA was an independent prognostic factor for survival in multicovariate analysis (HR 0.13, $P = 0.017$). **Conclusions:** Mutation testing of plasma exoNA for common *BRAF*, *KRAS*, and *EGFR* mutations has high sensitivity compared to clinical testing of archival tumor tissue and better specificity than PCR testing of plasma cfDNA. High MAF in exoNA is the independent prognostic factor for shorter survival.

11552 Poster Session (Board #252), Sat, 1:15 PM-4:45 PM

Tetrahydrouridine-decitabine for non-cytotoxic epigenetic therapy of NSCLC to enhance immunotherapeutic effect of anti-PD1 in vivo. *First Author: Kai Kang, Cleveland Clinic, Cleveland, OH*

Background: NSCLC response to anti-PD1 therapy is ~20%, largely because most NSCLC avoids immune-recognition in the 1stplace, e.g., by epigenetics to suppress neo-antigen expression. DNA methyltransferase (DNMT1) mediates this repression and is depleted by decitabine (Dec). Unfortunately Dec has trivial distribution into solid cancer tissues because of rapid deamination by cytidine deaminase (CDA). Therefore, to improve tissue-distribution of Dec with the low Cmax/long Tmax profile needed for DNMT1-depletion without cytotoxicity, we combined Dec with a CDA inhibitor tetrahydrouridine (THU). **Methods:** C57/BL6 mice were inoculated with LL3-luc cells via tail vein. After documentation of lung invasion by live-imaging, mice (n = 5/group) were randomized to PBS, THU-Dec (10/0.1 mg/kg sc 3×/wk), anti-PD1 (5 mg/kg ip q5d, DX400 from Merck) or THU-Dec/anti-PD1 combination. Antigen presentation, PD, MDSCs, and T-cells were measured in blood and tumor. **Results:** THU-Dec or anti-PD1 alone decreased tumor by imaging and increased survival, however, THU-Dec/anti-PD1 combination extended median survival the most and completely regressed tumor in 2/5 mice (median survival days PBS 37, THU-Dec 56, anti-PD1 62, THU-Dec/anti-PD1 77). Rechallenge of cured mice with LL2-luc confirmed immune-memory effect, with no engraftment vs expected engraftment in controls. Consistent with the pharmacologic rationale, THU-Dec produced > 2-fold more DNMT1-depletion in tumor vs PBS. Consistent with non-cytotoxic effect, absolute lymphocyte counts were preserved with THU-Dec, while numbers of G-MDSC decreased (2.9 k/μL PBS vs 0.3 k/μL THU-Dec/anti-PD1, $p < 0.01$). Expression of neoantigens MAGE-A1 and MAGE-A3 increased > 4-fold with THU-Dec vs PBS ($p < 0.01$). THU-Dec/anti-PD1 increased tumor infiltrating lymphocytes 6-fold vs PBS ($p < 0.01$) and decreased regulatory T-cells 2.5-fold vs PBS ($p < 0.01$). IFNγ expression in tumor increased 2.4-fold with THU-Dec/anti-PD1 vs PBS ($p < 0.01$). **Conclusions:** THU-Dec/anti-PD1 produced marked survival improvements and cures in tumor-bearing mice, scientific validation of our clinical trial NCT02664181 combining THU-Dec/nivolumab in 2nd line for NSCLC.

11553 Poster Session (Board #253), Sat, 1:15 PM-4:45 PM

***CCL5* expression and tumor infiltrating immune cells in triple negative breast cancer.** *First Author: Jhajaira Araujo, Oncosalud-Auna, Lima, Peru*

Background: CCL5 is a chemo-attractant of regulatory T cells, promoting tumor immune avoidance and related to a poor outcome in several malignancies; however, in triple negative breast cancer (TNBC), it is related to a better outcome. Our aim was to evaluate the correlation between *CCL5* and tumor infiltrating immune cells and their prognosis value. **Methods:** We evaluated 72 TNBC patients with residual disease after neoadjuvant chemotherapy with matched data of tumor infiltrating lymphocytes (TILs) count and *CCL5* expression (profiled with NanoString). *CCL5* expression levels were log2 transformed and median centered. Correlation between TILs (log2 transformed) and *CCL5* was evaluated with the Spearman's rank test. Cox PH model was used to investigate the effect of *CCL5* (median as cutoff) and TILs ($<$ 20% and $\geq$20%) in distant-recurrence free survival. We used the CIBERSORT platform to evaluate the immune cells composition according to the expression of *CCL5* (higher vs. lower or equal than median) in 3 independent TNBC datasets (GSE25066, GSE58812 and GSE76124). **Results:** There was a significant correlation between TILs and residual tumor size (P = 0.017) and *CCL5* (ρ = 0.347, P = 0.003). In univariate analysis, TILs (HR = 0.276, 95%IC: 0.128-0.593; P = 0.001) and *CCL5* (HR = 0.401; 95%CI: 0.206-0.781; P = 0.007) were both associated with outcome. In a multivariate analysis with *CCL5* expression and TILs count, TILs was the only significant marker with a P = 0.008 (HR = 0.336; 95%CI: 0.150-0.753), in contrast to *CCL5* (HR = 0.573; 95%CI: 0.285-1.154; P = 0.124). CIBERSORT analysis suggested that high *CCL5* expression is associated with recruitment of CD8 cells (13% v 6%, P $<$ 0.001; 6% v 1%, P $<$ 0.001 and 12% v 8%, P = 0.003), activated CD4 memory T cells (4% vs. 2%, P $<$ 0.001; 5% vs. 0%, P $<$ 0.001; 3% vs. 0%, P $<$ 0.001) and Macrophages M1 (9% vs. 7%, P = 0.022; 13% vs. 8%, P = 0.005; 11% vs. 5%, P $<$ 0.001) in GSE25066, GSE58812 and GSE76124 datasets, respectively. **Conclusions:** TILs was the stronger and more significant prognostic immunological marker, even than *CCL5* expression. High *CCL5* expression was associated with enrichment of CD8 cells, activated CD4 memory T cells and Macrophages M1. Role of these cells in TNBC should be explored more deeply.

11554 Poster Session (Board #254), Sat, 1:15 PM-4:45 PM

Analysis of T-cell repertoires in early-stage breast carcinomas to evaluate tumor immunogenicity. *First Author: Javier Carrasco, Grand Hôpital de Charleroi, Charleroi, Belgium*

Background: Breast carcinomas (BC) are often considered to be weakly immunogenic and thus poorly sensitive to immunotherapy. **Methods:** We analyzed the repertoire of tumor-infiltrating T cells (TILs) in 41 early BC by sequencing their T cell receptor β genes (TCRβ). Libraries were built using a digital sequencing approach, barcoding each sequenced molecule to improve accuracy and quantification. T cell repertoires were also obtained from paired blood samples allowing identification of T cell clones enriched in the tumors as compared to blood. For 5 patients, $CD8^+$ TILs were cloned *ex-vivo* from a tumor sample and screened for recognition of autologous predicted neoepitopes. **Results:** T cell infiltration differed from one tumor to another. Its amount varied of more than 30 fold and its diversity ranged from $<$ 100 to $>$ 5000 different clonotypes. In 34% of the tumors, there was an important T cell infiltration and we detected several clonotypes with a $\geq$500 fold enrichment as compared to blood. In 22% of the tumors, an important T cell infiltration was observed but without significantly enriched clonotypes. In 43% of the tumors the T cell infiltration was very limited. For 5 tumors with a high T cell infiltration, we screened *ex-vivo* isolated $CD8^+$ T cell clones for recognition of predicted neoepitopes. In 4 of these tumors, with no enriched clonotypes, no recognition was observed. In 1 of these tumors, with enriched clonotypes, 6 different $CD8^+$ T cell clones recognized 4 predicted neoepitopes. Three of these clones were $>$ 100 fold more frequent in the tumor as compared to blood. **Conclusions:** About 30% of early BC were infiltrated by T cell clonotypes significantly enriched relative to blood. In one of these tumors some of the most enriched clonotypes recognized neoepitopes, demonstrating that some primary BC are spontaneously immunogenic. About 20% of the tumors had an important T cell infiltration without enriched clonotypes. None of the TIL clones isolated from 4 such tumors recognized predicted neoepitopes. Our results suggest that the detection of intratumorally enriched T cell clonotypes could identify immunogenic tumors, which may be sensitive to treatment with immunostimulatory antibodies.

11555 Poster Session (Board #255), Sat, 1:15 PM-4:45 PM

Tumor kinetic modeling and identification of predictive factors for tumor response to durvalumab in patients with non-small cell lung cancer (NSCLC). *First Author: Yanan Zheng, MedImmune, Mountain View, CA*

Background: Durvalumab is a human monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 and CD80. The primary objectives of this analysis were to describe the longitudinal tumor size profiles and identify the key factors predicting tumor growth and regression following durvalumab. **Methods:** Longitudinal tumor size data obtained from NSCLC patients in study 1108 (all lines of therapy) and ATLANTIC (third line and beyond) following durvalumab treatment were modeled using nonlinear mixed effect modeling. Tumor kinetics were described by four key parameters: tumor growth and killing rate constants, fraction of durvalumab-sensitive tumor cells, and delay time for tumor killing. Potential predictive factors for tumor growth and regression were evaluated in a multi-variable covariate analysis. The model was used to simulate response rates at different tumor PD-L1 expression cutoffs. **Results:** Tumor kinetic modeling accurately described the longitudinal tumor response profiles from NSCLC patients in both studies. The factors associated with more rapid tumor growth were liver metastases, ECOG score $>$ 0, high neutrophil-to-lymphocyte ratio and EGFR/ALK mutation. Tumor cell PD-L1 expression, baseline tumor size and smoking history were identified as significant predictive factors for tumor killing or the fraction of sensitive tumor cells. Simulations using the tumor kinetic model showed increased response rates in patients with higher tumor cell PD-L1 expression (increased by 9-11% and 10-14% with 25% and 50% cutoff, respectively), patients receiving durvalumab as first-line therapy (increased by 12% vs. 2nd line/above), and patients with smoking histories (increased by 4-5% vs. non-smokers). **Conclusions:** Tumor kinetic modeling identified factors that predict tumor progression and response following durvalumab in NSCLC patients. The multivariate analysis accounts for various predictive factors within predictive biomarker strata, allowing better interpretation of different biomarker cutoffs. The modeling technique can potentially guide patient selection/enrichment, clinical trial design strategies and tumor biology. Clinical trial information: NCT02087423 and NCT01693562.

11556 Poster Session (Board #256), Sat, 1:15 PM-4:45 PM

Prognostic value of NK and T-lymphocytes markers in operable non-small cell lung cancer (NSCLC). *First Author: Marcin Tomasz Skrzypski, Medical University of Gdańsk, Department of Oncology and Radiotherapy, Gdańsk, Poland*

Background: Therapies aimed at activation of T and NK cells are developed to expand NSCLC treatments options. It is conceivable that markers of 'immune ignorant', 'immune excluding' or 'inflamed' tumor phenotypes could be prognostic or predictive of benefit from specific immune-targeting therapies. Aim: To assess the prognostic value of expression of T and NK cells mRNA markers and immune-related genes in early stage NSCLC. **Methods:** qRT-PCR was used to assess 48 mRNAs levels in frozen cancer tissue sections and matched normal lung parenchyma from 56 surgically treated stage I-IIIA NSCLC patients. The mRNA expression (normalized vs. 4 reference genes) was compared between the groups that did (44%) or did not relapse, as well as clinicopathological features (33% never-smokers, 75% lung adenocarcinoma). **Results:** Low expression of *FAS-L* (p.adj. = 0.048), *TIGIT* and *LAG3* was correlated with shorter distant metastasis free survival (DMFS) (p $<$ 0.04). Expression of *PD-1* (p = 0.024) and *CTLA4* (p = 0.04) was significantly lower in relapsed vs. non-relapsed NSCLCs, whereas there was no difference for *PDL-1* and *PDL-2*. Expression of NK activation markers: *NCR3* and *NCR1*, but not *NCR3-ligand 1* was significantly lower in relapsed vs. not relapsed NSCLCs. Other NK cell markers: *CD96* and *NKG2D* were expressed at lower levels (p = 0.02) in relapsed vs. not relapsed NSCLCs, whereas there was no difference for *NKG2C* and *NKG2A*. Expression of *CXCR3* was lower in relapsed NSCLCs (p = 0.03), however, the expression of its ligands (chemoattractants for lymphocytes) - *CXCL9, CXCL10* or *CXCL11* or *endothelin receptor type B* was not different according to metastatic status. *GITR* and *FOXP3* expression was significantly higher in cancers vs. normal lung parenchyma (p.adj. $<$ 0.003). There were no differences in expression according to gender, smoking or NSCLC histological types. **Conclusions:** Non-inflamed NSCLC phenotype is associated with higher risk of dissemination after primary resection. Neoplastic tissue is characterized by higher level of immune tolerance in comparison to normal lung tissue.

11557 Poster Session (Board #257), Sat, 1:15 PM-4:45 PM

Effect of chemoradiation for cervical cancer on transient decrease and variable expansion in T-cell infiltrate and diversity of T-cell repertoire. *First Author: Lauren Elizabeth Colbert, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The effect of fractionated radiation on intratumoral immune infiltrate is unclear. The purpose of this study was to characterize local immune changes and treatment response during chemoradiation (CRT). **Methods:** Cervical cancer patients underwent cisplatin based CRT over 5 weeks with brachytherapy. Cervical DNA swabs and cytology brushings were collected at baseline, one week, three weeks and five weeks. Deep T cell receptor β sequencing (TCR; Adaptive, Seattle WA) and multiparametric flow cytometry (MPFC) were performed for each time point. T cell density (TCD) and productive clonality (PC) were analyzed. Cells separated from the tumor brushings were stained and fixed with antibodies to T cell subsets with activation and suppressor markers including CD3, CD4, CD8, Ki67, PD-1, CTLA-4, and ICOS. Changes in T cell subsets were evaluated as percentage of live lymphocytes. **Results:** Eight patients were evaluated using MPFC. CD4 and CD8 percentages were lowest at one week and subsequently expanded. The percentage of proliferating CD4 (CD4+ Ki67+) was highest at week 5 (1.19%). There was no change in percentage of CD8+ cells expressing PD1, CTLA4 or ICOS over the course of treatment. TCR diversity was assessed for 9 patients. At baseline, week 1, week 3 and week 5, median TCD for all patients were 0.046 (IQR 0.008 to 0.097), 0.021 (IQR 0.005 to 0.043), 0.035 (IQR 0.015 to 0.083), and 0.033 (IQR 0.017 to 0.110). Median productive clonality at each point was 0.05 (IQR 0.06 to 0.02), 0.03 (IQR 0.06 to 0.02), 0.04 (IQR 0.05 to 0.02) and 0.03 (IQR 0.01 to 0.05). PC fold count increased (1.69, SD 1.3) for complete response (CR) patients and decreased 0.3 (SD 0.008) for patients with recurrent (REC) disease ($p = 0.1$). One TCR sequence was common in 4/9 patients at the end of treatment and six sequences were common in 3/9 patients. **Conclusions:** Chemoradiation induces a transient decline in tumor infiltrating CD8+ and CD4+ cells, followed by a variable expansion in T-cells at the end of treatment with an increase in proliferation phenotypes. TCR sequencing revealed increase in productive clonality during radiation for patients with a complete response to treatment.

11558 Poster Session (Board #258), Sat, 1:15 PM-4:45 PM

Adjuvant radiation therapy to induce a transitory adaptive up-regulation of programmed death ligand 1 (PD-L1) on circulating epithelial tumor cells (CETCs) to affect the anti-tumor immune response in primary breast cancer patients. *First Author: Dorothea Schott, Transfusion Center, Bayreuth, Germany*

Background: Radiation therapy (RT) is an integral part of the treatment of breast carcinoma but unfortunately many patients experience local recurrence. During the inflammatory response that accompanies radiation tumor cells may develop multiple resistance mechanisms for example the up-regulation of PD-L1 on tumor cells which leads to immune evasion. Since CETCs arise from the tumor it is conceivable that under evolutionary pressure they might share some of the immune escape mechanism inherent to tumor cells. In this study we demonstrate that RT leads to a transitory adaptive up-regulation of PD-L1 expression on CETCs. **Methods:** CETCs and the expression of PD-L1 and Ki-67 were analyzed from 25 patients with primary non-metastatic breast cancer using the maintrac method. The fraction of PD-L1 and Ki-67 positive CETCs were assessed at baseline, 3 and 6 weeks after start of RT and 6 weeks after end of therapy. Additionally, copy number status of PD-L1 was determined using FISH. **Results:** Fractionated-dose RT leads to a significant increase in PD-L1 expression on CETCs with the highest expression level midterm of irradiation as compared to baseline (49% vs. 74%, $p < 0.01$). 6 weeks after end of RT the number of PD-L1 positive CETCs returned to baseline value. The up-regulation of PD-L1 was dose dependent. Patients who received higher total dose had significantly more PD-L1 positive CETCs as compared to patients treated with lower total dose midterm of RT (64% vs. 43, $p < 0.05$). Before start of therapy there was a correlation between the fraction of PD-L1 and Ki-67 positive CETCs ($r = 0.6$, $p < 0.01$). PD-L1 copy number gains were significantly associated with PD-L1 expression ($r = 0.6$, $P < 0.05$). **Conclusions:** RTleads to an up-regulation of PD-L1 expression on CETCs, which could be a possible mechanism of acquired radioresistance. Combining immunomodulatory agents with radiation might have the potential to overcome this resistance and could improve clinical outcome in breast cancer.

11559 Poster Session (Board #259), Sat, 1:15 PM-4:45 PM

Breast cancer-related paraneoplastic neurologic disease. *First Author: Brittany L. Murphy, Mayo Clinic Department of Surgery and Robert D. and The Patricia E. Kern Center for the Science of Health Care Delivery, Rochester, MN*

Background: Paraneoplastic neurologic disease (PND) is an aberrant immune-mediated response against the nervous system triggered by occult malignancy. Given the rarity of this disease, a paucity of data exists describing breast cancer (BC)-related PND; thus, we sought to further examine this specific population of patients. **Methods:** Using an institution specific clinical search tool, we identified all patients at our institution from 1997-2016 with a diagnosis of BC-related PND, verified by an international expert. Retrospective review was used to record tumor and treatment factors associated with PND and BC. A descriptive analysis was performed of the characteristics associated with BC-related PND. **Results:** BC-related PND was diagnosed in 58 female patients. Average age at BC diagnosis was 54.0±10.3 years. Most had invasive cancer of Stage II or higher [Stage 0 (10.3%), I (10.3%), II (44.8%), III (13.8%), IV (6.9%), unknown (13.8%)]. Most patients were hormone receptor (HR)+ (63.8%), while 4 (6.9%) were HR-, and 17 (29.3%) were unknown. Of the 34 patients where Her2/neu (Her2) data was available, 7 (20.6%) were Her2+ and 27 (79.4%) were Her2-. The majority (62.1%) had neurological symptoms prior to BC, 5.2% were concurrent, and 32.7% developed PND after initial BC. The interquartile range for time from PND to BC diagnosis was -8.5 to 10.5 months. Of the 58 patients, 29 (50%) had autoantibodies detected: Purkinje Cell Cytoplasmic Autoantibody Type-1 (PCA-1[anti-Yo]) (10), amphiphysin-IgG (n = 9), Anti-Neuronal Nuclear Autoantibody Type-2 (ANNA-2[anti-Ri]) (n = 5), and other (n = 5). The most common syndromes were cerebellar ataxia (n = 14), myelopathy (n = 11), and myopathy (n = 11). Immunotherapy was used for PND in 53 of 58 (91.4%) patients; benefit from immunotherapy was assessed as complete 0 (0%), robust 11 (20.8%), mild to moderate 28 (52.8%), none 9 (17%), and indeterminate 5 (9.4%). **Conclusions:** BC-related PND is rare, with only 58 cases over 20 years at a large academic institution. Paraneoplastic symptoms often present prior to BC diagnosis and BC characteristics are typical of the general population. Over 75% of patients benefit from immunotherapy. These data may provide helpful information to providers treating this population of patients.

11560 Poster Session (Board #260), Sat, 1:15 PM-4:45 PM

Metabolic barriers to immunotherapy in renal cell carcinoma. *First Author: Katy Beckermann, Vanderbilt University, Nashville, TN*

Background: Cancer cells can inhibit effector T cells through both immunomodulatory receptors and alteration of the tumor microenvironment as a result of cancer metabolism. A majority of patients treated with immune checkpoint inhibitors recently approved by the FDA fail to exhibit a clinical response. The extent to which metabolic conditions within the tumor impede T cell activation and anti-tumor effector function in renal cell carcinoma (RCC) are unknown. **Methods:** Under the IACUC protocol M1600005-00, BALB/c or Rag mice were subcutaneously injected with 100,000 Renca cells obtained from ATCC and growth monitored by caliper measurements in 3 dimensions every 3 days. *In vivo*PD-1 blockade was performed by 200 mcg/i.p. injection every 3 days using purified mPD-1 (BioXcell, J43). Deidentified tissue donations from patients with RCC were collected under the IRB protocol #151549 and processed into single cell suspensions following mechanical dissociation for the functional assays indicated below. **Results:** Through work with Rag deficient mice lacking functional B and T cells, we have established that tumor growth is regulated in a T cell dependent manner as evidenced by earlier formation and faster tumor growth. In a syngeneic mouse model of RCC (RenCa), we find that inhibition of PD-1 delays tumor growth and size. Tumor infiltrating lymphocytes (TILs) were abundant in patient-derived RCC, but are phenotypically distinct and are impaired both functionally and metabolically from healthy control. Instead of efficient use of aerobic glycolysis, TILs fail to increase glucose metabolism, and instead display increased reactive oxygen species (ROS) and mitochondrial dysfunction. CD8 effector cells found in tumors have notable differences in mitochondrial morphology compared to healthy control CD8 T cells by electron microscopy and immunofluorescence where CD8 TIL are punctate and dispersed throughout the cell while healthy control CD8 mitochondria are fused in networks. Thus bypassing metabolic defects may partially restore TIL activation. **Conclusions:** Preclinical data suggests that improved understanding of metabolic dysfunction in TILs of RCC may allow for combined therapies to improve response rates of checkpoint inhibition in this disease.

11561 Poster Session (Board #261), Sat, 1:15 PM-4:45 PM

Cell surface GRP78 expression on T and NK cell sub-populations of breast cancer patients. *First Author: Rinat Yerushalmi, Davidoff Cancer Center, Petah Tikva, Israel*

Background: The targeting of unfolded protein response (UPR) in tumor cells has received much attention. However, data are sparse on the impact of UPR on T and NK cells. The master regulator of UPR is the glucose-regulated protein 78 (GRP78) that is expressed in some tumor cells or normal stressed cells. There are few studies concerning GRP78 expression on T and NK cells in cancer and its relationship to stress induction by chemotherapy. We aimed to reveal the effect of UPR activation on the peripheral T and NK cells of breast cancer patients by the evaluation of cell surface GRP78 expression on T and NK cells before and after neoadjuvant chemotherapy. **Methods:** Forty-seven patients with triple negative, ER positive/Her2 negative and Her2 positive breast cancer were included. FACS analysis of their blood specimens before and after neoadjuvant treatment was performed. For multicolor FACS analysis, anti-CD3, CD4, CD8, CD56, CD16, NKG2D, CD45RA, CD45RO, CCR7 CD62L and anti-GRP78 antibody (AF488) were added to one of the tubes. A second tube was incubated with IgG-AF488 as isotype control. Analysis of the different T and NK subpopulations that expressed cell surface GRP78 were analyzed with the Gallios Flow cytometer and Kaluza Flow Analysis Software (Beckman Coulter, Inc.). **Results:** The percentage of cell surface GRP78 baseline expression in CD3 (1.8±0.9), CD8 (2.9±1.5), NKG2D (4.8±2) and CD45RO/CD62L/CCR7 active T memory cells (2.1±0.5) in Her2 positive patients were significantly higher than in triple negative and ER positive/Her2 negative patients. GRP78 expression on CD56, CD16 and NKG2D cells measured after neoadjuvant treatment was significantly higher in patients with complete response (CR) compared to patients without CR. 89% of the CR patients presented with Her2+ subtype. The non-CR patients include triple negative and Her2 negative subtypes. **Conclusions:** GRP78 was found to be expressed in the different T and NK sub-populations. The level of expression changed with each breast cancer subtype and response to chemotherapy. These novel findings suggest that GRP78 may be used as a new predictive biomarker. It sets the stage for understanding the mechanism of UPR activation on the immune system in breast cancer.

11562 Poster Session (Board #262), Sat, 1:15 PM-4:45 PM

Fatty-acid-binding proteins as a novel target for the treatment of anti-PD-1-resistant tumors. *First Author: James William Welsh, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The mechanisms underlying immunosuppression and resistance to PD1 inhibitors in cancer are not well understood. We attempted to fill this gap with an integrated transcriptome analysis in an anti-PD1-resistant lung adenocarcinoma mouse model. The model was created by in vivo passage of 344SQ murine lung cancer cells ($p53^{R172H\Delta g}/+K\text{-}ras^{LA1/+}$) in a syngeneic host repeatedly dosed with anti-mouse PD1 antibodies. Anti-PD1-resistant 344SQ (344SQ_R) and 344SQ parental (344SQ_P) cells were then inoculated into syngeneic 129Sv/ev mice, which were then dosed twice with anti-PD1 or control IgG antibodies. **Methods:** Tumor tissues were collected and analyzed as follows: transcriptome with Affymetrix; protein levels by reverse phase protein array analysis; signature enrichment by gene set enrichment analysis; metabolome by mass spectrometry; and lipid content with fluorescent probes Oil O and BODIPY. We also isolated tumor-infiltrating immune cells for flow cytometry and gene expression analyses. **Results:** We identified lipid-related metabolic pathways as being the most highly enriched in anti-PD1-resistant tumors (344SQ_R) vs. their 344SQ_P counterparts; the resistant cells also had more lipid droplets than the 344SQ_P cells. The anti-PD1-resistant tumors overexpressed several genes involved in lipogenesis and fatty acid pathways, including fatty acid binding proteins (FABPs). Specifically, FABP overexpression promoted fatty acid uptake and lipid-droplet accumulation in resistant tumors. 344SQ_R tumors promoted immune suppressive cells by upregulating FABPs expression in M2-like macrophages, marked by increased fatty acid intake and fatty acid oxidation. Conversely, percentages of CD4+ and CD8+ tumor-infiltrating lymphocytes were reduced in the resistant tumors. **Conclusions:** These results suggest that lipid metabolic rewiring drives resistance PD1 inhibitors supporting the accumulation of immunosuppressive cells, including M2-like macrophages, preventing type I immune responses elicited by T cells. Collectively, these findings reveal new potential lipid-related targets for drug development or new treatments combining inhibitors of these targets with anti-PD1 therapy.

11563 Poster Session (Board #263), Sat, 1:15 PM-4:45 PM

Combining chemotherapy and programmed death 1 (PD-1) blockade to induce a T-cell response in patients with metastatic triple negative breast cancer (mTNBC). *First Author: Elias Obeid, Fox Chase Cancer Center, Philadelphia, PA*

Background: Correlative studies to determine the effect of combining chemotherapy (CT) simultaneously with checkpoint inhibition on the peripheral immune response are planned as part of a clinical trial in MTNB. The trial design is a Safety run-in, into a randomized phase II trial of combination pembrolizumab (P) with carboplatin (C) and gemcitabine (G) in patients with mTNBC. One key concern is that CT may suppress immune cell function, thereby diminishing the efficacy of PD-1 blockade. **Methods:** Patients with a diagnosis of mTNBC are recruited to this trial with a Safety Run-in (N = 6-12 subjects), followed by a randomized design of C + G with/without P (2:1 randomization, N = 75). Safety run-in consists of P 200 mg on day 1 of each 21-day cycle, and C (AUC2) + G (800mg/m^2) on days 1 and 8. Patients are consented for a peripheral blood (PB) collection pre-cycle 1 and on day 1 of cycle 3, in order to phenotype immune system changes by flow-cytometry. **Results:** Six patients have been recruited as of this interim analysis. Data from PB analysis of 3 on-treatment patients is available. In 2 subjects, the activation marker CD69 increased on CD4+ and CD8+ T cells from baseline, indicating enhanced T cell function. Also the ratio of CD8+ T cells to regulatory T cells ($CD25^{high}$ $CD127^{low}$) has increased. Both patients expressed PD-1 on T cells at baseline. The 2 subjects with evidence for enhanced immune response have a continued clinical benefit (12 cycles subject 1, 8 cycles subject 2). In contrast, subject 3 (who discontinued P and received corticosteroids for grade a 2 immune-related hepatitis during cycle 2) lacked expression of PD-1 on T cells and did not exhibit these immune changes, and her disease clinically progressed after 4 cycles of CT. **Conclusions:** Although comprising a very limited number of patients, early analysis from our correlative studies of combining CT with the PD-1 blockade revealed evidence for effective immune stimulation in two subjects. Furthermore, immune changes accompanied a lasting clinical response. Although early, we conclude that combining CT with checkpoint blockade can achieve its goal of unleashing an anti-tumor immune response in mTNBC patients. Clinical trial information: NCT02755272.

11564 Poster Session (Board #264), Sat, 1:15 PM-4:45 PM

Genetic variants in CCL5 and CCR5 genes and serum VEGF-A levels to predict efficacy of bevacizumab in metastatic colorectal cancer patients receiving first-line chemotherapy. *First Author: Mitsukuni Suenaga, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Early VEGF-A reduction by targeting abundant VEGF-A is a potential predictive marker of bevacizumab (BV). CCL5/CCR5 axis modulates VEGF-A production via endothelial progenitor cells migration. We tested whether genetic polymorphisms in CCL5/CCR5 pathway will predict outcomes in metastatic colorectal cancer (mCRC) patients (pts) receiving BV in first-line setting. **Methods:** Genomic DNA was extracted from 215 samples of three independent cohorts: 61 pts receiving FOLFOX+BV (median age 60 yrs, median follow-up 39.2 mos); 83 pts receiving FOLFOX (median age 61 yrs, median follow-up 57.6 mos); 71 pts receiving FOLFOX/XELOX+BV as exploratory for serum biochemistry assay (median age 60 yrs, median follow-up 28.9 mos). Single nucleotide polymorphisms of genes in CCL5/CCR5 pathway were analyzed by PCR-based direct sequencing. Serum VEGF-A levels at baseline and day 14 were measured using ELISA. **Results:** In univariate analysis for the FOLFOX cohort, pts with the *CCL5* rs2280789 G/G variant or any *CCR5* rs1799988 T allele had shorter overall survival (OS) compared to the those with any A allele or the C/C variant (18.7 vs. 29.4 mos, HR 1.93, 95%CI: 1.05−3.53 P= 0.025; 22.0 vs. 31.2 mos, HR 1.74, 95% CI: 0.98-3.90, P= 0.055). The trend remained in multivariable analysis (P= 0.090 and P= 0.026). The differences were not confirmed in the FOLFOX+BV cohort. Pts with any *CCL5* rs2280789 G allele had longer progression-free survival (PFS) and OS when receiving FOLFOX+BV than FOLFOX (PFS: 19.8 vs. 11.0 mos, HR: 0.44, 95%CI: 0.25-0.78, P= 0.002; OS: 41.8 vs. 21.1 mos, HR: 0.43, 95%CI: 0.24-0.77, P= 0.002); pts carrying any *CCR5* rs1799988 T allele had longer PFS and OS (P= 0.025 and P= 0.008, respectively). No significant difference was shown in pts with either A/A or C/C variant. In the exploratory cohort, any *CCL5* rs2280789 G allele was associated with higher VEGF-A levels at baseline and greater decrease of VEGF-A levels at day 14 compared with the A/A variant. **Conclusions:** CCL5 and CCR5 impact the angiogenic environment. Our data suggest the genotypes may identify specific populations who benefit from BV-based chemotherapy in first-line treatment for mCRC.

11565 Poster Session (Board #265), Sat, 1:15 PM-4:45 PM

Algorithmic prediction of response to checkpoint inhibitors: Hyperprogressors versus responders. *First Author: Shipra Gandhi, Roswell Park Cancer Institute, Buffalo, NY*

Background: Predicting response to checkpoint inhibitors (CPIs) using biological knowledge-based decision processes with machine learning (ML) has a great potential to predict rapid progression in patients treated with checkpoint inhibitors (CPIs) (hyperprogressive disease (HPD)) as well as responders. ML models risk overfitting data and do not always evaluate the underlying biology, thus performing well in the initial training cohort but lack generalizability when extended to other cohorts. Biology-based decision may not perform as well initially due to limited understanding and a simplified rule set, but often perform equally well when extended to larger similar cohorts of patients. **Methods:** A custom NGS cancer immune gene expression assay compared 87 patients treated with CPIs classified as CR, PR, or SD versus 12 HPD. A ML-based polynomial regression model based on 54 immune-related genes combined with mutational burden was optimized for prediction of response. A biological 4-gene decision tree model was constructed independently based on ML. A second biological decision tree incorporated the weighted average relative rank of the expression of multiple genes in 4 different immune functions including immune cell infiltration, regulation, activation, and cytokine signaling. Bayesian model average (BMA) incorporated all three models' results into the final prediction. **Results:** For87 patients classified as CR, PR, or SD the PPV >96% for responders and a NPV >90% for non-responders was achieved with the regression model, however with response indeterminate for 24% of the population. While the two biological decision tree models' PPV were in the 70% range, they accurately revealed the critical genes' roles in immune response with strong literature support. BMA process integrated these three models resulted in a PPV >96% and a NPV >90% and eliminated the indeterminate group. For HPD a unique biology related to priming of short term memory T-cells was identified. **Conclusion:** Prediction of response to CPIs is best attained by combining ML with biological knowledge. Decision tree models using a large panel of immune related genes in the context of archival samples from patients treated with CPIs can be used to better understand the biology of responders versus non-responders and provides new insights into HPD.

11566 Poster Session (Board #266), Sat, 1:15 PM-4:45 PM

Computer extracted measurements of vessel tortuosity on baseline CT scans to predict response to nivolumab immunotherapy for non-small cell lung cancer. *First Author: Monica Khunger, Cleveland Clinic, Cleveland, OH*

Background: Immune-checkpoint blockade treatments, particularly drugs targeting the programmed death-1 (PD-1) receptor, demonstrate promising clinical efficacy in patients with non-small cell lung cancer (NSCLC). We sought to evaluate whether computer extracted measurements of tortuosity of vessels in lung nodules on baseline CT scans in NSCLC patients(pts) treated with a PD-1 inhibitor, nivolumab could distinguish responders and non-responders. **Methods:** A total of 61 NSCLC pts who underwent treatment with nivolumab were included in this study. Pts who did not receive nivolumab after 2 cycles due to lack of response or progression per RECIST were classified as 'non-responders', patients who had radiological response per RECIST or had clinical benefit (defined as stable disease >10 cycles) were classified as 'responders'. A total of 35 quantitative tortuosity features of the vessels associated with lung nodule were investigated. In the training cohort (N=33), the features were ranked in their ability to identify responders to nivolumab using a support vector machine (SVM) classifier. The three most informative features were then used for training the SVM, which was then validated on a cohort of N=28 pts. **Results:** The maximum curvature (*f1*), standard deviation of the torsion (*f2*) and mean curvature (*f3*) were identified as the most discriminating features. The area under Receiver operating characteristic (ROC) curve (AUC) of the SVM was 0.84 for the training and 0.72 for the validation cohort. **Conclusions:** Vessel tortuosity features were able to distinguish responders from non-responders for patients with NSCLC treated with nivolumab. Large scale multi-site validation will need to be done to establish vessel tortuosity as a predictive biomarker for immunotherapy.

AUC values of the top ranked tortuosity features on training and validation cohorts.

	Features			
	f1	*f2*	*f3*	*f1,f2,f3*
Training	0.75	0.65	0.60	0.84
Validation	0.68	0.57	0.70	0.72

11567 Poster Session (Board #267), Sat, 1:15 PM-4:45 PM

Pathogenic variants in DNA damage response (DDR) genes in patients with advanced solid tumors. *First Author: Ecaterina Elena Ileana Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Deleterious mutations in DDR genes are frequently associated with response to poly(ADP-ribose) polymerase (PARP) inhibitors and platinum chemotherapy. However, much remains unknown about their association with specific molecular signaling pathways. We report the prevalence of pathogenic variants in DDR genes and their co-alteration with other somatic variants. **Methods:** Targeted exome sequencing of 201 genes was performed in 1,189 patients (pts) with advanced solid tumors enrolled in a molecular testing protocol (NCT01772771), using matched normal and tumor DNA. We assessed germline and somatic alterations in 15 cancer-related DDR genes, their co-occuring genomic alterations and the tumor mutation burden (TMB), defined as number of somatic non-synonymous mutations. **Results:** A total of 124 pathogenic or likely pathogenic variants in DDR genes were identified in 111/1189 (9%) pts with 57% of these alterations being somatic. These variants were found in the following genes: ATM 17 pts (1.4%); BAP1 5 pts (0.4%); BRCA1 18 pts (1.5%); BRCA2 17pts (1.4%); CHEK1 8 pts (0.7%); CHEK2 16 pts (1.3%); ERCC3 4 pts (0.3%); ERCC4 2 pts (0.2%); ERCC5 3 pts (0.2%); MLH1 4pts (0.3%); MSH2 8 pts (0.7%); MSH6 6 pts (0.5%); PALB2 3 pts (0.2%) and RAD51 1pt (0.1%). DDR alterations were found more frequently in the following tumor types tested: breast 14%, colorectal 12%, melanoma 8%, glioblastoma 6% and ovarian 6%. The most relevant somatic co-alterations with DDR mutations were activation of the PI3K/AKT/mTOR pathway through mutations or copy-number variations in AKT1, MTOR, NF1, PIK3CA, PIK3R1, PTEN, TSC1 and TSC2 ($p = 0.008$). Patients with deleterious variants in mismatch excision repair genes (MLH1, MSH2 or MSH6) had a significantly higher TMB than all other patients enrolled (median TMB = 62 vs 5, $p = 0.002$). Patients with somatic pathogenic DDR variants had a significantly higher TMB (median = 13) compared to patients with germline DDR variants (median = 5) ($p = 0.004$). **Conclusions:** The association of DNA repair mutations with alterations in signaling pathways provide rationale for novel therapeutic combinations. Variations in TMB based on distinct types of DDR gene alterations may have implications for immunotherapy.

11568 Poster Session (Board #268), Sat, 1:15 PM-4:45 PM

SEER study of breast cancer specific mortality (BCSM) in patients with lobular tumors treated based on recurrence score results. *First Author: Frederick L. Baehner, Genomic Health, Redwood City, CA*

Background: Linking the 21-gene assay RS result to the SEER Registries demonstrated very low 5-y BCSM with low RS and high 5-y BCSM with high RS across subgroups, such as nodal status, age, tumor size and grade (npj Breast Cancer 2016). Given the large sample size and interest in outcomes as a function of tumor characteristics, we characterized the relationship between RS results and BCSM in patients reported by SEER with lobular morphology. **Methods:** Patients with RS and lobular morphology based on the registry ICD-O-3 code 8520 were eligible if node negative (N0) or node positive up to 3 positive nodes (N+mic,1-3), HR+, HER2- negative, no prior malignancy, and diagnosed between Jan 2004 and Dec 2012. No information in SEER is available regarding lobulars, ie., trabecular, alveolar, solid and pleomorphic. 5-y BCSM was estimated using actuarial methods. **Results:** There were 6,075 eligible patients reported with lobular morphology (11% of cases). Median age was 59 years; 88%/12% were N0/N+; 31%/62%/7% grade 1/2/3; 61%/39% ≤2 cm/>2 cm. Median follow-up was 44 months. A minority (8%) had RS >25. Chemotherapy (CT) use and BCSM increased with increasing RS. In multivariable analysis in N0 disease, continuous RS result and tumor size predicted BCSM (p=0.003 and p=0.04, respectively), whereas age and tumor grade were non-significant. In multivariable analysis in N+ disease, continuous RS result alone predicted BCSM (p=0.002). **Conclusions:** In these analyses the prognosis of patients with lobular breast cancer treated based on RS results depends on both nodal status and the RS result. The 5-y BCSM for lobular breast cancer is excellent with RS of 25 or less, and increases for RS >25.

	NO HR+ HER2- (N=5,320)			N+(mic,1-3) HR+ HER2- (N=755)		
RS	**N**	**CT Use (% of N)**	**5-y BCSM (95% CI)**	**N**	**CT Use (% of N)**	**5-yBCSM (95% CI)**
RS <11	802	4%	0.5% (0.1%, 1.9%)	131	24%	0.0% (0.0%, 0.0%)
RS 11-17	2343	9%	0.8% (0.4%, 1.6%)	351	26%	0.0% (0.0%, 0.0%)
RS 18-25	1753	28%	1.1% (0.6%, 2.1%)	218	42%	1.2% (0.3%, 4.8%)
RS 26-30	294	53%	4.1% (1.9%, 8.6%)	37	60%	6.8% (1.7%, 24.5%)
RS ≥31	128	66%	1.4% (0.2%, 9.6%)	18	72%	20.7% (6.9%, 52.6)

11569 Poster Session (Board #269), Sat, 1:15 PM-4:45 PM

Baseline cell-free DNA (cfDNA) and metabolic tumor volume (MTV) independently predict outcome in metastatic chemorefractory colorectal cancer (mCRC). *First Author: Erwin Woff, Nuclear Medicine Department, Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium*

Background: No validated prognostic biomarker is currently available for mCRC. This trial assessed cfDNA and MTV before treatment with regorafenib as prognostic biomarkers for progression-free survival (PFS) and overall survival (OS) in mCRC. **Methods:** After signed informed consent, mCRC patients were enrolled in a prospective non-randomized trial aiming to define unlikelihood to benefit from regorafenib (EudraCT number: 2012-005655-16) and assessed for cfDNA and FDG PET/CT MTV at baseline. cfDNA was extracted from 3mL of plasma and quantified using the Qubit 2.0 fluorometer. All target lesions were delineated on FDG PET/CT using a PERCIST-based threshold and their volumes were summed to obtain total MTV. MTV and cfDNA optimal cutoffs for OS and PFS prediction were determined by the Contal and O'Quigley's method. MTV, cfDNA, age, gender, Body Mass Index (low, normal, high, obese), ECOG PS, number of chemotherapy lines (NCL), previous use of bevacizumab and presence of a KRAS mutation were included in a multivariate analysis. **Results:** MTV and cfDNA of 132 evaluable/141 eligible patients were well correlated (Spearman's correlation coefficient = 0.70; $p < 0.001$) and risk groups for both PFS and OS were identified on the basis of cfDNA (cfDNA < 1 μg/mL; cfDNA≥ 1 μg/mL) and MTV (MTV < 100 cm^3; 100-300 cm^3; > 300 cm^3). The multivariate analysis retained cfDNA, MTV, NCL, and obesity as independent parameters for PFS prediction, and cfDNA, MTV, NCL, BMI, and previous use of bevacizumab as independent parameters for OS prediction. Prognostic scores for PFS and OS were developed based on regression coefficients from the final Cox proportional hazards models. Prognostic scores for PFS (1.8 vs 5.3 months, HR: 3.15 for score $\geq$-3 vs $<$ -3, (95% CI, 2.08-4.76); $p < 0.001$) and for OS (4.2 vs 13.9 months, HR: 4.59 for score $\geq$-6 vs $<$ -6: (95% CI, 2.92-7.21); $p < 0.001$) both identified patients with much contrasted outcomes. **Conclusions:** Baseline cfDNA and MTV along with BMI parameters predict outcome in patients with mCRC before regorafenib onset. These parameters not related to treatment should be considered, if validated in further studies, as stratification factors in future clinical trials. Clinical trial information: 2012-005655-16.

11570 Poster Session (Board #270), Sat, 1:15 PM-4:45 PM

FDG PET/CT and N0 mediastinal nodal status in early stage non-small cell lung cancer: A single institution retrospective experience. *First Author: Shashank Reddy Cingam, Louisiana State University Health Sciences Center, Shreveport, LA*

Background: The increasing use of CT and now low-dose screening CT scans for at-risk patients have led to increasing detection of lung cancer at early stages. FDG PET/CT is used as an adjunct to conventional imaging to assess loco-regional lymph node spread. However, there is a potential for false-negative results, especially in smaller lesions or early nodal involvement. The main objective of this study was to study the value of PET/CT scan to evaluate for true negative mediastinal nodes in patients with early stage NSCLC. Accurate determination of N0 status can have a significant impact on the cost-effectiveness and timely management of early stage NSCLC. **Methods:** Of a total of 404 patients with NSCLC managed at our facility between 2008 to 2015, 29 adult patients whose PET scan showed no or equivocal mediastinal nodal involvement and subsequently underwent surgical exploration of mediastinal lymph nodes were included in the study. Data variables that were collected included the cancer site, date of PET, node status on PET, type and date of surgery, cancer histology, and the tissue diagnosis of the sampled nodes. SAS software was used for the analysis of the data. **Results:** Of the 29 patients with N0 or equivocal nodes on FDG PET/CT, 7 (24.13%) had evidence of malignancy on biopsy of the surgically resected lymph nodes. No statistically significant differences were noted between the site of the neoplastic lesion, cancer histology, duration between the date of PET and the date of surgery in the true negative (TN) and false negative (FN) groups. The recurrence rate was higher in the FN group 60 % (3/5) compared to 21 % (4/19) in the TN group who had follow up for atleast 2 years. **Conclusions:** Our findings suggest incidence of false negative results of FDG PET/CT for evaluation of N0 nodes in early stage NSCLC is 24.13%. This is comparatively higher than false negatives rates with mediastinoscopy (5-10%) reported in other studies. Although our sample size is small, if confirmed, such a relatively high incidence of false negative results on FDG PET/CT for N0 disease supports the current recommendations for exploratory mediastinoscopy and/or surgery for definitive staging in early stage NSCLC.

11571 Poster Session (Board #271), Sat, 1:15 PM-4:45 PM

Clinical utility of molecular testing to select therapy in relapsed/refractory non-Hodgkin lymphoma: Mayo Clinic Center for Individualized Medicine experience. *First Author: Nabila Nora Bennani, Mayo Clinic, Rochester, MN*

Background: Relapsed/refractory (R/R) non-Hodgkin lymphomas (NHL) have a poor prognosis with limited treatment options. Our expanding knowledge of molecular alterations seen in R/R NHL allows identification of patients that potentially may benefit from a precision medicine approach. However, experience in routine clinical implementation of precision medicine has been limited. Here, we summarize our clinical experience in molecular characterization of RR NHL targeted therapy (TT) using next-generation sequencing (NGS), and selection of targeted therapy (TT) based on molecular profile. **Methods:** We conducted a prospective study in RR NHL through the Center for Individualized Medicine at Mayo Clinic. Consenting patients underwent NGS using FoundationOne Heme panel from biopsies done at time of relapse. Results of NGS were discussed at the Genomic Tumor Board and recommendations for TT were given based on matching specific molecular alteration(s) with potential agent(s) predicted to be active based on NGS. The agents could include FDA-approved, off-label use and clinical trial therapies. **Results:** 28 cases were enrolled: 18 aggressive NHL, 10 follicular lymphoma (FL). Molecular alterations were present in all cases. In aggressive B-cell NHL, CDKN2A/B gene cluster alterations were seen in 73% (8/11), while seen in only 1/7 T-cell lymphomas (TCL), and 1/10 FL. TP53 deletions were second most common genomic alterations in DLBCL (57%) and seen in 40% FL. JAK-STAT and ERBB pathways were altered in TCL (2/7 each). IGH-BCl-2 gene rearrangement were common in FL (70%), followed by MLL gene alterations (50%). Targetable mutations were present in 86% (24/28) of cases. A TT was recommended in all 24 cases, but received by 2 patients only. Remaining patients did not due to benefit from current therapy (10/24), ineligibility or lack of clinical trial (7/24) or interim clinical deterioration (5/24). **Conclusions:** Targetable mutations were identified in most cases of RR NHL with TT recommended for all cases. However, access to TT limits potential clinical benefit of molecular-based matching strategy. More studies are needed to assess impact on clinical outcomes.

11572 Poster Session (Board #272), Sat, 1:15 PM-4:45 PM

The use of ^{18}F-fluoroestradiol (FES) and ^{18}F-fluorodeoxyglucose (FDG) PET in the evaluation of breast cancer heterogeneity. *First Author: Lanell M Peterson, University of Washington Seattle Cancer Care Alliance, Seattle, WA*

Background: ^{18}F-Fluoroestradiol (FES) is an estrogen analogue that has been shown to be a promising biomarker in ER imaging of breast cancer. FES uptake correlates to ER expression, provides qualitative and quantitative assessment of multiple tumor sites simultaneously, and can predict response to endocrine therapies. Tumor heterogeneity is a known feature of metastatic breast cancer. Our work and others has shown that patients that have tumors with high FDG-PET SUV and low FES-PET SUV uptake have a poorer prognosis. Biopsies of metastatic disease may be done initially for diagnosis of metastatic disease, but are generally only performed in the setting of target identification for clinical trials. A change in ER or HER2 expression, however, can result in a change in therapy. FES-PET imaging offers a virtual biopsy and can reveal heterogeneity of the entire tumor burden. **Methods:** We reviewed our prior evaluations of tumor heterogeneity with FES-PET from 3 different studies. 46 breast cancer patients with metastatic disease (de novo or recurrent) who had biopsy proven ER+ primary breast cancer underwent FES-PET and FDG-PET imaging and a biopsy of a metastatic lesion prior to therapy initiation. ER and HER-2 expression was reviewed. **Results:** Of the 46 patients, 5 (11%) had ER- metastatic biopsies. One (2%) biopsy changed from ER+/HER-2 neg to ER-/HER-2+, and one (2%) biopsy changed from ER+/HER-2+ to ER+/HER-2-. All 5 patients (11%) with changes in ER/HER2 expression underwent a change in therapy due to the unexpected findings by metastatic biopsy. FDG findings helped to guide selection of biopsy sites. FES quantitative measures correlated with biopsy findings. **Conclusions:** Biopsy resulted in a change in therapy for $>$ 10 % of patients enrolled in trials of FES imaging. Imaging can help identify heterogeneous tumor locations to assist identification of evolving tumor targets in breast cancer. In addition, FES imaging may reveal a change in tumor phenotype that can ultimately affect choice of therapy. Research Support: P01CA42045, R01CA72064

11573 Poster Session (Board #273), Sat, 1:15 PM-4:45 PM

Contribution of microarrays of gene expression (MAGE) to the definition of PET/CT as a qualified biomarker of early response in metastatic patients. *First Author: Manuel Sureda, Plataforma de Oncologia, Hospital Quironsalud Torrevieja. Catedra Oncologia Multidisciplinar-UCAM, Torrevieja, Spain*

Background: Proliferating cancer cells consume elevated quantity of glucose, converted into lactate regardless the presence of oxygen (Warburg effect). This effect has been useful for imaging metabolically active tumors with FDG-PET, although its use in early response is controversial. Molecular mechanisms of FDG uptake are not fully understood. We have used MAGE to determine the most relevant genes involved in FDG uptake. **Methods:** Fresh-frozen tumor biopsies and quantitative basal FDG-PET/CT were obtained from metastatic lesions in cancer patients. Total tumor RNA was hybridized to a whole human genome oligonucleotide microarray. Gene expression signature-based prediction, using the most relevant genes involved in FDG uptake measured by SUV, was finally determined by Partial Least Squares (PLS). The interpretation of biological phenomena (IBP) derived from the selected genes was made by means of different public statistical bioinformatics resources. **Results:** 71 patients with different histological diagnosis were included in the training cohort and 13 in the validation one. 909 probes correlated significantly with SUV: 333 positively and 576 negatively. A predictive signature based on these 909 probes was built using PLS-3, with an RMSE in the validation set of 0.645 (within the 95% CI of RMSE determined in the training set). In IBP, other biological processes were more relevant than glycolysis in FDG uptake: RNA processing, ribosome biogenesis, protein processing, cell adhesion, cytoskeleton organization, angiogenesis and autophagy. **Conclusions:** This PLS-3-built signature is the first reported one that can accurately predict SUV. FDG uptake is a complex phenomenon that involves multiple biological processes, confirming the value of PET/CT in early response.

11574 Poster Session (Board #274), Sat, 1:15 PM-4:45 PM

The mutational landscape of gastrointestinal malignancies as reflected by circulating tumor DNA. *First Author: Paul Riviere, University of California San Diego Moores Cancer Center San Diego School of Medicine, La Jolla, CA*

Background: Liquid biopsy of circulating tumor DNA (ctDNA) is a novel method of detecting genetic alterations in cancer patients without tissue acquisition. **Methods:** Our analysis surveyed the genomic landscape of 213 patients with various gastrointestinal malignancies using next generation sequencing of plasma ctDNA across a 68 gene panel (www.guardanthealth.com/guardant360/). Data analysis was performed following UCSD IRB guidelines for de-identified database (NCT02478931). **Results:** The most common cancer types were colorectal adenocarcinoma (N = 55 (26%)), appendiceal adenocarcinoma (N = 46 (22%)), hepatocellular carcinoma (N = 31 (15%)), and pancreatic ductal adenocarcinoma (N = 25 (12%)). 70% of patients had discernible alteration(s), and 58% of patients had $\geq$1 characterized alterations. The median number of characterized alterations per patient was 1 (range 0-13). The number of detected alterations per patient varied between cancer types: in hepatocellular carcinoma, 74% of patients (23/31) had $>$ 1 characterized alteration(s), whereas 76% of patients (35/46) with appendiceal adenocarcinoma had no characterized alterations. Overall, of 123 patients with characterized alterations, $>$ 99% (122/123) had $\geq$1 hypothetical (experimental or approved) treatment options available. Potentially targetable alterations varied between cancer types, proportionally to the detection rate of characterized alterations. The median percent ctDNA of characterized alterations was 2.50% (IQR 0.76-8.96%). Of interest, 95% of patients (117/123) had distinct molecular portfolios. Altogether, there were 143 unique characterized alterations within 56 genes. Overall concordance rates of 96%, 94%, 95%, and 91%, respectively, were found between ctDNA and tissue biopsy (105 patients) (https://www.foundationmedicine.com/) in the four most common alterations (*KRAS* amplification, *MYC* amplification, *KRAS* G12V, and *EGFR* amplification). **Conclusions:** Our observations suggest that many patients with gastrointestinal tumors have discernible and pharmacologically tractable ctDNA alterations. Hence, ctDNA assessment through non-invasive liquid biopsy may have an important role in clinical practice.

11575 Poster Session (Board #275), Sat, 1:15 PM-4:45 PM

Targeted next-generation DNA sequencing of paired tumor and normal DNA to reveal frequent actionable germline alterations. *First Author: Wolfgang Michael Korn, University of California, San Francisco, San Francisco, CA*

Background: Targeted next-generation DNA sequencing of paired tumor and normal DNA samples allows for detection of biologically relevant variants in the tumor with significantly greater accuracy than tumor-only sequencing. In addition, this approach presents with the opportunity of unveiling previously unknown cancer predisposition traits in a patient's germline DNA. **Methods:** We sought to determine the rate of pathogenic germline alterations in 546 consecutive pediatric and adult patients who underwent molecular profiling using the UCSF 500 assay, a hybrid capture-based DNA sequencing assay targeting the coding regions of ~500 cancer-related genes, TERT promoter, select introns from 40 genes (for detection of gene fusions and other structural variants), and intergenic regions at regular intervals along each chromosome (for chromosomal copy number and LOH assessment). **Results:** Pathogenic germline alterations were found in 89/546 patients (16.3%), including 25 pediatric and 64 adult cases. Germline variants were identified in 37 genes with MUTYH (n = 15, 17%), CHEK2 (n = 10, 11%), BRCA2 (n = 9, 10%), BRCA1 (n = 5, 6%), TP53 (n = 5, 5%), and APC (n = 4, 5%) being altered most frequently. Loss of heterozygosity of genes affected in the germline was seen in tumor DNA 37 (42%) cases, highlighting their likely role as drivers of tumorigenesis. Clinically relevant germline findings not associated with increased cancer risk were identified in 6 (7%) of the cases, for example a COL1A1 mutation associated with Ehlers-Danlos Syndrome. In In 73 (82%) of the cases, pathogenic germline alterations were new findings and genetic counseling was recommended. A possible, previously unknown, role of germline mutations was found in some instances, including a TSC2 germline mutation in a patient with hybrid oncocytoma/chromophobe tumor (HOCT) with loss of the normal TSC2 allele in the tumor. **Conclusions:** Our data suggest that paired tumor/normal DNA analysis uncovers actionable heritable traits in a substantial fraction of patients and represents the preferred approach to analyzing malignancies in children and adults.

11577 Poster Session (Board #277), Sat, 1:15 PM-4:45 PM

Function and expression of checkpoint inhibitors and immune agonists on immune cells in monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) and MM and tumor-specific T lymphocytes. *First Author: Jooeun Bae, Dana-Farber Cancer Institute, Boston, MA*

Background: Characterization of expression and function of immune regulatory molecules in tumor microenvironment will provide the framework for developing novel therapeutic strategies. **Methods:** We evaluated the expression and functional impact of various immuno-regulatory molecules, PD-1, PDL-1, PDL-2, LAG3, TIM3, OX40 and GITR, on the $CD138^+$ tumor cells, myeloid derived suppressor cells (MDSC), and T cell subsets from patients with MGUS, SMM and active MM (newly diagnosed, relapsed, relapsed/refractory), and the myeloma-specific cytotoxic T lymphocytes (CTL) induced with XBP1/CD138/CS1 peptides. **Results:** PDL-1/PDL-2 was more highly expressed on $CD138^+$ myeloma cells in active MM than SMM or MGUS. G-type MDSC ($CD11b^+CD33^+HLA\text{-}DR^{low}CD15^+$). Treg cells ($CD3^+CD4^+/CD25^+FOXP3^+$) numbers were increased and expressed higher levels of PD1/PD-L1 in active MM than in MGUS, SMM or healthy donors. Among the checkpoint molecules (PD-1, PDL-1, PDL-2, LAG3, OX40, GITR) evaluated, PD-1 showed the highest expression on $CD3^+CD4^+$ and $CD3^+CD8^+$T cells in BMMC and PBMC from patients with active MM. Functionally, T cells from MM patients showed increased proliferation upon treatment with an individual immune agonist ($>$ 150%) or checkpoint inhibitor ($>$ 100%). Interestingly, each individual anti-checkpoint molecule induced proliferation of T cells expressing other checkpoint molecules. In addition, the blockade of PD1, LAG3 or TIM3 enhanced MM antigen-specific cytotoxicity, assessed by parameters including CD107a, granzyme B and IFN-g production, which was most prominent within the memory CTL subset of MM antigen-specific T cells. **Conclusions:** These results demonstrate an increased frequency of immune regulatory cells, which highly express checkpoint inhibitors in active MM. Direct stimulation with an immune agonist or blockade of a checkpoint inhibitor increased MM patients' T cell proliferation and myeloma-specific CTL function, supporting development of combination immune regulatory therapies to improve patient outcome in MM.

11578 Poster Session (Board #278), Sat, 1:15 PM-4:45 PM

Rare tumor clinic: The UCSD Moores Cancer Center experience with a precision therapy approach. *First Author: Shumei Kato, Moores Cancer Center, La Jolla, CA*

Background: Rare tumors have an incidence of < 15/100,000 per year; ultra-rare, prevalence < 2000 in the USA. Patients (pts) may lack approved treatments and clinical trial access. Although each rare tumor is uncommon, cumulatively they account for > 20% of cancers. We recently initiated a Rare Tumor Clinic that emphasized a precision medicine strategy (genomic and proteomic analysis and individualized therapy). We report our preliminary experience. **Methods:** We investigated outcome among the first 40 pts presenting to the Rare Tumor Clinic at UC San Diego Moores Center for Personalized Cancer Therapy. Whenever possible, next-generation sequencing (NGS) of tissue and plasma-derived circulating tumor DNA (ctDNA) as well as proteomic markers were assessed. **Results:** Median age was 58 (range, 31 – 78 yo); 70% (28/40) were women; median number of previous systemic therapies, 2 (range, 0-7). The most common diagnoses were sarcoma (N = 7) for solid tumors; Erdheim-Chester disease (N = 5), for hematologic malignancies. Twenty distinct diagnoses were seen. Examples of ultra-rare tumors included ameloblastoma, yolk sac liver tumor, ampullary cancer, Castleman's disease, and desmoid tumor. 82.5% of pts (33/40) had tissue NGS (182 to 405 genes); 7.5% (3/40), inadequate tissue. The median number of characterized tissue alterations was 3 (range, 0 to 24); 32 pts (80%) had ≥1 characterized genomic alteration. 33 pts (82.5%) had ctDNA analysis; 15 pts had ≥1 characterized alteration. Among those 15 pts, median number of characterized alterations was 3 (range, 1 to 14). 92.5% (37/40) of pts had ≥ 1 actionable target based on either genomic (32 pts) or proteomic markers (27 pts) (FDA-approved [mostly off-label] or investigational agent). 52.5% (21/40) received matched therapy; 52.4% (11/21) achieved SD≥6 months (N = 3)/CR (N = 2)/PR (N = 6). Matched therapy resulted in significantly longer PFS compared to last prior unmatched therapy (HR: 0.26, 95% CI: 0.10 – 0.71 [p = 0.008]). **Conclusions:** Identifying genomic and proteomic markers in pts with rare and ultra-rare tumors was feasible. When therapies were matched, > 50% of pts attained SD≥6 months/CR/PR. Further clinical investigations focusing on rare and ultra-rare tumors are urgently needed.

11579 Poster Session (Board #279), Sat, 1:15 PM-4:45 PM

Persistence of AKT1 low quiescent cancer cells after neoadjuvant chemotherapy in triple negative breast cancer patients. *First Author: Sheheryar Kairas Kabraji, Massachusetts General Hospital, Boston, MA*

Background: The mechanisms that allow triple negative breast cancer (TNBC) tumors to survive neoadjuvant chemotherapy (NACT) are incompletely understood. Evidence suggests that proliferative heterogeneity may contribute to primary chemotherapy resistance in patients with localized triple negative breast cancer. However, the detailed characterization of a drug-resistant cancer cell state in residual TNBC tissue after NACT has remained elusive. $AKT1^{low}$quiescent cancer cells (QCCs) are a quiescent, epigenetically plastic, and chemotherapy resistant subpopulation initially identified in experimental cancer models. Here, we asked whether $AKT1^{low}$ QCCs actually exist in primary tumors from patients with TNBC and persist after treatment with NACT. **Methods:** We identified QCCs in primary and metastatic human breast tumors using automated, quantitative, immunofluorescence microscopy coupled with computational and statistical analysis. We obtained pre-treatment biopsy, post-treatment mastectomy, and metastatic specimens from a retrospective cohort of TNBC patients treated with neoadjuvant chemotherapy at Massachusetts General Hospital (n = 25). Using automated quantitative immunofluorescence microscopy, QCCs were identified as AKT^{low} / $H3K9me2^{low}$ / $HES1^{high}$ cancer cells using pre-specified immunofluorescence intensity thresholds. QCCs were represented as 2D and 3D digital tumor maps and QCC percentage (QCC-P) and QCC cluster index (QCC-CI) were determined for each sample. **Results:** We found that QCCs exist as non-random and heterogeneously distributed clusters within primary tumors. In addition, these QCC clusters are enriched after treatment with multi-agent, multi-cycle, neoadjuvant chemotherapy in both residual primary tumors as well as nodal and distant metastases in patients with triple negative breast cancer. **Conclusions:** Together, these data qualify QCCs as a non-genetic mechanism of chemotherapy resistance in triple negative breast cancer patients that warrants further study.

11580 Poster Session (Board #280), Sat, 1:15 PM-4:45 PM

Clinicopathologic features of non-small cell lung cancer (NSCLC) harboring an *NTRK* gene fusion. *First Author: Anna F. Farago, Massachusetts General Hospital, Boston, MA*

Background: Gene fusions involving *NTRK1/2/3* can generate oncoproteins containing the kinase domains of TRKA/B/C, respectively. Inhibition of TRK signaling has led to dramatic responses across tumor types with *NTRK* fusions. An estimated 0.1 – 1% of NSCLCs harbor *NTRK* fusions. To date, clinical and radiographic responses to TRK inhibitors have been reported for 2 *NTRK* fusion-positive NSCLCs (Farago et al., 2015; Hong et al., 2016). Despite the potential benefit of identifying these fusions, the clinicopathologic features of *NTRK* fusion NSCLCs are not well characterized. **Methods:** Physicians across multiple institutions contributed deidentified cases to an *NTRK* fusion NSCLC database. A central pathologist (M.M.) reviewed tumor histology in cases with available tissue. **Results:** 10 NSCLC cases with *NTRK* gene fusions were identified. Of these, TRK kinase domain-containing potentially activating fusions were verified by next-generation sequencing (NGS) in 7, forming the study cohort. Fusions involved *NTRK1* (6) and *NTRK3* (1) with 6 different partners. Four (57%) patients were male. Median age at diagnosis was 47.6 years (range 27.9 – 86.0). The average smoking pack year history was 8.9 (range 0 to 30). Five (71%) presented with metastatic disease. No concurrent alterations in *KRAS*, *EGFR*, *ALK*, *ROS1*, or other known drivers were identified in the study cohort cases. On pathologic review of 4 cases, all were adenocarcinoma, including 2 invasive mucinous adenocarcinomas and 1 adenocarcinoma with neuroendocrine features. Of the 3 remaining non-study cohort cases, 1 was a non-kinase domain-containing *NTRK1* fusion with a concurrent *KRAS G12C* mutation, 1 was an *NTRK2* intragenic deletion disrupting the exon 18 3' splice site, and 1 was an *NTRK1* alteration detected by FISH but not verified by NGS and with a concurrent *HER2* L755P mutation. **Conclusions:** *NTRK* fusions occur in both men and women across wide ranges in age and smoking history. We therefore suggest that all NSCLC adenocarcinomas without other oncogenic driver alterations be screened for *NTRK* fusions. Notably, not all *NTRK* alterations are activating, requiring validation of the specific position of the fusion.

11581 Poster Session (Board #281), Sat, 1:15 PM-4:45 PM

Molecular profiling comparison of breast cancer subtypes in young women and older women. *First Author: Antoinette R. Tan, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC*

Background: Young women with breast cancer (YWBC; ≤40 years) have a more aggressive clinical course and is associated with a poorer prognosis. In this analysis, we explore molecular features in tumors of YWBC and older women with breast cancer (OWBC; ≥65 years) by subtype. **Methods:** Somatic genomic profiles of 1879 breast tumors collected from 2013-2017 were assessed retrospectively and included in a de-identified data analysis if ER, PR and HER2 (immunohistochemistry [IHC] and/or *in situ* hybridization [ISH]) were available. Testing included IHC, ISH and massively parallel sequencing assays (next-generation sequencing [NGS]) at a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). Pearson's chi-square was utilized for comparisons and significance defined as $p < 0.05$. **Results:** Frequency of subtypes in YWBC (n = 536) and OWBC (n = 1343) were 45% and 55% HR+HER2-, 38% and 36% triple-negative (TN), 7% and 5% HER2+HR-, and 10% and 4% in HER2+HR+, respectively. Specimens tested were breast (53%, 43%) and a metastatic site (43%, 57%) in YWBC and OWBC, respectively. HR+HER2- YWBC exhibited higher rates of pathogenic mutations in TP53 (34%, 24.4%; n = 748; p = 0.008), BRCA1 (9%, 4.5%; n = 503; p = 0.047), BRCA2 (14.8%, 8.4%; n = 501; p = 0.032), gene amplifications in FGF3 (26.7%, 10.4%; n = 107; p = 0.034), FGF4 (26.7%, 9.1%; n = 107; p = 0.019), FGF19 (29.6%, 11.6%; n = 96; p = 0.033), CCND1 (36.7%, 18.2%; n = 107; p = 0.042), and overexpression of EGFR (18.6%, 8%; n = 364; p = 0.004). TN YWBC had higher rates of alterations in TP53 (80.2%, 67.4%; n = 577; p = 0.002) and BRCA1 (13.3%, 5.9%, n = 375; p = 0.015). YWBC that was HER2+HR+ exhibited a higher rate of APC mutations (10%, 0%; n = 84; p = 0.03). In OWBC, there were higher rates of PD-L1 expression in HER2+HR- (22.7%, 0%; n = 70; p = 0.009) and TN (13%, 6.3%; n = 458; p = 0.035). There were also higher PIK3CA mutations in HER2+HR+ (43.4%, 18.8%; n = 101; p = 0.008) and CDH1 mutations (12.8%, 0%; n = 85; p = 0.022) in TN. **Conclusions:** There were distinct molecular aberrations and significantly different frequency of alterations in subtypes of YWBC compared to OWBC. These molecular changes may contribute to increased understanding of breast cancer tumor biology and refinement of treatment strategies in YWBC and OWBC.

11582 Poster Session (Board #282), Sat, 1:15 PM-4:45 PM

Restoration of tumor suppression in vivo by systemic delivery of chemically-modified PTEN mRNA nanoparticles. *First Author: Mohammad Ariful Islam, Center for Nanomedicine and Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Background: The onset and maintenance of cancer frequently involves gain of oncogenic function along with loss of tumor suppression. *PTEN* is a well-characterized tumor suppressor gene that is lost or mutated in many human cancers including ~50% of metastatic castration-resistant prostate cancer (mCRPC). Reintroduction of functional PTEN for mCRPC treatment has proven difficult. **Methods:** PTEN mRNA was synthesized by *in vitro* transcription method and modified with ARCA capping and enzymatic polyadenylation, and then substituted with Pseudo-UTP, 5'-Methyl-CTP. A robust self-assembly approach was employed to prepare PTEN mRNA nanoparticles (NPs) using cationic lipid-like compound G0-C14 and PLGA polymer coated with lipid-PEG shell. PTEN expression in tumors and PI3K-AKT pathway were confirmed by IHC and western blot, respectively. Apoptosis was checked by flow cytometry and Tunel assays. *In vivo* toxicity was studied by hematologic and histologic tests, and immune response. **Results:** We successfully restored PTEN mRNA to PTEN-null prostate cancer (PCa) cells *via* systemic delivery of mRNA NPs. These mRNA NPs are stable in serum, demonstrate minimal toxicity, and provide highly effective transfection in PCa cells (substantially higher HA-PTEN expression than plasmid PTEN transfection) and PCa xenograft tumors, leading to ~85% inhibition of tumor cell growth *in vitro* and *in vivo*. We also confirm mRNA NP-mediated systemic restoration of PTEN function in PTEN-null PCa and delineate its tumor suppression through inhibition of the PI3K-AKT pathway and enhancement of apoptosis. **Conclusions:** The work provides proof of principle for the systemic reintroduction of mRNA-based tumor suppressor genes to tumors *in vivo*. Because PTEN loss is frequent in late-stage PCa, this approach may have feasibility in this patient population. Considering the strong potential of mRNA therapy and the lack of systemic studies of *in vivo* mRNA transfection of tumors, this study sheds light on the useful application of NP-mediated mRNA delivery for validating tumor suppressors (e.g., *PTEN*) as a therapeutic target in cancer treatment where loss of a tumor suppressor contributes to the underlying genetic mechanism of cancer.

11583 Poster Session (Board #283), Sat, 1:15 PM-4:45 PM

Role of ERBB signaling in RET-rearranged lung cancer and contribution of EGFR amplification to cabozantinib resistance. *First Author: Roger Smith, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Lung cancers driven by oncogenic *RET* fusions have lower response rates to targeted monotherapy such as cabozantinib (28%) relative to response rates typically observed in *ALK*- or *ROS1*- rearranged lung adenocarcinomas (60-80%). **Methods:** To identify targetable co-dependencies or cooperating pathways for *RET* fusion-positive lung cancers, we performed high-throughput chemical and genetic screens to find FDA-approved drugs or genes that when inhibited, would synergize with cabozantinib in *RET* fusion-positive lung cancer cell lines. In addition we performed NGS of a pair of pre-treatment and post-cabozantinib progression samples. **Results:** We identified *EGFR* siRNAs and anti-EGFR drugs as synergistic with cabozantinib. Combinations of drugs that target EGFR (cetuximab, afatinib, erlotinib, gefitinib, neratinib) and RET (cabozantinib, CEP-32496, lenvatinib, vandetanib) were more effective at reducing growth of RET cell lines than any single agent *in vitro* and in xenograft models. Cabozantinib treatment of *RET* fusion-positive cell lines inhibited EGFR and RET phosphorylation, an observation not seen in *RET* wild-type cell lines. Co-immunoprecipitation studies reveal that RET and EGFR interact. Ectopic expression of *CCDC6-RET* in NIH-3T3 or human bronchial epithelial cells resulted in upregulation of multiple ERBB receptors and ligands (not seen in a *ROS1* fusion-positive cell line) and a concomitant increase in EGFR stability. Treatment with ERBB pathway ligands or overexpression of EGFR decreased sensitivity to cabozantinib in two *RET* fusion-positive cell lines. Finally, sequencing of a pair of pre-treatment and post-progression samples from a lung cancer patient treated with cabozantinib revealed acquired amplification of *EGFR* in the latter sample. **Conclusions:** Taken together, these results suggest that the tumorigenic potential of RET fusion oncogenes is dependent on deregulation of ERBB-activated pathways and that a combination of RET and EGFR drugs could be more effective in treating *RET* fusion-positive tumors. Moreover, amplification of *EGFR* is a potential driver of resistance to cabozantinib in *RET*-rearranged lung cancers.

11584 Poster Session (Board #284), Sat, 1:15 PM-4:45 PM

Alterations in the B-catenin pathway in non-small cell lung cancer to define a distinct molecular subtype with prognostic and therapeutic implications. *First Author: Saveri Bhattacharya, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: The treatment of non-small cell lung cancer (NSCLC) has been revolutionized by the development of targeted therapy for distinct molecular subsets. Activation of the β-catenin pathway is essential for colorectal carcinoma tumorigenesis and has been implicated in hepatocellular, thyroid and ovarian cancer. The β-catenin pathway is involved in the cell adhesion complex and Wnt signaling. While mutations in this pathway have been reported in NSCLC and β-catenin overexpression correlates with worse survival, its role in lung tumorigenesis is poorly understood. **Methods:** We performed targeted next generation sequencing using the Ion Torrent Hotspot Cancer Panel v.2 on tumor tissue from 244 NSCLC patients in which we have defined key demographic and clinical parameters including stage and survival. This cohort contained 91 Stage I cases with mRNA expression data using an Illumina platform. Co-occurrence of genes in the β-catenin pathway and 27 other genes in the panel were assessed by Fisher's exact test, with Benjamini-Hochberg adjustment for multiple comparisons. **Results:** Seventeen of 244 tumors had mutations in the β-catenin pathway (APC, CTNNB1, and NOTCH1): 10/170 non-squamous NSCLC (6%, 95% CI 3%-10%), and 7/70 squamous NSCLC (10%, 95% CI 5%-19%). The rate of EGFR and RB1 mutations was higher in tumors with b-catenin pathway mutation (5/17 and 2/17) than in those without (13/227 and 0/227, adjusted $p = 0.06$ for both). The presence of an APC mutation was also associated with higher mRNA expression of the pro-survival protein, BCL2 ($n = 91$; 5/41 vs. 0/50, unadjusted $p = 0.022$, adjusted $p = 0.3$). Furthermore, APC mutations were more frequently observed in tumors with higher levels of EMT markers (high VIM 8% vs. low VIM 0%, unadjusted $p = 0.16$) and EMT transcription factors (10% vs. low expression 2%, unadjusted $p = 0.16$). Finally, we observed a trend toward worse overall survival in non-squamous tumors with mutations in the β-catenin pathway ($n = 170$, log rank test $p = 0.07$). **Conclusions:** These studies suggest that tumors with b-catenin pathway alterations are defined by a more mesenchymal and potentially drug resistant subtype which portends a poor prognosis.

11585 Poster Session (Board #285), Sat, 1:15 PM-4:45 PM

Identification of novel fumarate hydratase gene alterations in prostate cancer. *First Author: Sherri Z. Millis, Foudation Medicine, Inc., Phoenix, AZ*

Background: Fumarate hydratase (FH), an enzyme involved in the Krebs cycle, plays a crucial role in the generation of energy and oxygenation of cells. Genomic alterations (GAs) of FH, a tumor suppressor gene, have been shown to cause chronic hypoxia that encourages tumor formation and have been linked to hereditary leiomyomatosis and renal cell cancer. Only few reports have associated FH mutations with other cancers, and none in prostate cancer. **Methods:** Identification of an FH V435M pathogenic alteration, which likely changes fumarate binding kinetics, in a prostate cancer patient, with negative family history for renal cancer and cutaneous leiomyomatosis, led to review of a database of 1781 prostate cancer patients, whose tissue was assayed by hybrid-capture based comprehensive genomic profiling (CGP) in the course of clinical care to evaluate genomic alterations (GA: base substitutions, indels, amplifications, copy number alterations, fusions/rearrangements) and targeted therapy opportunities. Tumor mutational burden (TMB) was calculated from a minimum of 1.11 Mb sequenced DNA and reported as mutations/Mb. **Results:** Profiling identified 49 prostate adenocarcinoma patients (3%) with FH gene alterations, 2 of which harbored the V435M GA identified in the original prostate patient. Ten of 40 alterations were H476_k477 insertions, in the C terminus domain, and 14 were amplifications. The rest were variants of unknown significance (VUS). **Conclusions:** A FH GA, known to impact other cancers, found in a prostate cancer, led to the discovery of a frequency that suggests deregulation of metabolic pathway activation may contribute to prostate cancer pathogenesis for a subset of patients. The somatic FH GA's are likely to be substantially more common than germline mutations, and identifying metabolic-enzyme mutations that are pathogenic in prostate cancer could lead to pharmacologic manipulations that are more effective and less toxic than existing therapies. No FDA approved therapies currently exist for this patient's tumor type nor of any other tumor type with FH GA's. In our case, alterations in the C-terminal binding domain of FH might inform drug development.

11586 Poster Session (Board #286), Sat, 1:15 PM-4:45 PM

Induction of a BRCAness state by oncometabolites and exploitation by PARP inhibitors. *First Author: Ranjit Bindra, Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT*

Background: 2-Hydroxyglutarate (2HG) exists as two enantiomers, R-2HG and S-2HG, and both are implicated in tumor progression via their inhibitory effects on α-ketoglutarate (aKG)-dependent dioxygenases. The former is an oncometabolite induced by isocitrate dehydrogenase-1 and -2 (IDH1/2) mutations, while the latter is produced under pathologic processes such as hypoxia. Recurring IDH1/2 mutations were first identified in gliomas and acute myeloid leukemia (AML). **Methods:** Our group recently reported that IDH1/2 mutations induce a homologous recombination (HR) defect which renders tumor cells exquisitely sensitive to Poly (ADP-Ribose) polymerase (PARP) inhibitors. Remarkably, this "BRCAness" phenotype can be completely reversed by mutant IDH1/2 inhibitors, and it can be entirely recapitulated by treatment with either 2HG enantiomer in cells with intact IDH1/2. We performed a comprehensive series of studies that directly implicate two aKG-dependent dioxygenases, KDM4A and KDM4B, as key mediators of the observed phenotype. **Results:** Using the methodology and preliminary data obtained above as a basis for further inquiry, here we have extended these findings to several related gene mutations, which similarly induce profound synthetic lethality with PARP inhibitors in these tumors, and our data suggest a similar mechanism of action via which HR is suppressed. Finally, we provide additional evidence that suppression of 2HG production with small molecule inhibitors of mutant IDH1/2 function does not lead to any detectable decreases in cell growth or viability in several unique models. **Conclusions:** Small molecule inhibition of oncogenic kinases is a pillar of precision medicine in modern oncology, and this approach has been extrapolated to treat IDH1/2-mutant and other oncometabolite-producing cancers with inhibitors blocking the neomorphic activity of the mutant proteins. The findings present here directly challenge this therapeutic strategy, and they instead provide a novel approach to treat these tumors with DNA repair inhibitors. Based on these findings, we are planning a multi-center Phase II trial testing the efficacy of olaparib for the treatment of recurrent IDH1/2-mutant tumors later this year.

11587 Poster Session (Board #287), Sat, 1:15 PM-4:45 PM

Impact and correlation of mutational load (ML) and specific mutations (mts) assessed by limited targeted profiling (LTP) with PD-L1 tumour expression (exp) in resected non-small cell lung carcinoma (NSCLC). *First Author: Jane Sze Yin Sui, Department of Medical Oncology, St. James's Hospital, Dublin, Ireland*

Background: The advent of immunotherapy represents a paradigm shift in the treatment of NSCLC compared to conventional chemotherapy. Recent studies have shown higher mts burden assessed by exome sequencing are associated with improved objective response and clinical benefit. We performed this study to evaluate the impact of ML assessment by LTP, correlating with PD-L1 exp and clinicopathological variables in resected NSCLC. **Methods:** NSCLC patients (pts) who underwent curative resection between 1998 and 2006 at our institution were included. PD-L1 status was assessed using Ventana SP124 antibody on archival FFPE surgical tumour specimens cores. PD-L1 was scored positive if membranous staining was present in >1% of tumour cells aggregated across the replicate cores to address heterogeneity. In collaboration with the Lung Cancer Genomics Ireland Study a targeted panel of 49 genes were assessed by Sequenom MassArray including genes in MAPK and PI3K pathways. Clinical data was obtained from hospital electronic database. **Results:** Ninety-one pts were included, of which 51 (56.0%) were males, with a median age of 65 years (range: 42 – 82). 51.6%, n=47 with squamous histological subtypes, 46.2%, n=42 were ex-smoker and 49.5%, n=45 had Stage I disease. 23.1%, n=21 had PD-L1 positivity. 149 mts were identified of which, 32(21.5%) with PHLPP2, 31(20.9%) with PIK3R1 and 21(14.1%) with TP53. The presence of PI3K and TP53 mts are associated with positive PD-L1 status (see table). An inverse correlation of PD-L1 positivity with ML of (1 vs 2 vs 3: 53.8% vs 30.8% vs 15.4%) was noted. **Conclusions:** We did not identify higher PD-L1 exp with higher ML assessed by a LTP widely used in clincial practice. However, positive PD-L1 exp was correlated with PIK3R1 and TP53 mts , warranting further investigation as potential modulators or surrogates of positve PD-L1 expression.

PD-L1 exp with driver mts.

Mts	PD-L1 positive, n=21	PD-L1 negative, n=70
TP53	29%	14%
PIK3R1	24%	20%
PHLPP2	14%	24%
BRAF	5%	1%
IDH1	5%	6%
KRAS	5%	6%
MET	5%	6%
PTPN11	5%	7%
CDKN2	5%	0%
PIK3CA	2%	10%
CTNNB1	0%	1%
EGFR	0%	1%
FBXW7	0%	1%
FGFR1	0%	0%
HRAS	0%	1%
MYC	0%	0%
NRAS	0%	0%
PTEN	0%	0%
TBX3	0%	0%

11588 Poster Session (Board #288), Sat, 1:15 PM-4:45 PM

Antitumor activity of indenoisoquinoline inhibitors of topoisomerase 1 (TOP1) via apoptosis and autophagocytosis pathways in animal models. *First Author: Robert J. Kinders, Clinical Biomarkers Program, Laboratory of Human Toxicology and Pharmacology, Applied/Developmental Directorate, Leidos Biomedical Research, Inc., Frederick, MD*

Background: We performed pharmacodynamic biomarker analysis for response to a panel of three indenoisoquinolines (LMP776, LMP400 and NSC706744, J. Med. Chem. 49:7740, 2006) that have demonstrated antitumor activity in dogs. In preclinical xenograft models treated with indenoisoquinolines, we observed that gH2AX was not a useful biomarker for the biological activity of compound 706744, but was a reasonable biomarker of drug activity (Clin. Canc. Res. 16:5447, 2010) for the other two compounds, even though *in vitro* data indicated that all 3 compounds inhibited TOP1 and killed tumor cells. It has been reported that irinotecan activates autophagy (Pharm. Rev. 65:1162, 2013) which correlated with its metabolism to SN-38; we therefore developed, validated and tested an immunofluorescence microscopy assay for LC3 as a marker of autophagy. **Methods:** Assays were developed to evaluate apoptosis by co-localization of cleaved caspase 3 and gH2Ax, and autophagy by LC3 immunofluorescence on formalin fixed, paraffin-embedded tissue sections of xenografts models or lymphomas from outbred dogs. Percent positive cells containing LC3 puncta were quantitated using a spot morphology algorithm. Analysis of gH2AX and cleaved caspase 3 cellular co-localization was developed using a blebbing morphology algorithm (Definiens). **Results:** LC3 reported that indenoisoquinoline 706744 activates autophagy *in vitro* with the absence of cleaved caspase 3-dependent apoptosis while the -776 and -400 compounds do not activate autophagy, but instead demonstrate apoptosis in response to drug treatment. Results in animal models confirmed that both autophagy and apoptosis were active. Clinical readiness of the assays was confirmed on canine biopsy FFPE slides. **Conclusions:** 1,Structurally-related TOP1 inhibitors may trigger alternative pathways of cell destruction; 2,Autophagy may report drug anti-tumor activity or tumor drug resistance according to current literature. This assay may be useful for determination of pharmacodynamic pathways associated with anti-tumor activity to elucidate mechanism of action of investigational agents used in clinical trials.

11589 Poster Session (Board #289), Sat, 1:15 PM-4:45 PM

Validation of an expanded neoantigen identification platform for therapeutic and diagnostic use in immuno-oncology. *First Author: Sean Michael Boyle, Personalis, Inc., Menlo Park, CA*

Background: Neoantigen identification is increasingly critical for clinical immuno-oncology applications including predicting immunotherapy response and neoantigen-based personalized cancer vaccines. Although standard research pipelines have been developed to aid neoantigen identification, building a robust, validated neoantigen identification platform suitable for clinical applications has been challenging due to the complex processes involved. **Methods:** To improve neoantigen identification, we extended standard sequencing and informatics methods. We developed an augmented and content enhanced (ACE) exome sequenced at 200X to increase sensitivity to SNPs and indels used for neoantigen identification as well as HLA performance. To accurately identify fusions and variants from RNA, we optimized our ACE transcriptome for FFPE tissue. To improve neoantigen pipelines based on MHC binding algorithms, we developed peptide phasing, high accuracy HLA typing, TCR interaction predictors, and transcript isoform estimation tools to detect neoantigens from indel and fusion events. We performed comprehensive analytical validation of the platform including the ACE Exome, somatic SNV/indel calls, RNA based variant and fusion calls, and HLA typing. This was followed by an overall in silico validation of neoantigen identification using 23 experimentally validated immunogenic neoepitopes spiked into exome data. **Results:** Analytical validation of our ACE exome platform showed > 97% sensitivity for small variants with a specificity of > 98% at minor allele frequency > 10%. From the ACE transcriptome we achieved a fusion sensitivity of > 99% and RNA based variant calls sensitivity of > 97%. Our ACE exome based HLA typing was 98% and 95% concordant with Class I and II HLA results (respectively) from clinical testing. Our in silico validation of neoantigen predictions resulted in identification of 22 out of 23 immunogenic neoepitopes. **Conclusions:** We developed sequencing and informatics improvements to standard approaches that can enhance neoantigen identification and demonstrated a comprehensive validation approach that may support neoantigen use in future clinical settings.

11590 Poster Session (Board #290), Sat, 1:15 PM-4:45 PM

Characterisation of CCS1477: A novel small molecule inhibitor of p300/CBP for the treatment of castration resistant prostate cancer. *First Author: Neil Pegg, CellCentric Ltd, Cambridge, United Kingdom*

Background: Targeted degradation of androgen receptor (AR) and AR variants (ARV) remains an attractive therapeutic opportunity for patients with castrate resistant prostate cancer (CRPC). E1A binding protein (p300) and CREB binding protein (CBP) are two closely related transcriptional activators of AR. We have developed CCS1477 which is a potent, selective and orally active small molecule inhibitor of the bromodomain of p300/CBP and investigated its role in regulating androgen receptor expression and function. **Methods:** Binding of CCS1477 to p300, CBP and BRD4, was measured in a surface plasmon resonance (SPR) assay. Potency and functional activity (proliferation and biomarker knockdown) was demonstrated in prostate cell lines *in vitro* (22Rv1, VCaP). Cross species *in vivo* pharmacokinetic (PK) properties were assessed, and *in vivo* efficacy, linked to inhibition of biomarkers, was determined in 22Rv1 and LNCaP xenograft models. **Results:** CCS1477 binds to p300 and CBP with high affinity (Kd = 1.3/1.7nM) and selectivity (Kd = 222nM; BRD4). It is a potent inhibitor of cell proliferation in prostate cell lines (IC50 = 96nM,22Rv1; 49nM,VCaP) with minimal effect in AR-ve lines. In 22Rv1 cells, p300/CBP inhibition down-regulates AR-FL, AR-V7 and c-Myc protein by Western, an effect not seen with the BET inhibitor, JQ1 at equivalent proliferation IC50s. Inhibition of p300/CBP also reduces c-Myc, KLK3 and TMPRSS2 gene expression (qPCR) in 22Rv1 cells *in vitro*. The *in vivo* PK properties of CCS1477 are consistent with qd or qod oral dosing in mouse. CCS1477 dosed at 10mg, 20mg/kg qd or 30mg/kg qod, caused complete tumour growth inhibition over 28 days in a 22RV1 xenograft model, including extended duration in the absence of the drug for a further 24 days. This was accompanied by complete inhibition of plasma PSA and significant knockdown of tumour AR-FL, AR-V7, and C-Myc protein as well as C-Myc and TMPRSS2 mRNA expression. **Conclusions:** Taken together these data support the clinical testing of CCS1477 in castrate resistant prostate cancer by down-regulation of AR, AR-SV and c-MYC expression and function.

11591 Poster Session (Board #291), Sat, 1:15 PM-4:45 PM

Co-amplification of *MET* and *PIK3CA* in NSCLC and data on a PDX mouse model. *First Author: Jin Kang, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: Amplification of the mesenchymal-epithelial transition (*MET*) proto-oncogene or phosphatidylinositol3-kinase (*PI3K*) is common in non-small-cell lung cancer (NSCLC) and represents a potential therapeutic target. NSCLC with coexisting driver mutations or amplifications is a cause of great concern. **Methods:** From 2013 until now, fluorescence in situ hybridization was used to screen for *MET* amplified NSCLC patients.The amplification of the *MET* was defined as centromere 7 ratio $\geq$ 2.0 and the criterion of Cappuzzi. The amplification of the *PIK3CA* was copy numbers $\geq$ 4.0. We established the patient-derived exnograft (PDX) mouse model from a dual *MET/PIK3CA*-amplified patient. Preclinical efficacy of single versus dual inhibition was evaluated in vivo. Six groups were allocated to receive the treatment of vehicle control, bozitinib,crizotinib, taselisib (PI3K inhibitor), bozitinib+taselisib, or crizotinib+taselisib, respectively. **Results:** Totally, 568 (568/2321, 24.47%) patients harbored positive *MET* amplification and 6 (6/568,1%) were comfirmed with dual *MET/PI3K* amplification. The two stageIV patients received *MET* inhibitor treatment.One trial (NCT02896231) patient was treated with bozitinib and achieved confirmed PR, but with 3 months PFS and 5 months OS. The best response was PR and PFS was 5.6 months for the other one receiving the study drug capmatinib (NCT02276027). In the PDX mouse model experiment, we found three single-anget inhibitors monotherapy to be active but only transiently effective in controlling the growth of PDX. The PDX models showed more sensitivity to taselisib among the three single-anget groups. In contrast, the combination of the two inhibitors caused a stronger and long-lasting growth inhibition in PDX models. The addition of taselisib to bozitinib or crizotinib monotherapy provided obvious enhanced activity. Regretfully, two mice died because of the toxicities in the crizotinib+taselisib group. **Conclusions:** Patients with dual *MET/PIK3CA* amplification represent a rare molecular subtype of NSCLC and have a relatively short duration of response to *MET* inhibitors.The combination of *MET/PI3K* inhibitors is synergistic preclinically.

11592 Poster Session (Board #292), Sat, 1:15 PM-4:45 PM

Phosphopeptide mapping of DLC1 in ER+ breast cancer reveals AMOTL2, a key hippo pathway component, as an important target. *First Author: Yesim Gokmen-Polar, Indiana University School of Medicine, Indianapolis, IN*

Background: Metastases suppressor genes are believed to control tumor progression and metastases. Deleted in Liver Cancer 1 (DLC1) acts as a gatekeeper for tumor and metastasis suppression. Low expression of DLC1 correlates with poor prognosis in patients with ER+ breast cancer. It is essential to understand the impact of DLC1 and its functional network in preventing tumor and metastasis suppression. **Methods:** T47D cells with stable DLC1-Full-Length (DLC1-FL) were generated using mammalian expression cloning vector, pcDNA3.1+/C-(K)-DYK, and CloneEZ™ technology. Growth rate of control and DLC1-FL knock-in cells was assessed for 2 weeks using clonogenic assay. Proteomic and phosphopeptide enrichment assays (Pierce TiO2 enrichment kit) were performed in triplicates to examine the basis of altered growth phenotype. The PeakJuggler node in Proteome Discoverer was utilized for label-free quantitation of both protein and peptide MS peak areas. In addition, GO term enrichment analysis was performed in DAVID for the significantly changed phosphopeptides. **Results:** Stable knock-in of T47D-DLC1-FL inhibits cell growth significantly in vitro compared to T47D-control in clonogenic assay. The phosphopeptide enrichment proteomic analyses showed 199 phosphopeptides were identified only in T47D-DLC1-FL and 182 peptides were identified only in T47D-control cells. Pathway analysis using DAVID showed 3 main clusters of significantly differently identified phosphopeptides (p-values $\leq$ 0.01) involving cadherin binding (p = 4.9e-12), cell-cell adherens junction (p = 3.9e-10), and cell-cell adhesion (p = 9.4e-7). Analysis of specific phosphopeptides showed canonical pathways such as CTNNB1 (Thr552), and BCL2L13 (370-385). More importantly, phosphorylation of HIPPO-pathway component AMOTL2 at S766, critical for promoting YAP signaling and invasion was only identified in T47D-control but not T47D-DLC1-FL (p = 5.78e-5). **Conclusions:** This data suggest that the absence of DLC1 promotes phosphorylation of AMOTL2, and thereby activating YAP-TAZ signaling leading to invasiveness. This data provides mechanistic basis for targeting this pathway to prevent recurrence in ER+ breast cancer.

11593 Poster Session (Board #293), Sat, 1:15 PM-4:45 PM

Genomic alterations in 670 patients with diverse cancers analyzed by next-generation sequencing (NGS) of circulating tumor DNA (ctDNA). *First Author: Maria Clemence Schwaederle, Center for Personalized Cancer Therapy and Division of Hematology and Oncology, UCSD Moores Cancer Center, La Jolla, CA*

Background: NGS of blood-derived ctDNA allows non-invasive tumor profiling. Liquid biopsy studies with clinical correlation have so far been mainly limited to small size cohorts. **Methods:** We performed comprehensive plasma genomic testing of ctDNA (NGS) in 670 patients (pts) (54-70 genes); Guardant Health, Inc.; (Clinical Laboratory Improvement Amendment certified and College of American Pathologists accredited). **Results:** The most represented cancers were gastrointestinal (31.8%), brain (22.7%), and lung (20.7%) (Table). Sixty-three percent of pts (N = 423) had $\geq$1 alteration. The most frequent alterations (characterized and variants of unknown significance (VUSs)) were in *TP53* (32.5% of pts), followed by *EGFR* (13%), *KRAS* (12.5%), and *PIK3CA* (9.1%); for characterized alterations, the breakdown was 30.7% (*TP53*), 7.6% (*EGFR*), 12.2% (*KRAS*), and 7.7% (*PIK3CA*). Interestingly, 32% of brain tumors had $\geq$1 ctDNA alteration. Head and neck tumors were independently associated with a higher number of alterations (P=0.019). Forty-eight percent of pts (320/670) had potentially actionable alterations; in 241, (75% of 320), by an FDA-approved drug (mostly off label). Illustrative examples of clinical utility will be presented such as a patient with gastric cancer and *EGFR*amplification in ctDNA who received anti-EGFR treatment (60% regression), as well a patient with aggressive gynecologic malignancy who received immunotherapy based on a hypermutated ctDNA profile. **Conclusions:** Most pts, including a subset of those with brain tumors, demonstrated ctDNA alterations. Pts with head and neck tumors harbored higher numbers of alterations. Overall, three quarters of pts with alteration(s) had $\geq$1 aberration that could potentially be pharmacologically tractable, suggesting the need to further assess the utility of ctDNA in a therapeutic setting.

Characteristics	Total patients, N = 670
Turn over time (median, 95%CI; range)	15 days (15-16 ; 7-35)
Common Tumors	
Gastrointestinal	213 (31.8%)
Brain	152 (22.7%)
Lung	139 (20.7%)
Breast	55 (8.2%)
Head and neck	25 (3.7%)
No. of pts with ≥ 1 alteration*	423 (63.1%)
Median No. of alterations (range) *	1 (0-26)

*Characterized alterations and VUSs

11594 Poster Session (Board #294), Sat, 1:15 PM-4:45 PM

ABCG2 and TOP-1 mRNA expression as predictive biomarkers for adjuvant FOLFIRI treatment in stage III colon cancer patients: Results from the PETAAC-3 prospective randomized clinical trial. *First Author: Nils Brunner, University of Copenhagen, Frederiksberg, Denmark*

Background: FOLFIRI as adjuvant treatment in primary colon cancer was previously tested in two pivotal prospective randomized clinical trials (PETACC-3 and CALGB 89803), both of which failed to demonstrate significant beneficial effects when adding irinotecan to 5FU. As a consequence, FOLFIRI is presently not used as adjuvant treatment for colon cancer. **Methods:** The study included 580 patients with mRNA expression data performed on tumor samples (FFPE) from stage III colon cancer patients enrolled in the PETACC-3 study, which randomized the patients to 5FU plus Leucovorin +/- irinotecan. Primary end-points were recurrence-free survival (RFS) and overall survival (OS). Median ABCG2 and the 75 percentile TOP-1 mRNA expression data were used to allocate the patients into one of two groups: One with high ABCG2 expression (above median) and low TOP-1 expression (below 75 percentile) (n = 167) and another group including all other combinations of these two genes. Kaplan Meier curves and Cox proportional hazards model were used to visualize differences between groups and calculate p-values (log-rank test). **Results:** The survival statistics showed a significant difference for both RFS (HR: 0.63 (0.44-0.92); p = 0.017) and OS (HR: 0.6 (0.39-0.93); p = 0.021) between the two groups when the patients received FOLFIRI. In contrast, no significant differences were observed between the groups when patients received 5FU and Leucovorin alone (p-values: RFS: 0.58; OS: 0.75). **Conclusions:** We here show that the combination of two independent gene expression abundance with a strong association to irinotecan treatment (high ABCG2 drug efflux pump and low TOP-1, the latter being the target for irinotecan) identified a group of stage III colon cancer patients who will not benefit from FOLFIRI adjuvant treatment while patients with other combinations of expression of these two genes appear to significantly benefit from adjuvant FOLFIRI treatment. The lack of a similar effect in patients receiving treatment with 5FU and Leucovorin only, points to a predictive value of ABCG2 and TOP-1 measurements.

11595 Poster Session (Board #295), Sat, 1:15 PM-4:45 PM

Occurrence of ALK fusions in cancers other than non-small cell lung cancer in a wide variety of tumor types and response to anti-ALK targeted therapy. *First Author: Jeffrey S. Ross, Albany Medical College, Albany, NY*

Background: Genomic fusions of the anaplastic lymphoma kinase gene (*ALK*) are an established therapy target for patients with non-small cell lung cancer (NSCLC), but are not well-characterized in non-NSCLC malignancies. **Methods:** Comprehensive genomic profiling (CGP) of 92,784 clinically advanced malignancies was performed using a hybrid-capture, adaptor ligation based NGS assay to a mean coverage depth of >600X. Tumor mutational burden (TMB) was calculated from a minimum of 1.1 Mb of sequenced DNA. **Results:** 17,127/92,784 (18.5%) were NSCLC and 75,657 (81.5%) were non-NSCLC. Of the 697 (0.8%) of cases with *ALK* fusions, 554 (79%) were identified in NSCLC and 143 (21%) in non-NSCLC including 67 carcinomas; 39 sarcomas including 30 non-uterine and uterine leiomyosarcomas and inflammatory myofibroblastic tumors; 24 in hematolymphoid malignancies including non-Hodgkins lymphomas, myelomas and histiocytic malignancies; 3 in gliomas; 2 each in mesotheliomas, neuroblastomas and undifferentiated malignancies and 1 in melanoma. *ALK* fusions were significantly more frequently identified in NSCLC (3.2%) than in non-NSCLC ($p<0.0001$). The non-NSCLC *ALK* fusion positive patients were significantly older ($p<0.0001$) and more often female ($p<0.0001$) than the NSCLC *ALK* fusion positive patients. At 84%, the more frequent finding of *EML4* as the fusion partner in the NSCLC patients versus non-NSCLC patients at 31% was significant ($p<0.0001$). *ALK* fusion positive non-NSCLC had significantly lower TMB (mean 5.01 mutations/Mb) than non-*ALK* altered non-NSCLC (p=0.006). Non-NSCLC *ALK*fusion positive cases responding to ALK inhibitors will be presented. **Conclusions:** In non-NSCLC patients *ALK* fusions are rare and found in both epithelial and mesenchymal malignancies. Initial evidence strongly suggests that anti-ALK therapies can be effective in *ALK* fusion driven non-NSCLC .

11596 Poster Session (Board #296), Sat, 1:15 PM-4:45 PM

Rates of PD-L1 expression testing in U.S. community-based oncology practices (USCPs) for patients with metastatic non-small cell lung cancer (mNSCLC) receiving nivolumab (N) or pembrolizumab (P). *First Author: Sean Khozin, U.S. Food and Drug Administration, Silver Spring, MD*

Background: FDA approved N for previously treated squamous mNSCLC in 3/2015 and non-squamous mNSCLC in 10/2015 regardless of PD-L1 expression. P was approved for previously treated mNSCLC in 10/2015 for patients whose tumors express PD-L1 as determined by an FDA-approved companion diagnostic (CoDx). Post-FDA approval treatment patterns of N and P, including PD-L1 testing patterns, remain unclear. **Methods:** We conducted a retrospective analysis using de-identified patient-level electronic health record (EHR) data aggregated from USCPs by Flatiron Health in accordance to an institutional review board approved protocol. Data was abstracted using both structured and unstructured EHR content with 10% duplicate abstraction to confirm data quality. All patients in the database with clinically-confirmed mNSCLC diagnosed from 1/1/11 to 3/31/16 and documented order or administration of N or P were included in the analyses. PD-L1 expression testing results were abstracted from unstructured data in EHR documents. **Results:** Within the first year of FDA approval, 1,362 mNSCLC patients received N or P (96.2% N; 3.3% P, 0.5% N+P). The median duration of treatment was 113 days. Overall, 11.3% of patients were tested for PD-L1 expression, 42.2% of whom tested positive. PD-L1 expression testing increased quarterly (Q) from 3.0% in Q2 2015 to 12.8% in Q1 2016. An FDA-approved CoDx was used 30.5% of the time. Among patients who received N, 90.5% were not tested for PD-L1 expression, 3.2% tested positive, and 4.7% tested negative for PD-L1. Among patients who received P, 32.7% were not tested for PD-L1 expression, 50.0% tested positive, and 1.9% tested negative. **Conclusions:** We observed low rates of PD-L1 expression testing in USCPs for patients with mNSCLC receiving N or P. Testing rates increased quarterly following FDA-approval. The majority of patients were not tested using FDA-approved CoDx. Most patients who were not tested for PD-L1 expression or tested negative received N. Clinician education will be important as data on optimal PD-L1 testing strategies guiding immunotherapy treatment decisions accumulates.

11597 Poster Session (Board #297), Sat, 1:15 PM-4:45 PM

Programmed cell death ligands expression in pheochromocytomas (PCC) and paragangliomas (PGL): Relationship with the hypoxic response and malignant behaviour. *First Author: David James Pinato, Imperial College London, London, United Kingdom*

Background: The hypoxic response underlies the pathogenesis and malignant behaviour of PCC/PGL. Regulation of PD-1 receptor-ligand signalling, a therapeutically actionable driver of the anti-tumour immune response, is a hypoxic-driven trait across malignancies. We evaluated the prognostic role of PD ligands in association with biomarkers of hypoxia and angiogenesis in patients with PCC/PGL. **Methods:** Tissue microarrays sections including consecutive cases of PCC/PGL diagnosed between 1983-2011 were stained for PD-L1 & 2, Ki-67, hypoxia inducible factor 1a (Hif-1a), Carbonic Anhydrase IX (CaIX), Vascular Endothelial Growth Factor-A (VEGF-A). Candidate biomarkers were assessed for correlation with clinical variables including overall survival. **Results:** In total, 100 patients, 10% malignant, 64% PCC, 29% familial with a median tumour size of 4.7 cm (range 1-14) were included. Median follow-up was 4.7 years. PD-L1 expression was observed in 18% of cases and was independent of adverse pathological features including capsular (CI), vascular invasion (VI), necrosis (N) and expression of biomarkers of hypoxia. We observed a trend towards association with malignancy ($p = 0.08$). PD-L2 expression was found in 16% of tumors. PD-L2 overexpression strongly correlated with CI, VI, N ($p < 0.01$) and malignant behaviour ($p = 0.009$) and was associated with stronger Hif-1a and CaIX immunolabeling ($p < 0.01$). PD-L2 but not PD-L1 expression was predictive of shorter survival (162 versus 309 months, HR 3.1 95%CI 1.1-9.2, Log-rank $p = 0.03$). Gene set enrichment analysis on the TGCA PCC/PGL RNA-seq dataset (n = 184) revealed a positive correlation between PD-L2 and a number of transcripts involved in angiogenesis and immunity including Interleukin-6 (Pearson R = 0.57) and CD-8a (R = 0.56). **Conclusions:** We report for the first time PD-1 ligands expression in PCC/PGL with a distinctive prognostic and clinicopathologic role. These findings support a potential therapeutic role for PD-1/PD-L1 targeted checkpoint inhibitors in these tumors.

11598 Poster Session (Board #298), Sat, 1:15 PM-4:45 PM

Association of MLL2 mutation positive non-small cell lung cancer with prognosis. *First Author: Fatemeh Ardeshir-Larijani, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH*

Background: Myeloid/lymphoid or mixed-lineage leukemia protein 2 (MLL2) is an epigenetic regulator expressed in many tissues. Although MLL2 mutations are associated with poor prognosis in different types of cancer, the clinical impact of this gene in lung cancer remains unclear. Here, we evaluated the clinical and genomic characteristics of MLL2 alteration in non-small cell lung cancer (NSCLC) and compared it to small cell lung cancer (SCLC) **Methods:** Between 2014 and 2016 tumor samples of 194 Stage III and IV NSCLC patients and 50 SCLC patients underwent targeted-exome sequencing. The association of MLL2 mutation with survival outcomes was measured using KaplanMeier methods (PFS, OS). Cox s proportional hazards regression model was performed for multivariate survival analyses with known clinical prognostic features. All tests were two-sided and p-values = 0.05 were considered statistically significant. **Results:** The MLL2 mutation rate was 17.5% (N=34) in NSCLC. Patients with mutant MLL2 had significantly lower overall survival (OS) (9.97 vs. 30.2 months, $p < 0.0001$) and progression-free survival (PFS) (8.46 vs. 24.1 month, $p = 0.0007$) compared to those with wild type MLL2. The median overall survival in the entire NSCLC cohort was 23.3 months (95% CI: 16.5 34.4). Interestingly, MLL2 mutation was significantly more common in females ($p = 0.017$). There was no significant association of MLL2 mutation status with age, smoking history, race or histology . Using a multivariate Cox regression model with adjustments based on tumor stage, smoking histology and chemotherapy, MLL2 mutation remained the most remarkable prognostic factor in NSCLC: OS Hazard Ratio 2.79, $p = 0.0001$ and PFS Hazard Ratio 1.99, $p < 0.001$. By comparison, the MLL2 mutation rate in SCLC was 24% (N=12) and showed no gender bias (p=0.874). There was no significant decrease in survival associated with MLL2 mutation in SCLC (OS $p = 0.966$, PFS $p = 0.641$). **Conclusions:** This study demonstrates that MLL2 mutation specifically impacts survival outcome only in NSCLC but not SCLC.

11599 Poster Session (Board #299), Sat, 1:15 PM-4:45 PM

Survival profile in breast cancer molecular subtypes without systemic and locoregional treatment. *First Author: Sherry X. Yang, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: It is unclear whether survival varies among breast cancer molecular subtypes without systemic and locoregional therapy. This study aims to evaluate the survival profile by molecular subtypes after surgery. **Methods:** In total, we evaluated 301 women with invasive breast cancer with stage I, II or III disease. Patients were classified into four major breast cancer subtypes by immunohistochemistry/FISH classifiers: luminal-A (ER+ and/or PR+/HER2-), luminal-B (ER+ and/or PR+/HER2+), HER2-enriched (HER2+/ER-/PR-) or basal-like (ER-/PR-/HER2-; triple-negative). Overall survival (OS) was analyzed by Kaplan-Meier analysis, and log-rank test for differences. Association between clinical outcome and subtype adjusting for breast cancer prognostic factors was assessed by multivariable Cox proportional hazards model. **Results:** All patients did not receive systemic chemotherapy and hormone therapy as well as radiation therapy. Luminal A was the most common subtype (N = 224), followed by basal-like (N = 43), luminal B (N = 21) and HER2-enriched (N = 13). Median follow-up for OS was 197 months (range: 1 – 273 months). Age at diagnosis was statistically different among the subtypes, with basal-like and luminal B having high proportions less than 50 years ($P = 0.047$). Patients with basal-like and HER2-enriched had more high grade tumors ($P < 0.001$). Notably, there was no difference in OS among the four subtypes (log-rank $P = 0.983$). In multivariable analysis, the adjusted hazard ratio (HR) was 1.1 for luminal A vs. luminal B ($P = 0.781$), 0.62 in luminal A vs. HER2-enriched ($P = 0.273$), or 0.67 in luminal A vs. basal-like ($P = 0.158$). In contrast, the adjusted HR were 2.2 in age less than 50 years ($P = 0.0017$), and 1.1 for number of positive nodes ($P = 0.00074$). **Conclusions:** OS, through long-term clinical follow-up, is not significantly different among molecular subtypes if not controlling for other prognostic factors in patients who only received surgery. Age and number of positive nodes are independent prognostic factors in patients with no systemic and locoregional treatments.

11600 Poster Session (Board #300), Sat, 1:15 PM-4:45 PM

***RASA1* and *NF1* co-mutated non-small cell lung carcinomas: Cancer genomic data and evaluation of sensitivity to MEK inhibition.** *First Author: Takuo Hayashi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Ras-GTPase activating proteins (RasGAPs), notably NF1 and RASA1, mediate negative control of the RAS/MAPK pathway. While *NF1* mutations are enriched in non-small cell lung carcinomas (NSCLC) lacking *KRAS* alterations, they are not completely mutually exclusive. We evaluated clinical and molecular characteristics of NSCLC with *RASA1* mutations in comparison with *NF1*-mutated cases. **Methods:** Large genomic datasets of NSCLC [MSK-IMPACT™ dataset at MSKCC (n = 2004), TCGA combined lung cancer dataset (n = 1144)] were analyzed to define concurrent mutations and clinical features of *RASA1*-mutated NSCLCs. Functional studies were performed using immortalized human bronchial epithelial cells (HBECs) and NSCLC lines with RasGAP truncating mutations, in *RASA1* (RERFLCKJ), *NF1* (LCLC103H and H1838), or both (EPLC272H). **Results:** Overall, approximately 2% of NSCLCs had *RASA1* truncating mutations, and this alteration was statistically, but not completely, mutually exclusive with known activating *EGFR* ($p = .02$) and *KRAS* ($p = .02$) mutations. Unexpectedly, *RASA1* truncating mutations had a strong tendency to co-occur with *NF1* truncating mutations ($p < .001$), suggesting selection for loss of more than one RasGAP. Furthermore, all patients (16/16) with concurrent *RASA1/NF1* truncating mutations lacked other known lung cancer drivers, including *KRAS*. Knockdown of RASA1 in HBECs activated signaling downstream of RAS and promoted cell growth. Conversely, restoration of RASA1 expression in RERFLCKJ cells reduced MAPK and PI3K signaling. While growth of cell lines with inactivation of only one of these two RasGAPs showed moderate and variable sensitivity to inhibitors of MEK (trametinib) or PI3K (GDC0941, PI103), EPLC272H cells (with concurrent *RASA1/NF1* mutations) showed notably more profound sensitivity (IC_{50}: 0.040μM trametinib). Finally, simultaneous silencing of *RASA1* and *NF1* sensitized both HBECs and NSCLC cells to MEK inhibition. **Conclusions:** Cancer genomic and functional data nominate concurrent *RASA1/NF1* loss of function mutations as a strong mitogenic driver in NSCLC. Patients whose tumors show this distinctive genotype should be considered for trials of MEK inhibitors.

11601 Poster Session (Board #301), Sat, 1:15 PM-4:45 PM

Selecting patients with metastatic colorectal cancer for treatment with temozolomide using proteomic analysis of MGMT. *First Author: Sarit Schwartz, NantOmics, LLC, Rockville, MD*

Background: Temozolomide (TMZ) is a standard treatment for melanoma and glioblastoma and it has shown limited but encouraging activity in patients with metastatic colorectal cancer (mCRC). In multiple cancer types, the DNA repair protein O^6-methylguanine-DNA methyltransferase (MGMT) is a resistance marker for TMZ; MGMT promoter methylation is associated with loss of MGMT expression and response to TMZ. We hypothesized that mCRC patients whose tumors expressed quantities of MGMT protein below a pre-defined cutoff would have better outcomes on TMZ than patients with MGMT expression above the cutoff. To test our hypothesis, we assessed MGMT by mass spectrometry in the tumor samples of patients with refractory mCRC and MGMT promoter methylation receiving TMZ. **Methods:** Archived formalin-fixed, paraffin-embedded tissue sections were obtained from 24 patients from two phase 2 trials. A pathologist marked the tumor areas, which were microdissected and solubilized. In each tumor sample, multiple protein biomarkers including MGMT were quantified with selected reaction monitoring mass spectrometry. An MGMT cutoff of 200 amol/ug was based on the limit of quantitation from a concentration curve. The Mantel-Cox log-rank and the Fisher's exact tests were used for survival comparisons. **Results:** MGMT protein was detected in 13 of 24 (54.2%) colorectal tumor samples (range: 229.3-784.8 amol/μg). The overall response rate was 29%. Patients with MGMT protein levels below a cutoff of 200 amol/ug (n = 11) had a notably higher response rate than patients with MGMT levels above the cutoff (64% vs. 0%; $p = 0.001$ Fisher's test). Also a longer progression-free survival was observed (4.3 vs. 1.6 months, HR = 0.36, 95% CI = 0.13-1.10, $p = 0.054$). Results for overall survival were consistent but not statistically significant (8.9 vs 6.9 months, HR = 0.55, $p = 0.221$). **Conclusions:** Patients with mCRC whose tumors expressed low or undetectable levels of MGMT protein had a better outcomes following TMZ treatment than their counterparts. Quantitative proteomic analysis of MGMT could potentially be used to select CRC patients for TMZ treatment. The results of validation studies are forthcoming.

11602 Poster Session (Board #302), Sat, 1:15 PM-4:45 PM

Biomarker-driven indication selection in JTX-2011 ICONIC clinical trial. *First Author: Heather Anne Hirsch, Jounce Therapeutics, Cambridge, MA*

Background: ICOS (Inducible T cell CO-Stimulator) is a co-stimulatory molecule expressed primarily on T lymphocytes. Clinical and preclinical data suggest that ICOS mediates anti-CTLA-4 driven anti-tumor responses. JTX-2011 is an ICOS agonist antibody in clinical development in advanced solid tumors (ICONIC trial). JTX-2011 is designed to generate an anti-tumor immune response via stimulation of T effector cells and preferential reduction of intra-tumoral T regulatory cells. Single agent preclinical efficacy correlates with the percentage of ICOS-expressing T cells within the tumor. We report indication selection and patient enrichment strategy for ICONIC using *in silico* and IHC analysis and assessment of potential predictive biomarkers for JTX-2011 using *ex vivo* tumor histoculture. **Methods:** Integrated analysis was performed from the TCGA for ICOS expression in histologic and molecularly defined tumors and immune cell signatures. ICOS expression was analyzed by IHC in a subset of indications based on *in silico* analysis. ICOS expression on intra-tumoral Tregs and PD-L1 were analyzed in a cohort of 126 head and neck squamous cell carcinomas (HNSCC). *Ex vivo* histoculture assays of human HNSCC was treated with JTX-2011 and assessed for IFNg gene signature induction. **Results:** ICOS mRNA expression was analyzed in ~10,000 solid tumors samples across ~30 indications. ICOS expression in key indications was confirmed using IHC. Based on frequency of high ICOS expression, non-small cell lung cancer, HNSCC, triple negative breast carcinoma, gastric cancer, and melanoma were selected as indications for ICONIC. Results were confirmed in clinical samples using multiplex immunofluorescence and ICOS IHC. A wide range of ICOS expression was observed suggesting that identification of an ICOS "high" group may enrich for patients likely to benefit from ICOS agonist therapy. In *ex vivo* histoculture assays of human HNSCC tumors treated with JTX-2011, ICOS IHC and ICOS RNA gene signatures correlated to response endpoints. Comparison of ICOS and PDL1 expression identified subsets of tumors in multiple indications with high ICOS but low PDL1 expression. **Conclusions:** These data support prioritization of specific tumor types the ICONIC trial.

11603 Poster Session (Board #303), Sat, 1:15 PM-4:45 PM

Preliminary correlative analysis of PD-L1 expression from the SUNRISE study. *First Author: Nikoletta Lea Kallinteris, Peregrine Pharmaceuticals, Inc., Tustin, CA*

Background: SUNRISE, a global, double-bind, Phase III trial of docetaxel (D) plus bavituximab (B) or D plus placebo (P) in previously treated non-squamous non-small cell lung cancer, demonstrated similar overall survival (OS) in both treatment arms. Biomarkers including pre-treatment PD-L1 expression are being retrospectively assessed in on-going exploratory analyses. **Methods:** Archival tissue obtained at the time of diagnosis was requested but not required in the SUNRISE trial. FFPE slides were stained with a panel of lymphoid cell markers: CD3+, CD8+, FoxP3+, PD-L1+, CD163+, CK+ and DAPI using a 6-plex quantitative immunohistochemistry (IHC) assay (OPAL, PerkinElmer, Hopkinton, MA, USA). Baseline PD-L1 expression was retrospectively scored on tumor cells (TC) as a percentage of PD-L1 expressing tumor cells: TC3$\geq$50%, TC2$\geq$5% and $<$ 50%, TC1$\geq$1% and $<$ 5%, and TC0 $<$ 1%. Cox regression models for PD-L1 IHC subgroup populations were used for correlation with OS. **Results:** In the subset of patients with available diagnostic biopsies (110 out of 597 randomized patients), the prevalence of PD-L1 expression was 5% for TC3, 18% for TC2/3, 35% for TC1/2/3, 65% for TC0. Median OS (mOS) of the D+B arm is 11.5 months (TC0, $<$ 1%) and 6.0 months (TC1/2/3, $\geq$1%) with HR 0.38 (95% CI, 0.19-0.76); p-value = 0.004. mOS of the D+P arm is 11.1 months (TC0, $<$ 1%) and 10.4 months (TC1/2/3, $\geq$1%) with HR 0.93 (95% CI, 0.47-1.87); p value = 0.844. **Conclusions:** Baseline PD-L1 expression in a subset of SUNRISE patients demonstrated that PD-L1 expression (TC0) was associated with a significantly prolonged OS compared to positive PD-L1 expression (TC1/2/3) in patients receiving D+B. No difference in OS was observed in the D+P group by PD-L1 expression. These observations are consistent with the hypothesis that bavituximab may demonstrate more effect in PD-L1 negative or low expressing "immune cold" tumors. Clinical trial information: NCT01999673.

11604 Poster Session (Board #304), Sat, 1:15 PM-4:45 PM

A novel prognostic signature based on centrosome amplification-based genes to predict clinical outcomes in breast tumors. *First Author: Angela Ogden, Georgia State University, Atlanta, GA*

Background: A majority of breast tumors exhibit centrosome amplification (CA), which imparts aggressive phenotypes like chromosomal instability and invasive behavior. Nevertheless, it is unclear whether CA is associated with poor clinical outcomes after adjusting for potentially confounding factors, like stage and age at diagnosis. **Methods:** We developed a twenty-gene signature, "CA20," composed of genes related to centrosome structure and/or whose dysregulation induces CA and tested its prognostic value compared with that of CIN25, a chromosomal instability (CIN) signature, in combined multivariable Cox models using the METABRIC and TCGA microarray breast datasets. The n = 1,969 primary breast cancers of the METABRIC dataset were split randomly and approximately equally into training and validation sets, unlike the n = 524 primary invasive breast cancers of the TCGA dataset, which could not be split to preserve power $\approx$ 0.80, so bootstrapping was instead used. CA20 and CIN25 were dichotomized by average scores and optimal cutpoints based on the log-rank test. **Results:** In both discovery and validation METRABRIC sets, CA20 was a significant independent predictor of worse breast cancer-specific survival (HR = 2.9, $p < 0.001$ and 2.4, $p < 0.001$, respectively, using average scores as cutpoints; similar results obtained using optimal cutpoints) in multivariable Cox models, unlike CIN25. CA20 score was highly correlated with CIN25 score ($\rho = 0.93$, $p < 10^{-6}$). In the TCGA dataset, high CA20 score was associated with 3.8- and 3.7-fold worse overall survival (bootstrap-p = 0.001 and 0.002, respectively, for average and optimal cutpoints) after adjusting for tumor stage and age at diagnosis, unlike CIN25. Also in the TCGA dataset, CA20 correlated very strongly with CIN25 ($\rho = 0.95$, $p < 10^{-6}$). Finally, using the TCGA dataset, we identified processes and pathways enriched in the CA20-high group ($q < 0.05$) that may be potential therapeutic targets, such as DNA repair processes, the DNA integrity checkpoint, and regulation of microtubule dynamics. **Conclusions:** CA20 is a novel signature with robust prognostic value in breast cancer and identifies patients who might respond to centrosome declustering drugs.

11605 Poster Session (Board #305), Sat, 1:15 PM-4:45 PM

Comprehensive analysis of potential immunotherapy genomic biomarkers by profiling paired tumor/normal exome of 1,000 Chinese cancer patients. *First Author: Qiang Xu, GenomiCare, Shanghai, China*

Background: With the broadening landscape of immunotherapy use, it is important to identify patients who are likely to benefit from the therapy. We reported the comprehensive analyses of potential predictive biomarkers for PD1/PD-L1 inhibitors based on Chinese patients' exome profiling data. **Methods:** Over 1,000 cancer patients from 70 hospitals across 20 provinces in China were recruited and the whole exome of tumor/normal samples of each patient were sequenced. Four potential genomic biomarkers: tumor mutation burden (TMB), mismatch repair deficiency (MMR), microsatellite instability (MSI), and PD-L1 (CD274) amplification (PD-L1 AMP) were analyzed in this Chinese cohort and compared with the mainly Caucasian cohort in TCGA database. **Results:** At least one of the four preselected genomic biomarkers was identified in 40.8% of this Chinese cancer patient cohort by clinical whole exome sequencing (CWES) analysis. Similar to TCGA cohort, the top 3 high TMB tumor types are lung, esophagus and colorectal cancer. Chinese hepatocellular carcinoma (HCC) patients showed higher TMB than the TCGA cohort (Median: 106 vs. 65 non-synonymous mutations per tumor NMT), which might be due to different etiologies. Five late stage cancer patients (3 lung, 1 melanoma and 1 gallbladder) using PD1/PD-L1 blockade with high TMB showed durable clinical benefit (SD$\geq$6months/PR/CR). Comparing with TCGA data, Chinese colorectal cancer cohort (252 patients) had relative lower MSI-high or MMR related mutations (8.33% vs. 12.5%, and 3.97% vs. 10.0% respectively). PD-L1 AMP most frequently occurred in lung squamous (14.3% VS 9.8% TCGA), HER2-positive breast cancer (8.8% VS 6.8% TCGA with unknown HER2 status) and sarcoma (6.0% VS 9.4%TCGA). One Chinese renal cell carcinoma patient with PD-L1 AMP received anti-PD-1 treatment and on-going PFS is 7 months by far. **Conclusions:** Our CWES analysis and limited clinical follow-up observations suggested that about 40% Chinese cancer patients had at least one of the 4 potential immunotherapy predictive biomarker mutations. Long-term follow-up is needed to verify the validity of those markers.

11606 Poster Session (Board #306), Sat, 1:15 PM-4:45 PM

Case-control study of PD-1, PD-L1 and B7-H3 expression in lung cancer (CA) patients (pts) with and without human immunodeficiency virus (HIV) infection. *First Author: Katherine Ann Scilla, University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD*

Background: PD-1, PD-L1 and B7-H3 are co-signaling molecules involved in CA immunology. There are limited data on expression of these molecules in HIV-infected (HIV+) lung CA pts and these pts are routinely excluded from immunotherapy trials. **Methods:** We reviewed archived lung CA tissue samples from HIV+ cases (n = 13) and HIV-uninfected controls (n = 13) from 2001-2015. Cases and controls were matched by histology and stage. Baseline demographics were collected for all pts. CD4 count and HIV RNA viral load (VL) were collected for HIV+ pts. Immunostained tumor sections were analyzed for percent of tumor cells expressing PD-L1 and B7-H3 (Abcam), and percent of tumor-infiltrating lymphocytes (TIL) expressing PD-1 and PD-L1 (Abcam). Positive expression was defined as $>$ 5%. Statistical analysis was performed using the non-parametric Mann-Whitney test and the chi-square test. Proportions are specified as percentage with 95% confidence limits in parentheses. **Results:** Lung CA HIV+ case pts were predominantly male (62%), black race (100%), adenocarcinoma histology (77%), stage 4 disease (62%), and had a median age of 48 years. Of case pts with available data, mean CD4 count was 307 (range 37-617) and mean HIV VL was 29,400 (range 0-100,000). PD-L1 expression on tumor cells was positive in 23% (8%, 50%) of cases and 46% (23%, 71%) of controls. B7-H3 expression on tumor cells was positive in 92% (67%, 99%) of cases and 69% (42%, 87%) of controls. PD-1 expression on TIL was positive in 69% (42%, 87%) of cases and 54% (29%, 77%) of controls. PD-L1 expression on TIL was positive in 31% (13%, 58%) of cases and 69% (42%, 87%) of controls (p = 0.05). B7-H3 percent expression on tumor cells was significantly higher in cases vs controls (median 90% vs 20%, p = 0.005), but there were no significant differences in percent expression of PD-L1 on tumor cells, PD-1 on TIL or PD-L1 on TIL. **Conclusions:** HIV+ lung CA pts had significantly higher B7-H3 tumor percent expression compared to HIV-uninfected controls, with similar rates of PD-L1 tumor percent expression, PD-1 TIL percent expression and PD-L1 TIL percent expression. These results support inclusion of HIV+ lung CA pts in future immunotherapy trials.

11607 Poster Session (Board #307), Sat, 1:15 PM-4:45 PM

A technical feasibility report on correlative studies from the investigator-initiated phase II study of pembrolizumab (Pembro) immunological response evaluation (INSPIRE). *First Author: Derek L. Clouthier, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Validated biomarkers of response to immune checkpoint inhibitors are needed. **Methods:** INSPIRE (NCT02644369) is a biomarker-driven study to comprehensively evaluate changes in genomic and immune landscapes in tumors and blood of patients (pts) treated with pembro at 200 mg IV Q3W. It consists of 5 histological cohorts of 20 evaluable pts each: head and neck squamous cell cancer (SCCHN), triple negative breast cancer (TNBC), high grade serous ovarian cancer (HGSOC), melanoma (MM) and mixed solid tumors (MST). All pts undergo pre- and on-treatment (week 6-9) fresh tumor biopsies (bx), and at progression for responders. The first core bx is for immunohistochemistry and subsequent cores are pooled to create single cell suspension for 5 prioritized biomarker assay groups: (1) whole exome/RNA-/TCR-sequencing; (2) T/B/NK, APCs, and/or Treg phenotyping; (3) patient-derived xenografts; (4) RNA-seq on viably sorted immune populations; (5) TIL expansion and characterization. Serial blood samples for immunophenotyping, chemokines/cytokines and ctDNA are collected. **Results:** 53 pts were enrolled from March 21, 2016-January 16, 2017 (5 SCCHN, 8 TNBC, 17 HGSOC, 7 MM, 16 MST). 84 tumor bx (53 pre-, 30 on-treatment, 1 progression) and 244 blood-based biomarker samples have been collected. The most common sites of tumor bx were: lymph nodes (27%), liver (22%) and skin (14%) (see table). For the 5 cohorts, the % of tumor bx with sufficient cellularity for biomarker assay groups 1 and 2 are: SCCHN (33%), TNBC (9%), HGSOC (52%), MM (55%), MST (55%). **Conclusions:** This report provides robust technical feasibility data to plan immune and molecular characterization of tumor and blood-based biomarkers in pts receiving ICI. Clinical trial information: NCT02644369.

Technical feasibility parameters.

Tumour bx site	Average (range) # of cores	Average (range) # of cells per core	% of samples adequate for biomarker evaluations groups 1, 2, 3, 4, 5
Lymph node	3.2 (1-5)	3.0E5 (0.024–1.4E6)	74, 61, 39, 13, 9
Liver	3.5 (2-6)	1.9E5 (0.19–7.7E5)	74, 63, 10, 10, 5
Skin	3.2 (3-4) [punch/excisions]	5.1E5 (0.012–2.2E6) NA	100, 40, NA, 0, 20 86, 71, NA, 29, 14
Other	3.7 (1-8)	1.9E5 (0.002–1.6E6)	55, 55, 16, 6, 3

11608 Poster Session (Board #308), Sat, 1:15 PM-4:45 PM

Genetic variations in semaphorin/neuropilin signaling to predict clinical outcome in patients (pts) with metastatic colorectal cancer (mCRC) receiving bevacizumab-based chemotherapy. *First Author: Yuji Miyamoto, Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Neuropilin (*NRP*) is known to be an important *VEGF* co-receptor that acts as a key mediator of angiogenesis. Its ligands, semaphorins (*SEMA*), compete with *VEGF* for NRP binding and can themselves have angiogenic activity. Plexins are also receptors of SEMAs, and have the GTPase activating proteins (GAPs) domain for *RAS*. NRPs are shown to signal through RAS pathways. We aimed to evaluate whether single nucleotide polymorphisms (SNPs) of genes involved in the *SEMA/NRP*pathways predict clinical outcome in bevacizumab-treated mCRC pts. **Methods:** Associations between nine SNPs in 7 genes (*SEMA3A*, *SEMA3D*, *SEMA3F*, *NRP1*, *NRP2*, *PLXNA1* and *PLXND1*) and clinical outcomes were evaluated in mCRC patients receiving first-line FOLFIRI-bevacizumab in a phase III trial: TRIBE (*N*= 228). Associations between genotype and RAS mutation status with clinical outcomes was also examined. Main characteristics were the following: male/female = 138/90; median age = 60; *RAS*-wildtype/mutant = 55/116; median PFS = 9.7 months; median OS = 26.1 months, median follow-up time = 49.3 months. **Results:** *NRP1* rs2228638 Any A (*N*= 40) showed a significantly longer PFS compared to G/G variant (*N*= 188) in the univariate (11.6 months (M) vs. 9.5 M, HR = 0.64, 95%CI = 0.43-0.95, p = 0.022) and the multivariate analysis (HR = 0.59, 95%CI = 0.38-0.90, p = 0.016). *SEMA3F* rs12632110 A/A (*N*= 20) showed a significantly shorter PFS compared to any G variant (N = 205) in the multivariate analysis (HR = 1.89, 95%CI = 1.02-3.49, p = 0.043). Among *RAS*-mutant pts, *SEMA3F* rs12632110, *SEMA3F* rs1046956, *SEMA3D* rs7800072, *NRP1* rs228638, *PLXNA1* rs4679323 and *PLXND1* rs2255703 polymorphisms were significantly associated with PFS in the univariate and multivariate analysis. *PLXNA1* rs4679323 was also significantly associated with OS in the univariate and multivariate analysis. There was no association between these polymorphisms and outcome in patients with *RAS*wildtype tumors. **Conclusions:** Genetic variants within *SEMA/NRP* pathways may be prognostic markers in *RAS* mutant mCRC patients treated with bevacizumab-based chemotherapy.

11609 Poster Session (Board #309), Sat, 1:15 PM-4:45 PM

Simultaneous molecular alterations in solid tumors with *IDH1* or *IDH2* mutations. *First Author: Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Somatic mutations in *IDH1* or *IDH2* genes are prevalent in diverse solid tumors and implicated in tumorigenesis. Therapeutic responses to IDH inhibitors are infrequent plausibly due to presence of simultaneous alterations activating compensatory molecular pathways. **Methods:** We retrospectively reviewed results from clinical genomic profiling with targeted next-generation sequencing in two independent data sets of archival formalin-fixed paraffin-embedded (FFPE) tumor samples (Ion Torrent $<$ 50 genes, 300; FoundationOne $<$ 343 genes, 30; Oncomine 128 genes, 4) and plasma liquid biopsies (Guardant360 $<$ 73 genes panel, 337 samples) from patients with solid tumors of all stages. **Results:** In 334 FFPE samples the most represented cancers were gliomas (50%), melanomas (14%), cholangiocarcinomas (11%), and non-small cell lung cancer (NSCLC, 6%). In 296 *IDH1*-mutated FFPE samples the most frequent simultaneous alterations were in *TP53* (45%), *BRAF* (11%), *KRAS* (9%), and *PIK3CA* (26, 9%). In the most represented *IDH1*-mutated tumor types commonly altered genes were *TP53* (66%) in gliomas, *BRAF* (53% [V600K/R 30%, V600E 19%]) in melanomas, *PIK3CA* (13%), *CDKN2A* (13%) in cholangiocarcinomas and *KRAS* (65%) in NSCLC. In 38 *IDH2*-mutated FFPE samples the most frequent simultaneous alterations were in *TP53* (32%), and *KRAS* (16%). In 337 plasma samples the most represented cancers were NSCLC (39%), cholangiocarcinoma (13%), and breast cancer (8%). In 172 *IDH1*-mutated plasma samples the most frequent simultaneous alterations were in *TP53* (40%), *KRAS* (23%), *EGFR* (16%) and *BRAF* (16%). In the most represented *IDH1*-mutated tumors commonly altered genes were *TP53* (48%), *KRAS* (37%) in NSCLC and *TP53* (37%), *KRAS* (24%), *BRAF* (18%) in cholangiocarcinoma. In 161 *IDH2*-mutated plasma samples the most frequent simultaneous alterations were in *TP53* (43%), *EGFR* (20%), and *KRAS* (19%). In the most represented *IDH2*-mutated tumors commonly altered genes were *TP53* (43%), *EGFR* (32%), *KRAS* (18%) in NSCLC and *TP53* (18%), *ESR1* (18%), *KRAS* (18%) in breast cancer. There were 4 tumors with *IDH1* and *IDH2*mutations. **Conclusions:** *IDH1* and *IDH2* mutations often coexist with simultaneous oncogenic alterations including these in potentially druggable molecular targets.

11610 Poster Session (Board #310), Sat, 1:15 PM-4:45 PM

Variable DNA mismatch repair-associated gene profiles in colorectal versus uterine cancers. *First Author: Tabari Baker, Caris Life Sciences, Phoenix, AZ*

Background: DNA mismatch repair (MMR) plays an important role in maintaining DNA synthesis fidelity in the genome. Mutation in MMR genes occurs in colorectal and uterine cancers and leads to increased mutation burden that is associated with response to immune checkpoint inhibitors. It is unknown if there is an MMR gene-specific mutation signature in MMR-deficient tumors, or whether mutations in MMR genes drive specific mutation patterns. **Methods:** The study cohort consisted of 1060 uterine cancer (UtCa), and 797 colorectal cancer (CRC) cases consecutively submitted to Caris Life Science for molecular profiling using multiple technologies, including next generation sequencing (NGS), immunohistochemistry (IHC), and in situ hybridization (ISH). Mutation, IHC-positive, and ISH-positive frequencies were compared using Fisher's exact test (p-value < 0.05 considered significant). **Results:** In total, 1,857 tumors were examined. Of the 797 CRC cases, 115 (14.4%) had at least one mutation in MLH1, MSH2, or MSH6. Nineteen (19; 2.3%) of the CRC cases had mutations in multiple MMR related genes. Of the 1060 UtCa cases, 52 (4.9%) had at least one mutation in MLH1, MSH2, or MSH6. Twenty-two (22; 2.1%) of the UtCa cases had mutations in multiple MMR related genes. Colorectal cancers that were MLH1, MSH2, and MSH6 mutated enriched for rare, lineage specific co-mutations, including KRAS A146T (4/32 MLH1-mutated cases; 12.5%). Uterine cancers that were MLH1, MSH2, and MSH6 mutated also enriched for several co-mutations, including ARID1A (8/9 MLH1-mutated cases; 88.9%), a SWI-SNF chromatin remodeling complex family member. Further analyses revealed differences in PD-L1 positivity between MMR mutated CRCs versus UtCa (8/131; 6.1% versus 8/51; 15.7%). Tumor mutational load (defined as the total number of non-synonymous mutations per Mb sequenced) was 35 mutations per Mb in CRC and 51 mutations per Mb in UtCa. **Conclusions:** There are differences in mutation signatures between uterine and colorectal cancer, and possible additional molecular targets for combination with immune checkpoint therapies. Further analysis of MMR gene-specific differences in molecular profiles is ongoing and will be discussed.

11611 Poster Session (Board #311), Sat, 1:15 PM-4:45 PM

Deficient necroptosis pathway as a negative prognostic factor in acute myeloid leukemia. *First Author: Silvia Lo Monaco, Bologna University School of Medicine, Bologna, Italy*

Background: Necroptosis is a type of necrotic cell death involving several genes transcription and activation of molecular mechanisms as death receptors, interferon, toll-like receptors, intracellular RNA and DNA sensors. The process is leading by the family of receptor-interacting protein kinase (*RIPK3*, *RIPK2*, *RIPK1*) and the *MLKL* substrate. Losses of *RIPK3* or *MLKL*, as well as deficiency in apoptosis, could allow tumor cells to escape the immunomediated cells death (ICD). **Methods:** We performed SNP Arrays (Cytoscan HD and SNP 6.0, Affymetrix) on a cohort of 300 non-M3 AML patients at diagnosis and we analyzed the Overall Survival (OS) of our patients with deficiency on necroptosis pathways. Survival was analyzed with Kaplan-Mayer method and Log-Rank test. We further analyze the relevance of different prognostic factors by the use of COX-Hazard Ratio statistical analysis. **Results:** We find that 18 patients presented a loss of *RIPK1* or *MLKL* (nobody presented losses in *RIPK3/RIPK2*) and 13/18 patients were older than 65 years old. The Overall Survival (OS) of patients with alterations in these genes is significantly lower than control group, with a median OS of 3 vs 6 month respectively ($p<.0.001$). With Fisher Exact Test we further demonstrate that copy number loss of *RIPK1* or *MLKL* are associate to loss of *TP53* or *FANCA*genes, complex karyotype and advanced age. COXHR model with *RIPK1* or *MLKL* loss, *BRACA1* loss, *TP53* mutation, *FANCA* loss, secondary disease and diagnosis karyotype considered as categorical variable shows that necroptosis deficiency (HR 1.98, CI 95% 1.04-3.78), *TP53*mutation , and secondary AML are independent negative prognostic factors in an optimal model. **Conclusions:** Our study shows that losses in necroptosis pathways are an uncommon alteration in AML, prevalent in old population. Moreover, we hypothesize that the loss of genes involved in necroptosis could be a real mechanism of tumor immune-escape and could be a rational to select patients that have high probability to be resistant at chemotherapy promoting ICD mechanism. Acknowledgment: ELN,AIL,AIRC, progetto Regione-Università 2010-12, FP7 NGS-PTL project,HARMONY.

11612 Poster Session (Board #312), Sat, 1:15 PM-4:45 PM

HER3-EGFR score to predict clinical outcomes in triple-negative breast cancer. *First Author: Angela Ogden, Georgia State University, Atlanta, GA*

Background: Limited preclinical evidence suggests that the ErbB family member HER3 may have prognostic value in TNBC. However, HER3 is a pseudokinase that cannot homodimerize, so in order to signal it must bind to other ErbB family members such as HER2 or EGFR. EGFR is frequently overexpressed in TNBC; consequently, it may be necessary to consider HER3 levels in the context of EGFR levels in TNBC to derive clinically meaningful insights. **Methods:** Towards this end, we tested the prognostic value of a combined immunohistochemical HER3-EGFR score (the sum of the individual H-scores, with the median used as a cutpoint) in a multi-institutional study of n = 510 TNBC patients using Cox proportional hazards regression. We also compared the HER3-EGFR-high and low groups in terms of 105 immunohistochemical biomarkers using Mann-Whitney U tests as well as Ingenuity canonical pathways using gene expression data from RNA-seq. **Results:** Among chemotherapy-treated TNBC patients, high HER3-EGFR score conferred a 2.30-fold increased risk of dying from breast cancer and a 1.78-fold increased risk of distant metastasis ($p = 0.006$ and $p = 0.041$, respectively) after adjusting for age and stage. Individual HER3 and EGFR H-scores were not associated with outcomes in simple or multivariable models. We also found that tumors from chemotherapy-treated TNBC patients with high HER3-EGFR scores exhibited higher immunohistochemical expression of luminal cytokeratins, DNA damage response proteins, and P-cadherin compared with tumors from chemotherapy-treated TNBC patients with low scores ($q < 0.25$). The top canonical pathway whose components were overexpressed in HER3-EGFR-high TNBCs was Hepatic Fibrosis ($p = 0.008$), which is linked to distant metastasis, and the top upstream regulator was HNF4A ($p = 0.012$), a transcription factor for *ERBB3* with isoforms that promote liver and gut tumorigenesis. **Conclusions:** Collectively, our study reveals that HER3-EGFR score may identify chemotherapy-treated TNBC patients at increased risk for distant metastases and death whose tumors may be characterized by fibrotic processes. Our immunohistochemical test thus identifies high-risk TNBCs who may benefit from agents that inhibit HER3-EGFR signaling.

11613 Poster Session (Board #313), Sat, 1:15 PM-4:45 PM

Association of immune-related genes to neutrophil-lymphocyte ratio (NLR) with survival of cetuximab treatment for metastatic colorectal cancer (mCRC): JACCRO CC-05/06AR. *First Author: Yu Sunakawa, Division of Medical Oncology, Showa University Northern Yokohama Hospital, Yokohama, Japan*

Background: The antitumor activity of cetuximab (cet) may be affected by extracellular immune mechanisms. We have reported that immune-related genes are associated with survival in mCRC patients (pts) treated with cet (ASCO 2016 abstract#11591). NLR reflects cancer-related inflammation and is a validated prognostic maker in many types of cancers; however, it is not currently used for treatment decision-making. The association between NLR and clinical outcome of cet treatment for mCRC is unknown, and which genes are affecting the NLR remain to be identified. **Methods:** We enrolled 77 pts (57% males and 15% right-colon cancer) with *KRAS* exon 2 wild-type from 2 phase II trials (JACCRO CC-05 or CC-06) of 1st-line therapy with FOLFOX or SOX plus cet. All patients' tissues were measured for expression levels of 354 immune-related genes by *HTG EdgeSeq Oncology Biomarker Panel* using next generation sequencing for quantitative analysis of targeted RNAs. The association between the NLR and clinical outcome was evaluated using Spearman's rank correlation coefficient. In addition, the two-sample t-test was performed to investigate which genes had significantly different expression level between NLR-low and high groups in top 100 genes associated with survival among all measured genes. **Results:** Seventy-one of 77 pts were available for NLR data. The NLR was associated with progression-free survival (PFS) and overall survival (OS) ($r = 0.24$; $p = 0.04$, $r = 0.29$; $p = 0.01$, respectively). When stratified by median value of NLR, the Kaplan-Meier curve of NLR-low ($n = 36$) vs. high ($n = 35$) had a significant difference in both PFS (median 11.8 vs. 9.1 m, $p = 0.036$) and OS (median 42.8 vs. 26.7 m, $p = 0.029$). The two-sample t-test revealed that *LYZ*, *TYMP*, and *CD68* genes expressed significantly differently between NLR-low and high groups (t-test p-value < 0.005, FDR p-value < 0.150). **Conclusions:** NLR is significantly associated with survival of 1st-line cet treatment for mCRC. Genes encoding for activities on tissue macrophages and endothelial cells may affect the level of NLR associated with outcome of cet combination chemotherapy. Clinical trial information: UMIN000010635.

11614 Poster Session (Board #314), Sat, 1:15 PM-4:45 PM

Effect of Wnt5a on aggressiveness of ER-positive breast cancer and cancer cell migration through JNK-ALCAM pathway. *First Author: Yoshie Kobayashi, Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan*

Background: Wnt5a is a representative ligand that activates β-catenin-independent pathways and involved in cell motility and cell polarity, and the like, being mediated by JNK. We elucidated the implication of Wnt5a expression in breast cancer. **Methods:** One hundred seventy eight breast cancer patients (mean age ± SD: 60.0 ± 13.2 years) with clinical Stage I-III between January 2011 and February 2014, were prospectively evaluated. We examined relationships between Wnt5a expression and clinicopathological factors by immunohistochemical analyses. 5-year relapse-free survival rates and sites of recurrence were analyzed. In addition, molecules induced by Wnt5a in cultured cells were identified by DNA microarray analysis. **Results:** Wnt5a expression was significantly more frequent when estrogen receptor (ER) was present, 68/153 (44%) than when ER was absent, 1/25 (4%) (P <0.001) (Table). In ER-positive breast cancer, a significant interaction between expression of Wnt5a with lymph node metastasis (P<0.001), high nuclear grade (P=0.004), and lymphatic invasion (P=0.001). 5-year relapse-free survival rates were 81.1% and 100% in Wnt5a-positive and Wnt5a-negative breast cancers, respectively (P = 0.024). All recurrent breast cancer patients in this study had bone metastasis. We established MCF7 stably expressing Wnt5a (Wnt5a/MCF7 cells) and microarray analyses identified several genes induced by Wnt5a (>3.0 fold), involving activated leukocyte cell adhesion molecule (ALCAM). ALCAM is known to be related with apoptosis, invasion and prognosis of breast cancer. We focused on ALCAM and investigated its protein expression by Western blotting, and found remarkable increase of ALCAM in Wnt5a/MCF7 cells. **Conclusions:** Wnt5a expresses in ER-positive breast cancer and is associated with high-grade malignancy and a poor prognosis through JNK-ALCAM pathway. Wnt5a could be a novel prognostic factor of ER-positive breast cancer.

Wnt5a expression in intrinsic subtypes.

ER status	Total	HER2 Positive	Status Negative	*P* value
Positive	68/153 (44%)	5/11 (45%)	63/142 (44%)	
Negative	1/25 (4%)	1/8 (13%)	0/17 (0%)	<0.001

11615 Poster Session (Board #315), Sat, 1:15 PM-4:45 PM

PD-L1 assessment in FNA (EBUS) dervied samples. *First Author: Andrew Lerner, Johns Hopkins School of Medicine, Department of Medicine Pulmonary Division, Baltimore, MD*

Background: Pembrolizumab therapy for non-small cell lung cancer requires PD-L1 immunohistochemistry (IHC). FDA approval was based on staining of resections or core biopsies. Little is known about PD-L1 expression in fine needle aspiration (FNA) specimens including EBUS of mediastinal lymph nodes. **Methods:** IHC was performed using the PD-L1 IHC 22C3 pharmDx test on formalin fixed paraffin embedded FNA cell blocks of 8 squamous cell carcinomas and 15 adenocarcinomas (ACA) (age: 42-84, mean: 63, median: 63; 11 female and 12 male). Mutation data (50 gene NGS panel, and ALK, ROS1, RET and MET FISH) was available for 14 ACA. Membranous PD-L1 staining of any intensity and extent was recorded in at least 100 tumor cells (tumor proportion score). The tumors were grouped as: no staining (<1%), low expression (1-49%) and high expression (50% or more). **Results:** Six (26%) tumors showed no staining, 6 (26%) low expression and 11 (48%) high expression (table 1). High PD-L1 expression was seen in 1 ALK, 1 braf, 1 EGFR, 1 Her2 exon20, 2 kras mutated tumors and 2 tumors with no or unknown mutation status, low PD-L1 expression in 1 braf and 1 EGFR mutated case and 1 tumor without mutation. No expression was seen in 1 ROS1, 1 kras mutated tumor and 1 tumor without mutation. One EBUS biopsy also had PD-L1 assessed on a transbronchial biopsy of the primary tumor showing similar staining (30% versus 20%). **Conclusions:** PD-L1 immunohistochemistry appears to be feasible using cell blocks of fine needle aspirates containing adeqaute number of viable tumor cells. The majority of ACA were also adequate for NGS mutation and FISH analysis. High PD-L1 expression was seen in approximately half the tumors, which is greater than has been observed in resections/core biopsies, this finding merits further study. High expression of PD-L1 was seen in both squamous cell carcinoma and adenocarcinoma, and tumors with and without common driver mutations.

PD-L1 Expression according to histologic type.

Histologic type	No expression	Low expression	High expression
Adenocarcinoma (n15)	4 (27%)	3 (20%)	8 (53%)
Squamous cell carcinoma (n8)	2 (25%)	3 (37.5%)	3 (37.5%)
Total (n23)	6 (26%)	6 (26%)	11 (48%)

11616 Poster Session (Board #316), Sat, 1:15 PM-4:45 PM

Development of a pan-cancer 15 gene expression signature to detect a subgroup driven by EMT/MAPK signalling. *First Author: Nuala McCabe, Almac Diagnostics, Craigavon, United Kingdom*

Background: Epithelial–mesenchymal transition (EMT) is the conversion of epithelial cells to mesenchymal cells and involves loss of cell–cell adhesion and cell polarity and increased motility, invasiveness and metastases. The EMT process has therefore been under investigation as a new target for anticancer drug discovery. The aim of this work was to develop an EMT biomarker suitable for formalin-fixed paraffin embedded (FFPE) tissue that could be used for patient treatment selection. **Methods:** Unsupervised hierarchical clustering of ovarian cancer gene expression data (TCGA. 2011) previously identified an EMT subgroup. We confirmed this EMT subgroup in FFPE tissue using 265 high grade serous ovarian cancer (HGSOC) FFPE samples. The analysis was extended to show existence of an EMT subgroup across a range of solid tumours including colon, lung, melanoma and prostate cancer. Further to this, a common gene list was generated to include only transcripts with high variability and expression across diseases, and used as a starting list for development of a 15 transcript assay which can be used to prospectively identify the EMT subgroup from archived tissue. **Results:** The 15 gene expression assay was a poor prognostic marker in Colorectal, (Relapse free survival: HR = 1.46 [95% CI:1.07-1.98]); Lung, (Relapse free survival: HR = 2.18 [95% CI:1.33-3.56]); Prostate cancer, (Biochemical recurrence: HR 2.49 CI: 1.43-4.34) and was associated with activated MAPK (phospho-MAPK) in preclinical models and clinical samples ($p < 0.05$). The assay score was reduced by MEK inhibition ($p < 0.05$) and elevated by KRAS, NRAS and MEK1 overexpression ($p < 0.05$). The assay predicted response to the MEK inhibitors Trametinib and Selumetinib in cell line models ($p < 0.001$). **Conclusions:** A 15 gene expression assay has been developed from FFPE samples across multiple diseases to detect an EMT molecular subgroup associated with MAPK signalling. The assay predicted sensitivity to MEK inhibitors in pre-clinical model systems. Further work aims to validate the assay as a predictive biomarker in clinical samples from patients treated with EMT or MEK targeted therapies.

11617 Poster Session (Board #317), Sat, 1:15 PM-4:45 PM

Comparing programmed death ligand-1 expression on tumor cells before and after acquiring resistance to tyrosine kinase inhibitor in EGFR harbouring non-small cell lung cancer. *First Author: Siwat Sakdejayont, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Background: Although anti-PD1/PD-L1-targeting immunotherapy has been successful in the treatment of non-small cell lung cancer (NSCLC) patients, the benefit is unclear in EGFR mutation(mEGFR) NSCLC. To date, there are several clones of anti-PD-L1 antibody which provide different predictive values and the level of expression also dynamically changed after treatment. The study examined changes of PD-L1 expression in mEGFR harbouring NSCLC tissues, comparing between before and after treatment with tyrosine kinase inhibitors(TKIs) using an FDA-approved PD-L1 assay. **Methods:** We retrospectively reviewed tumor specimen from 24 patients with mEGFR NSCLC who had been treated with gefitinib, erlotinib, afatinib and received second tissue biopsy after acquiring resistance to TKIs. The collected FFPE specimens were stained with commercial anti-PD-L1 22C3 assay monoclonal antibody. Tumor proportion score(TPS) and H-score were measured before and after TKIs. **Results:** Of the study patients,54.2% patients were exon 19 deletion(n = 13), 41.7% were exon 21 point mutation(L858R) (n = 10), and 1 case was L858R/S761I. After TKIs resistance 10/13 (76.9%) of exon 19del and 8/10 (80%) of L858R revealed presence of +T790M. Pretreatment PD-L1 expression was positive(TPS≥1%) in 6 cases (25%). Mean TPS of positive cases was 34.0% and H-score was 78.2, All except 2 of 6 positive cases had adequate specimens from second biopsy(n = 22). Among 4 positive cases,PD-L1 expression tended to be higher after TKIs; mean TPS changed from 23.9 to 40.9 (p = 0.171) and H-score were from 49.3 to 91.1 (p = 0.172). 18/24 patients with TPS and H-score zero at the beginning remained zero after progression. Median TTP were similar in patients with positive PD-L1 expression and negative,13.8 m vs 14.5 m (n = 24,p = 0.644) with TKIs and 3.9 m vs 2.5 m (n = 14, p = 0.560) with chemotherapy. **Conclusions:** Prevalence of PD-L1 expression in mEGFR NSCLC was low. PD-L1 expression tended to be higher after TKIs for this with positive cases which may guide the sequences of treatment. Nevertheless no changes of PD-L1 expression for those with negative, hence re-biopsy may not be necessary.

11618 Poster Session (Board #318), Sat, 1:15 PM-4:45 PM

Nanomechanical profiling of human breast tumors as prognostic marker for breast cancer. *First Author: Rosemarie Anne Burian, Breast Center, University Hospital Basel, Basel, Switzerland*

Background: Assessment of tumor aggressiveness is crucial when making treatment decisions. Established prognostic markers may be insufficient to stratify cancer patients into treatment relevant risk groups. Emerging evidence indicates mechanical properties of cancer cells and their microenvironment play a vital role in cancer invasion and metastases. Detecting and measuring these nanomechanical changes could be a marker of cancer aggressiveness. **Methods:** We developed an atomic force microscope (AFM) based method: ARTIDIS (Automated and Reliable Tissue Diagnostics) for measuring nanomechanical properties of human tissue biopsies. These were performed on fresh, non-fixed tissue under physiological conditions. This novel method uses a micro-fabricated 20nm tip indenting and measuring stiffness of thousands of locations within 60-180minutes. This quantitative, biopsy-wide, nanomechanical profile strongly correlates to the tissue's biological composition. Post-AFM this biopsy is analyzed by pathology. We sought to differentiate benign from cancerous lesions based on nanomechanical properties; then link the cancerous nanomechanical profiles prospectively to the clinical outcomes. **Results:** Our results demonstrate the first AFM based nanomechanical profiling to detect aggressive breast cancer subtypes using fresh tissue in a clinical setting. We have shown that nanomechanical profiles of human breast cancer biopsies display stiffness profiles distinct from surrounding normal tissue. Breast cancer subtypes were distinguishable by their nanomechanical properties only. We have discovered specific nanomechanical profiles of tumor subtypes likely to metastasize. When the primary tumor displayed the same soft nanomechanical profile as adjacent tissue, this was associated with positive nodal status. **Conclusions:** Our results demontrate nanomechanical profiling is a fast and sensitive method to stratify malignant biopsies into relevant subgroups in a clinical setting. Relative stiffness and distribution values provide a nanomechanical profile indicating cancer aggressiveness. This will help optimize specific cancer diagnosis, orientate therapy choice and support patient follow up.

11619 Poster Session (Board #319), Sat, 1:15 PM-4:45 PM

Androgen receptor (AR) activation in breast cancer (BC) liver metastases. *First Author: Corinne Ramos, Theranostics Health, Inc., Rockville, MD*

Background: AR is expressed in the majority of BCs and its signaling may contribute to the development of BC metastases (mets). The expression pattern of AR, its phosphorylated form, p-AR S650, and correlations with other BC growth and survival pathways were evaluated in BC mets by reverse phase protein array (RPPA). **Methods:** RPPA was performed on 93 FFPE primary BCs and mets at a CLIA-certified laboratory. Immunostaining with 24 antibodies was directed against AR, p-AR S650, p-MET, and total and p-HER1/2/3 pathway proteins. Clinical and genomic data were obtained from pt chart review. Analysis of variance (ANOVA) was used to assess any statistically significant differences between the groups. **Results:** 35 tissues were primary BCs (38%); 58 were mets (62%). Sites of mets: liver (n = 41); lung (n = 8); chest wall (n = 9). Of the 41 liver mets, 2 were triple negative (TN), 32 were ER+/HER2-, and 7 were HER2+. AR expression was increased in chest wall (1.7-fold; p = 0.038) compared to primary BCs. p-AR was increased in liver (2.0-fold; p = 0.039) and chest wall (1.8-fold; p = 0.026) compared to primary BCs. ER+ liver mets especially showed strong liver-specific activation of AR along with overexpression of HER1, HER3, VEGFR, and activation of mTOR, S6 Ribo, 4EBP1, and STAT3. MEK/ERK pathway was not activated in ER+ liver mets. HER2+ liver mets had pan-HER1/2/3 activation along with MET, SRC, S6 Ribo, 4EBP1, and JAK2/STAT3. In the 2 TN liver mets, EGFR, VEGFR, mTOR, S6 Ribo, 4EBP1, and JAK2/STAT3 were activated while AR and MEK/ERK were not. The ER+ liver mets showed higher expression of p-AR (p = 0.079), p-HER3 (p = 0.002), p-HER2 (p = 0.010) and p-Jak2 (p = 0.002) compared to primary ER+ BCs whereas the HER2+ liver mets showed lower level of p-IGFR (p = 0.049) and p-MET (p = 0.010) compared to primary HER2+ BCs. Interestingly, TN chest wall mets had higher levels of AR and p-AR (p = 0.008 and 0.044 respectively) compared to TN BCs. **Conclusions:** ER+ liver mets have strong expression of AR and p-AR, and all liver met subtypes showed accumulation of S6 Ribo/4EBP1 and activation of JAK2/STAT3, but not the MAPK pathway. HER1/3 and HER1/2/3 were activated in ER+ and HER2+ liver mets, respectively. These data suggest that targeting AR, HER1/3, and mTOR in ER+ liver met would be of interest.

11620 Poster Session (Board #320), Sat, 1:15 PM-4:45 PM

Phosphoproteomic analysis of matched primary breast cancer (BC) and lymph node (LN) metastases. *First Author: Corinne Ramos, Theranostics Health, Inc., Rockville, MD*

Background: Therapeutic recommendations are often based on molecular markers expressed in primary BCs. However, LN metastases (mets) may more accurately reflect the lethal potential of the disease (Ries 2007). Whether activated oncogenic pathways in axillary LN mets can be reliably identified in the associated primary BCs is unknown. We evaluated the activation of key signaling pathways in pts' matched primary BC and axillary LN mets using reverse phase protein array (RPPA). **Methods:** 60 pts' matched FFPE primary BC and axillary LN mets (20 TN, 20 ER+/HER2-, 20 HER2+) are to be evaluated by RPPA at a CLIA-certified laboratory. The first 20 matched BC/LN (3 TN, 14 ER+/HER2-, 3 HER2+) and 7 unmatched (1 TN LN, 1 ER+/HER2- BC, 5 ER+/HER2- LN) results are reported here. Immunostaining of 14 HER1/2/3 and downstream pathway proteins was performed. Mann-Whitney U tests (p value) were utilized to compare BC vs LN mets protein level. **Results:** Increased expression of HER1 (6-fold) and p-Akt (2-fold) was observed in TN compared to Luminal (Lum) and HER2+ primary BCs. AR expression was upregulated in TN and HER2+ (2-fold) compared to Lum primary BCs. The LN mets showed higher expression of HER1 (p = 0.004), p-HER3 (p = 0.040), p-IGFR (p = 0.009), p-S6 (p = 0.033), p-4EBP1 (p = 0.027) and p-MEK1/2 (p = 0.023) compared to primary BCs. TN had higher level of p-Akt T308 (p = 0.077) in the LN mets compared to the primary BCs while HER2+ showed a downregulation of p-Akt T308 (p = 0.049) in the LN mets. HER2+ also had higher level of HER1 (p = 0.049), p-HER3 (p = 0.049), p-FGFR (p = 0.083), and p-4EBP1 (p = 0.049) in the LN mets compared to primary BCs. Higher levels of HER1 (p = 0.043) and p-MEK1/2 (p = 0.027) were observed in Lum B LN mets compared to p-IGFR (p = 0.041), p-Akt S473 (p = 0.088), p-S6 (p = 0.063) and p-4EBP1 (p = 0.097) in Lum A LN mets. **Conclusions:** In TNBC, preliminary results show that p-Akt is differentially upregulated in LN mets while HER1, p-HER3 and p-4EBP1 are overexpressed in HER2+ LN mets. Lum A LN mets showed higher levels of p-IGFR, p-Akt, p-S6 and p-4EBP1 vs Lum B LN mets which had higher levels of HER1 and p-MEK1/2. These data suggest different signaling pathways in BC LN mets compared to primary BCs. Analyses of 60 pts' matched primary BC/LN samples will be presented.

11621 Poster Session (Board #321), Sat, 1:15 PM-4:45 PM

Molecular landscape of BRAF mutations in large cell neuroendocrine carcinoma of lung: An analysis of BRAF mutations and a case report of a BRAF non-V600E mutated tumor responding to targeted therapy. *First Author: Keerthi Tamragouri, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: In advanced stages, large cell neuroendocrine carcinoma of the lung (L-LCNEC) mimics small cell lung cancer (SCLC) despite its traditional classification as a non-small cell lung cancer (NSCLC). Here we present a focused analysis of BRAF mutations in this population. **Methods:** Comprehensive genomic profiling of tumor tissues was performed from a cohort of 300 patients with biopsy proven L-LCNEC. Specimens were either from a primary lung lesion or metastatic site. **Results:** 14 unique BRAF alterations (amplifications, mutations) were identified in 13 patients. The importance of biomarker driven therapy is subsequently highlighted with our case of a 69 year-old male diagnosed with metastatic L-LCNEC that did not respond to cisplatin/etoposide. He then demonstrated a significant durable response with therapy targeted toward a BRAF non-V600E mutation (G469R) associated with biomarker response identified through circulating cell free tumor DNA analysis. A change in clonal allele frequency from nearly 50% to non-detectable was observed. **Conclusions:** Though uncommon, L-LCNEC does appear to contain activating and therefore actionable alterations. We thus highlight the value of pursuing NGS for these patients.

Specimen site	BRAF protein change	BRAF MAF (mean allele frequency?)	BRAF mutation characterization
Bone	G469A	0.41	Activating (Carter *et al.*, 2015)
Liver	K601N	0.45	Activating (Yao *et al.*, 2015)
Other	G469R	0.59	Activating (Damm *et al.*, 2014, Yao *et al.*, 2015)
Soft Tissue	G466V	0.32	Kinase impaired (Zheng *et al.*, 2015)
Liver	N581I	0.35	Uncharacterized
Lung	E220K	0.18	Unknown
Bone	E26_A27insAG	0.25	Unknown
Lymph Node	W210L, G9D	0.35, 0.2	Unknown
Soft Tissue	P149T	0.31	Unknown
Soft Tissue			amplification (CN = 9)
Liver			amplification (CN = 14)
Lymph Node			amplification (CN = 6)
Lung			amplification (CN = 8)

11622 Poster Session (Board #322), Sat, 1:15 PM-4:45 PM

Microarray analysis to identifiy novel copy number alterations in acute myeloid leukemia. *First Author: Maria Chiara Fontana, University of Bologna, Bologna, Italy*

Background: SNP microarray can detect Copy Number Alterations (CNAs) which could be predictive of response and can help define therapeutic strategies. Our aim is to improve conventional cytogenetic analysis and identify new genetic alterations relevant to leukemogenesis by a SNP array-based genotyping approach. **Methods:** We performed SNP 6.0/Cytoscan HD (Affymetrix) on 235 Acute Myeloid Leukemia (AML) patients at diagnosis. Seventy-eight/235 samples were also performed by Whole Exome Sequencing, WES (HiSeq,Illumina). SNP Array data were analyzed by Nexus Copy Number (BioDiscovery) and R Core Team. **Results:** We found several genes preferentially deleted, including *MRPS5* (14.8%), *PHF6* (9.3%), *SCAPER* (7.2%), *CASK* (5.9%), *WNK* (4.6%), *STAG2* (4.2%), *LRRK1* (3.4%), *PALB2* (3.4%), genes preferentially amplified were *RABL2B* (16.1%), *NF2* (10.2%), *NBPF9* (7.6%), *JAK2* (6.8%), *RB1*, *NF1* and *KMT2A* (4.2%), *PTEN* (3.4%), *TP73* and *SMAD2* (2.5%). Single-copy losses and deletions were enriched ($p < .001$) for genes mapping in these pathways: aberrant PD-1 signaling, loss of function of *SMAD4* in cancer and *SMAD4* MH2 Domain mutants in cancer. The pathways significantly ($p < .001$) deregulated in our cohort with single copy gain and homozygous amplification were: regulation of transcription and nucleic acid, negative regulation of metabolic processes, constitutive signaling by aberrant PI3K in cancer and PI3K/AKT network. In order to define driver alterations, we correlate deletions and losses with mutational data. We found losses are also targeted by mutations (*BRCA2*, *LRRK1*), while deleted genes, as *CASK*, *CDK6* and *MAPT*, were involved in pathways affected by genomic mutations (*CASK* deletion and *MPP6* mutation, *CDK6* deletion and *PPM1D* mutation, *MAPT* deletion and *SPAG5*mutation). **Conclusions:** We have identified new CNAs and pathways involving novel potential leukemia-related genes. The comparison between SNP and WES data could provide important findings on prognosis of AML patients. Minimal deleted regions of genes in deregulated pathways deserve further investigation in order to identify new genes which could be relevant AML biomarkers. Ackn**:** ELN, AIL, AIRC,prog. Regione-Università 2010-12 (L. Bolondi),FP7 NGS-PTL project,HARMONY.

11623 Poster Session (Board #323), Sat, 1:15 PM-4:45 PM

Parallel VENTANA IHC and RT-PCR of ALK status in non-small cell lung cancer and response to crizotinib. *First Author: Chunwei Xu, Fujian Cancer Hospital, Fuzhou, China*

Background: Advanced NSCLC patients who harbor (ALK) rearrangement were sensitive to crizotinib. However, not all ALK-positive patients benefit equally from crizotinib. A method for determining ALK rearrangement is RT-PCR, the Chinese FDA has approved RT-PCR to detect ALK rearrangement. In this regard, VENTANA IHC is a standard method to identify ALK protein overexpression in NSCLC. However, up to now, it is still largely unknown about the response to crizotinib for Chinese NSCLC patients having ALK overexpress detected by VENTANA IHC. To better clarify the clinical implication of VENTANA IHC to detect ALK rearrangement, we compared the curative effect and survival by the two methods in advanced NSCLC patients and analysis VENTNA IHC and RT-PCR inconsistent cases. **Methods:** A total of 1720 patients with NSCLC who had their ALK rearrangement detected by IHC and/or RT-PCR were included in this analysis. And we compared the efficacy and survival of patients with ALK positive detected by IHC and RT-PCR. We used next-generation sequencing (NGS) to detect patients whom two methods were not consistent. **Results:** 187/1720 patients were identified as ALK-positive by IHC and/or RT-PCR and 66 patient received crizotinib. We identified 172/1674 patients had ALK positive by IHC method, 41/322 patients had ALK rearrangements by RT-PCR method. And 29/276 patients with ALK positive were simultaneously analyzed by IHC and RT-PCR. The overall response rates (ORR) were 65.90% by IHC and 55.88% by RT-PCR, respectively. And the disease control rates (DCR) were 86.36% by IHC and 76.47% by RT-PCR. The median PFS of IHC was 8.5 months and RT-PCR was 9.2 months Targeted next-generation sequencing in the special type: Among 6 cases of 17 cases ALK positive patients were inconsistent by IHC and RT-PCR performed with NGS, 4 cases were identified to have EML4-ALK fusions, and 2 cases were KCL1-ALK (ND) and FBXO36-ALK (PFS 21.2 months). **Conclusions:** VENTANA IHC is a reliable and rapid screening tool in routine pathologic laboratories for the identification of suitable candidates for targeted therapy. It has a moderate sensitivity and a slightly higher curative effect, and some VENTANA IHC positive but RT-PCR negative cases may benefit from crizotinib.

11624 Poster Session (Board #324), Sat, 1:15 PM-4:45 PM

KRAS in non-small cell lung cancer: Single institution experience—What factors are involved? *First Author: Idoroenyi Usua Amanam, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Disease heterogeneity with variable molecular mutations is one of the main contributory factors in non-small cell lung cancer (NSCLC). The goal of this study was to better understand the *KRAS* patients with co-occurring mutations. **Methods:** We identified 60 patients with a diagnosis of NSCLC and a *KRAS* mutation in the COH Cancer Registry from 2009 to 2016. Next generation sequencing was performed. **Results:** Of the 60 patients identified, 42 (70%) were Stage IV at diagnosis, 7 (12%) Stage I and 7 (12%) stage II and 4 (6%) Stage III. 47 (78) patients were smokers. Caucasian was the most common (n = 44, 73%) racial group, followed by Asians (n = 9, 15%), African-Americans (n = 3, 5%), other (n = 3, 5%) and Pacific Islander (n = 1, 1.7%). The average age at diagnosis was 67 (median 69.50) years; 30 patients (50%) were over 70 years, 23 (38%) patients were 51-69 years, and 7 (12%) 50 years or below. Majority of the patients had metastatic disease (n = 52, 87%) with 20% (n = 12) having brain metastasis with average metastatic sites 1.6. An average of 1.97 (range = 0-5) lines of therapy including chemotherapy, biologic agents or immunotherapy were received. 12 (20%) patients received immunotherapy, radiation in 28 (47%) and surgery in 22 (37%) with a median overall survival at 15 months. The most frequent molecular alteration was codon 12 mutation (n = 47, 78%), followed by codon 13 (n = 7, 12%) and codon 61 (n = 6, 10%) mutations. The most common co-occurring mutations in this cohort were TP53 (n = 15, 25%), ATM (n = 9, 15%), LRP1B (n = 9, 15%), ARID1A (n = 8, 13%), STK11 (n = 8, 13%), ARID1B (n = 7, 12%), TERT (n = 7, 12%), EGFR (n = 6, 10%), RBM10 (n = 6, 10%), SPTA1 (n = 6, 10%). We are currently evaluating the relevance of the Circos plot analysis for these mutations, clinical response to immunotherapy and potential biomarkers. **Conclusions:** KRAS mutations are among the most common molecular alterations identified in NSCLC. Effective treatments targeting KRAS mutations have represented a challenge so far. Understanding the significance of co-mutations and their therapeutic implications, especially in response to immunotherapy and other agents represents an important step to develop better treatment options for KRAS mutated lung cancers.

TPS11625 Poster Session (Board #325a), Sat, 1:15 PM-4:45 PM

WINTHER: An international study to select rational therapeutics based on the analysis of matched tumor and normal biopsies in subjects with advanced malignancies. *First Author: Jean-Charles Soria, Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France*

Background: Today, personalized cancer medicine implies matching the patient's tumor genomic characteristics with molecularly and immune targeted agents. Although there are an increasing number of DNA aberrations that can now be matched to a cognate therapy, some patients do not display such druggable oncogene drivers. **Methods:** WINTHER is an open non-randomized study involving 6 cancer centers in France, Spain, Israel, Canada and USA applying genomic and also transcriptomic assays to guide treatment decisions. The novelty of the WINTHER approach lies in the use of tumor and matched normal tissue biopsies together and an algorithm for predicting efficacy of therapies. The aim is to provide a rational therapeutic choice for all of the patients enrolled in the study whether or not they harbor actionable DNA alterations. The study endpoint is the comparison of the progression-free-survival (PFS) under the WINTHER selected therapy to the PFS of the last therapeutic line. Patients included have refractory metastatic cancer of any histological type, with at least one prior therapeutic regimen and performance status of 0 to 1. Patients who have received a matched treatment based on a molecular anomaly as their immediate prior therapy were excluded. After consent, patients undergo a tumor and histologically-matched normal tissue biopsy. Extracted DNA and RNA of both tumor and normal from frozen tissues at the local center under common standard operating procedures are sent to centralized laboratories for omics investigations. DNA is investigated at Foundation Medicine Inc. and RNA at Gustave Roussy using Agilent technology. For RNA, the WINTHER algorithm is applied on the differential RNA expression data between tumor and normal tissues and establishes the list of drugs with the presumed higher score of efficacy for each patient. Patients with actionable genomic events enter in ARM A, and patients without any druggable anomaly of the DNA enter in ARM B and are treated using the WINTHER algorithm RNA-based treatment decision tool. To date, the trial has recruited 303 patients. Clinical trial information: NCT01856296.

TPS11626 Poster Session (Board #325b), Sat, 1:15 PM-4:45 PM

A phase I, first-in-human, dose escalation study of intravenous TK216 in patients with relapsed or refractory Ewing sarcoma. *First Author: Noah Federman, University of California, Los Angeles, Los Angeles, CA*

Background: Ewing sarcoma (ES) is a rare cancer that affects children and young adults. Patients with recurrent/refractory ES have a poor prognosis (5-year survival 10-15%) with no improvement despite advances in cytotoxic and targeted therapies. Genomic rearrangements resulting in fusion proteins and over-expression of *ets* family transcription factors occur in 95% of ES. In particular, the EWS-FLI1 oncogenic fusion creates a constitutively active transcription factor that drives the malignant ES phenotype. Strategies to target the EWS-FLI1 fusion protein have been limited by lack of specificity. A promising approach is to target the interaction of the *ets* transcription factor with its critical protein partner, RNA helicase A (RHA). TK216 is a novel small-molecule that directly binds to EWS-FLI1 and inhibits its function by blocking binding to RHA. TK216 demonstrates potent anti-proliferative effects on ES cell lines and xenografts. **Methods:** We initiated a Phase 1, first-in-human, open-label, multi-center, dose-escalation/dose-expansion trial of TK216 in patients with recurrent/refractory ES who are ≥12 years of age (ClinicalTrials.gov: NCT02657005). TK216 is dosed based on body surface area and administered as a continuous intravenous infusion for 7 days followed by 14 days rest every 21 days. Treatment may continue in the absence of disease progression. One intrapatient dose escalation is allowed. Enrollment of 6 to 8 cohorts using a 3+3 dose-escalation design is anticipated. During dose expansion, a total of 18 patients with ES will be accrued at the recommended Phase 2 dose (RP2D). The primary objective of the study is to determine the maximum tolerated dose and RP2D of TK216. Secondary objectives are to assess the safety profile, pharmacokinetics, pharmacodynamics, and antitumor activity of TK216. Molecular assays will be performed to characterize EWS-FLI or EWS-ets abnormalities in archival tumor tissue. The overall response rate, duration of response, progression-free survival, and overall survival will be determined in the expansion cohort. Nine patients have been enrolled since June 2016. Accrual to cohorts 1, 2, and 3 completed and cohort 4 opened in January 2017. Clinical trial information: NCT02657005.

TPS11627 Poster Session (Board #326a), Sat, 1:15 PM-4:45 PM

CEA, CA15.3 and 18-FDG PET in the follow-up of early breast cancer (BC) patients (pts): A prospective, multicentric, randomized trial—KRONOS patient-oriented new surveillance study Italy. *First Author: Claudio Zamagni, Policlinico S. Orsola-Malpighi Hospital, Bologna, Italy*

Background: Current recommendations for breast cancer (BC) surveillance in asymptomatic patients (pts) include only mammography and physical examination and arise from two trials conducted in the 80's. Since then new findings about BC biology, treatment and the introduction of cutting-edge diagnostic technologies such as 18-FDG PET have deeply modified our clinical scenarios. The aim of this prospective randomized trial is to verify if the serial measurement of CEA and CA15-3 followed by 18-FDG PET can anticipate the diagnosis of BC recurrence compared to control arm by estimation of the difference of restricted mean survival time (RMST) between the two arms. If the end-point will be met a subsequent extension trial will investigate the impact of the earlier diagnosis of distant metastases on survival. **Methods:** Pts diagnosed with stage I-III BC, who underwent adequate surgery are eligible. Special histologies and low-risk cases according to St. Gallen criteria are excluded. The study includes pts at the beginning of the follow-up after the conclusion of primary treatment (cohort 1), and pts that have concluded without relapse the first 5 years of follow-up (cohort 2). Eligible pts will be randomized in a 1:1 ratio to follow-up according to local practice (control arm) or to three-monthly serial dosing of CEA and CA15-3 and subsequent 18 FDG-PET only in case of an increase of CEA and/or CA 15.3 greater than a critical difference compared to baseline (experimental arm). The following stratification factors will be used: node negative *vs* positive, HER2 negative *vs* positive, ER positive *vs* negative. Eight-hundred pts will be enrolled over 3 years. For such a calculation, we made the assumption of a 20% baseline 5-year incidence of relapse. The target reduction of three months in RMST implies a median time of diagnostic anticipation, conditional on having BC recurrence, of 10 months. The follow-up will continue until 10 years from surgery. Since 23rd October 2014 573 pts have been enrolled. The present trial was approved by the Ethical Committee of each participating centre and is registered on Clinical trial information: NCT02261389.

TPS11628 Poster Session (Board #326b), Sat, 1:15 PM-4:45 PM

A pharmacodynamic study of sirolimus and metformin in patients with advanced solid tumors. *First Author: Amikar Sehdev, Indiana University, Indianapolis, IN*

Background: Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR). Metformin has shown anti-cancer activity through its cellular (e.g., AMPK activation) and systemic effects (e.g., inhibition of IGF-1). We conducted a pilot study to test the hypothesis that metformin may potentiate mTOR inhibition by sirolimus. **Methods:** An open-label, randomized study was conducted in which eligible patients with advanced solid tumors were started on sirolimus (3mg daily) alone for the first 7 days. On day 8, patients were randomized to either receive metformin XL (500 mg daily) plus sirolimus (Arm A) or sirolimus alone (Arm B) for until day 21. From day 22 onwards, all patients recieved metformin XL plus sirolimus. The pharmacodynamic (PD) biomarkers were collected at baseline, day 8 and day 22 of cycle 1. The primary endpoint was to compare the change in PD biomarker phospho-p70S6K, using a two-sample t test (log ratio D22/D8 in arm A vs. arm B). The phospho-p70S6K was measured in peripheral blood T cells using Western blot. The secondary endpoints were to assess objective response rate (RECIST 1.1), toxicity (CTCAE V4.0) and changes in the serum levels of PD biomarkers: fasting glucose, triglycerides, insulin, C-peptide, IGF-1, IGF-1R, IGF-BP, leptin and adiponectin using two-sample t tests. **Results:** 24 patients were enrolled, at which time an interim futility analysis was conducted. 18 patients were evaluable for the primary endpoint (8 in arm A; 10 in arm B). The mean log ratios D22/D8 in phospho-p70S6K in arms A and B were -0.12 (SD = 0.13) and -0.16 (SD = 0.29), respectively (P = 0.64). Of the 17 pts evaluable for response, the best response was stable disease in 9 patients and progressive disease in 8 patients. There were no dose-limiting or unexpected toxicities. Of the 21 patients evaluable for serum PD biomarkers, there were no significant differences between arms A and B in fasting glucose, triglycerides, insulin, C-peptide, IGF-1, IGF-BP1, IGF-BP3, leptin and adiponectin ($P > 0.05$ for all). **Conclusions:** The addition of metformin to sirolimus, although well-tolerated, was not associated with significant changes in phospho-p70S6k and other PD biomarkers. Based on the results of the interim analysis, the trial was terminated. Clinical trial information: NCT02145559.

Publication-Only Abstracts

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Abstract First Author Index

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A

Aakhus, Erin 6597
Aanur, Praveen TPS4137
Abbasi, Saqib e18103
Abdel Rahman, Zaid e18239
Abdel-Rahman, Omar e21623
Abdel-Wahab, Reham e15660
Abdou, Yara e15781
Abdueva, Diana e23214
Abdul Sater, Houssein Talal 1094
Abe, Hajime 567
Abe, Yoshinobu e14561
Abraham, Michal e14544
Abramson, Jeremy S. 7513
Abrao, Fernando e21638, e21666
Abrol, Srishti 2015
Abu Zaid, Mohammad Issam LBA10012
Abudayyeh, Ala e18536
Abuhijla, Fawzi Jamil e20091
Ackland, Stephen P. 2530
Acoba, Jared David e18214
Acosta, Luciana Paola e23034
Adachi, Takuya e15674
Adam, Liana e15800
Adamo, Vincenzo e12565
Adams, Christopher Peter e20016
Adams, Daniel 11503
Adams, Richard e15044
Adams, Sarah Foster e17052
Adams, Sylvia 1008, 1088
Addepalli, Srikala e19512
Adebamowo, Sally Nneoma 1510
Adler, Kenneth B. e23017
Adra, Nabil 4520
Aedinova, Irina V. e17554
Afkhami, Michelle e12041
Afshar, Solmaz F. e19520
Aftimos, Philippe Georges 2504
Agelaki, Sofia e20520, e23030
Aggarwal, Anita 1559
Aggarwal, Charu 6073, 9055
Aggarwal, Rahul Raj 5056, e16562
Aghajanian, Carol 5545
Agrawal, Vartika e13019
Agresta, Laura 10547
Aguado De La Rosa, Carlos e16504
Aguiar, Pedro Nazareth 6612
Ahamad, Anesa Waheda e16014, e18261
Ahmad, Alia e22021
Ahmed, Shahid Sattar e16043
Ahmed, Tamjeed 9047
Ahmed, Zaheer 8563
Ahmedova, Aysel e17543, e17544
Ahn, Myung-Ju 2006, e20503
Ahn, Sung Gwe e23198
Ahuja Parikh, Divya e18323
Aiello, Marco M. 3032
Airoldi, Mario e17501
Ajani, Jaffer A. e15612
Akagi, Junji e23071
Akashi-Tanaka, Sadako e12111
Akbulut, Hakan e15103
Akce, Mehmet e15645
Akinboro, Oladimeji e18111
Akita, Kenji e20070
Akoulitchev, Alexandre e23054
Al-Batran, Salah-Eddin 4004
Al-Farhat, Yousuf e12066
Al-Hajri, Thuraiya Nasser e15145
Al-Huniti, Nidal e20606
Al-Kali, Aref 7056, e18560
Al-Rajhi 1, Naser e17541
Al-Taee, Ahmad e15716
Al-Ward, Ruaa e12096
Alamgir, M.Ahsan e21634
Alanya Rodríguez, Enrique e12112
Albanell, Joan 1017, 1099
Alberti, Saverio e14002
Albitar, Maher e14500
Albuquerque, E.L. e14558
Alcaraz-Sanabria, Ana Lucía e17089
Aldubayan, Saud H. 1500
Alese, Olatunji Boladale 6559, e18069
Alexander, Brian Michael 2005, TPS2079
Alexandre, Jerome e17093
Alfonso Pierola, Ana e18555
Algazi, Alain Patrick 2578
Alghamdi, Mohammed Abdullah 4084
Ali, Ayesha 1024
Ali, Nadia Dawn 3566
Ali, Naveed e18250
Ali, Shamsher e18183
Aliaga Llerena, Karina Mayra e21082
Alistar, Angela Tatiana e15661
Aljubran, Ali Husain e15021
Alken, Scheryll Paula e18327
Allayous, Clara 9551
Almeida, Gustavo Fernandes Godoy e18229
Alsaid, Nimer 8030
Alsharedi, Mohamed Farouq e20013
Alsidawi, Samer 6048, e17529
Alsina, Maria 2522
Altahan, Alaa e19022
Alter, Raanan e17118
Altman, Jessica K. 7003
Alvarez, Elysia Marie 6561, 10538
Alvarez, Sara e14588
Alvarez-Gallego, Rafael e18202
Aly, Abdalla 2039
Amanam, Idoroenyi Usua 11624
Amaro, Carla Pires e18243
Amato, Robert J. e23064
Ambinder, Richard F. 7006
Ameratunga, Malaka e13512
Ameri, Bita e12080
Ammakkanavar, Natraj Reddy 102
Anam, Jay Rashmi e15167
Anampa Mesias, Jesus Del Santo TPS2611
Anampa-Guzman, Andrea Carolina e18044
Anand, Aseem 5068
Anantharaman, Archana e23055
Anders, Carey K. 1011, TPS1107
Anderson, Peter Meade TPS11079
Ando, Reiko Makihara e18221
Andorsky, David Jacob 7502
Andre, Thierry 3500, 3531
Andreadis, Charalambos TPS7566
Andruzzi, Luisa e13102
Andtbacka, Robert Hans Ingemar 9510
Angeles, Arkhjamil e15007
Angelov, Sophia e14080
Angevin, Eric 2509, TPS3113
Angus, Steven P. 1027
Antill, Yoland Catherine TPS5614
Antonarakis, Emmanuel S. 5077
Antonia, Scott Joseph e20504
Aparicio, Ana 5013
Aparicio, Thomas TPS3628
Apolo, Andrea B. 4528, 4562
Apostolidis, Leonidas 4096, 10092
Arafat, Waddah 4537, 4579
Aragon-Ching, Jeanny B. e16068
Arain, Saad A. e18523
Araujo, Daniel Vilarim e21045
Araujo, Jhajaira 11553
Arbour, Kathryn Cecilia e20673
Arciero, Vanessa Sarah 10029
Ardeshir-Larijani, Fatemeh 11598
Areses, M.C. e20564
Argiris, Athanassios 6000
Argos, Maria 1511
Ariyasu, Ryo e23105
Arkhiri, Peter 11037
Armstrong, Andrew J. 5006, 5022
Arora, Divya 565
Arun, Banu e13121
Asare, Matthew e18077
Aschebrook-Kilfoy, Brisa 1509
Ascierto, Paolo Antonio 9518, 9520, TPS9598
Aseyev, Olexiy 10123
Asher, Nethanel e18029
Askan, Gokce e15721
Aspinwall, Lisa G. 1582
Assi, Rita 7025, 7064
Assouline, Sarit E. 7565
Atagi, Shinji 8532
Atkins, Michael B. 4505
Atrafi, Florence 8530
Attard, Gerhardt 5004
Attarian, Shirin e19002
Attia, Steven 11005
Attili, Suresh VS e21635
Audenet, Francois 4556
Audet, Sophie e14026
Aung, Kyaw Lwin e15715, e15776
Autier, Philippe 4126
Awad, Mark M. 8511
Awidi, Abdallah e18548
Ayuhara, Hideaki 10091
Azad, Gurdip Kaur e12539
Azad, Tej D. 4055
Azaro, Anal?A 2554
Azeredo, Andressa Cardoso e15073
Azharuddin, Muhammad e13053
Azoulay, David e21702

B

Bacha, Jeffrey A. TPS2082
Bachet, Jean-Baptiste 11509
Badalamenti, Giuseppe 11040
Badamchi-Zadeh, Alexander e14632
Badwe, Rajendra A. 6502
Bae, Jooeun 11577
Bae, Min Sun 1508
Baehner, Frederick L. 11568
Baek, Jeong-Heum e18204
Baek, Sun Kyung e15104
Baez Vallecillo, Luis 1090
Bagai, Varun e12518
Bagchi, Arindam 6581
Bagegni, Nusayba Ali TPS592
Bagley, Stephen Joseph 2027
Bahary, Nathan 4128
Bahl, Amit TPS1122
Bahlis, Nizar J. 8025
Bahrabadi, Arvin e18041
Bai, Xue e21017
Bairati, Isabelle e17076
Baird, Richard D. 2008
Bais, Carlos 3037
Bajorin, Dean F. 4501
Baker, Laurence H. e21579
Baker, Tabari 11610
Bal, Anjali e18503
Balasubramanian, Suresh Kumar e13516
Balaya, Vincent 5529, e17007
Baldi, Licia e15732
Baliga, Sujith 6035
Balko, Justin M. 3076
Ballinger, Tarah Jean TPS1592
Balmana Gelpi, Judith 574
Balmanoukian, Ani Sarkis 9085
Bando, Etsuro e15536
Bandovkina, Valeria e17019, e21069
Banegas, Matthew P. 6611

Banerjee, Susana N. TPS5609
Banerji, Udai 2503
Bang, Yung-Jue 4012
Bany Hamdan, Abdullah Ahmed e18218
Bao, Ting e21706
Bao, Yong Xing e15617
Baraibar, Iosune e20553
Barata, Pedro C. e16031
Bardia, Aditya 1014
Barinoff, Jana e17031
Barjas, Rolando e13520
Barkhoudarian, Garni e13506
Barnes, Chad e15766
Barnes, Tristan Alexandra e18329, e18336
Barni, Sandro e21651
Barr, Paul M. TPS7577
Barrios, Carlos H. 1033
Bartlett, John 505
Barua, Reeta e18158
Barve, Minal A. e15100
Barzi, Afsaneh 10056, e23183
Basal, Fatma Bugdaycı e15500
Basappa, Naveen S. e16078
Basch, Ethan M. LBA2
Baselga, Jose TPS1119
Basnet, Alina 578, e12119
Basso, Umberto 4568
Baste, Neus 6031
Basu, Chinmay e19021
Basu, Gargi D. 1040
Bates, James Edward 10501
Batlevi, Connie Lee 7544
Battaglin, Francesca e15042
Bauernhofer, Thomas e16520
Bauman, Julie E. 6038
Bauml, Joshua TPS6095
Bautista, Maria Diana Aileen Chua e20580
Baverel, Paul 2566
Baxi, Shrujal S. e21652
Bayani, Jane 524
Bayar, Mohamed-Amine 575
Bazhenova, Lyudmila 9065, e20682
Beamer, Staci e15563
Bean, Marta e17508
Becerra, Carlos 5548, 9052
Bechara, Rabih e12549
Beck, J. Thaddeus 6501
Beck, Julia 6055
Becker, Aline P. 2064
Beckermann, Katy 11560
Bednar, Erica 1590
Beebe-Dimmer, Jennifer Lynn e16527
Beerkens, Frans e23037
Beg, Muhammad Shaalan 6577
Behera, Madhusmita 8562
Beith, Jane McNeil LBA10000
Bekaii-Saab, Tanios S. 4106, TPS4148
Belcher, Sarah M. e18083
Bellmunt, Joaquim 4532, 4540
Beltran, Himisha 5011
Ben Ami, Eytan 11513
Benavides, Manuel e15790
Bendell, Johanna C. 3529, 3539, TPS4139
Bennani, Nabila Nora 11571
Bennett, Antonia Vickery e21681
Bennette, Caroline Savage 6515
Bennouna, Jaafar 9004
Bentley, Tanya Gk 6603
Benton, Christopher Brent e13117, e18521
Berardinelli, Gustavo Noriz e23185
Berciano-Guerrero, Miguel-Angel e21052
Berdeja, Jesus G. 3010
Berenson, James R. 8013, e19528
Berger, Martin D. 11507
Berger, Zackary e21558
Bergerot, Cristiane Decat e18184
Berghoff, Anna Sophie 3562
Beri, Nina 1534
Berk-Krauss, Juliana e21029
Berkowitz, Callie 10062
Bernard, Joseph e13069
Bernardo, Carina e16013
Bernatchez, Chantale 2545
Bernhardt, Erica e20585
Berry, Donald A. 7021
Berthold, Frank 10555
Besen, Ali Ayberk e12564
Besse, Benjamin 11540
Bessho, Akihiro e20614
Bestvina, Christine M. e21510
Betge, Johannes TPS10124
Bezan, Angelika e16038
Bhakta, Nickhill 10560
Bhamra, Inder e14094
Bhamre, Rahul e15056
Bharmal, Murtuza e21070
Bhateja, Priyanka 9060, e20017
Bhatt, Ananta e13071, e18227
Bhatt, Geetika 10044
Bhattacharya, Gaurav e22526
Bhattacharya, Saveri TPS9105, 11584
Bhattacharyya, Gouri Shankar e18199
Bhide, Shreerang 6043
Bhojwani, Deepa 10512
Bhulani, Nizar e18302, e21521
Bi, Feng e15682
Bickell, Nina A. 6586
Bigot, Frederic 3029, 11544
Biltaji, Eman e18318
Bindra, Ranjit 11586
Biran, Noa e19522
Bischoff, Farideh Z. e12519
Bishnoi, Rohit e17515, e19048
Bissonnette, Reid Paul e14055
Bista, Amir e18090
Biswas, Bivas e22504
Bjarnason, Georg A. 4514, 4574
Bjelic-Radisic, Vesna 1074
Blaes, Anne Hudson 1550
Blakely, Collin M. 9009
Blankenship, Leann 6580, e18160
Blay, Jean-Yves TPS11080
Blinder, Victoria Susana 6523
Block, Keith I. e21650
Bloomfield, David J. e12002
Bockorny, Bruno e23134
Boddu, Prajwal 7018
Bodei, Lisa 4091
Body, Amy e16517
Boedigheimer, Michael 3523
Boegemann, Martin e16514
Boer, Hink 4561
Boige, Valerie e15151
Bolaman, Ali Zahit e18564
Boland, Fiona e18128
Bonanni, Bernardo 1546
Bonetti, Andrea 6622
Bonneterre, Jacques 2007
Bonomi, Marcelo Raul e17548
Bonomo, Pierluigi TPS6094
Bonotto, Marta e12010
Bonta, Ioana e14579
Boonyawan, Keeratikarn e13527
Borad, Mitesh J. TPS4145
Borba, Roseana Melo 11523
Bossard, Celine e14592, e14599
Bosse, Dominick e16065
Bossi, Paolo 9543
Bota, Daniela Annenelie e13535
Botta, Gregory P. e15713
Bottino, Dean e14022
Boucher, Nathan Adam e21682
Boudadi, Karim 5035
Boulet, Gaelle e23116
Bourhis, Jean 6015
Bourlon, Maria Teresa e16037, e16543
Boursi, Ben e15780
Boutros, Celine 9549
Boye, Mark 1060
Boyle, Sean Michael 11589
Bozza, Claudia e21632
Bradbury, Angela R. 1504
Bradbury, Penelope Ann 9024
Braga, Virginia e18045
Brahm, Cyrillo Gerardo 2018
Brahmer, Julie R. 9000
Braicu, Elena Ioana e17063
Braune, Jan 9564
Breese, Erin Haag 11514
Brell, Joanna M. 10071
Brenner, Andrew Jacob 2055
Brenner, Baruch 4057
Brenner, Ronen Mordechay 1566
Brett, Christopher e21567
Brewster, Abenaa M. 6569
Briggs, Andrew e18320
Brisson, Ryan J. 6039
Brooke, Russell J. 10502
Brooks, Eric 8501
Brooks, Gabriel A. e18121
Brose, Marcia S. 6084
Brouwer, Nelleke Pietronella Maria e15160
Brown, Audrey e21516
Brown, Austin L. 10571
Brown, Jacqueline T. e13010
Brown, Krystal 1532
Brown, Thomas D. 6506
Brown, Timothy J. 2025, 2057
Bruckner, Howard e15711
Bruera, Gemma e15041
Brunner, Andrew Mark 7054, e18509
Brunner, Georg 9560
Brunner, Nils 11594
Bruno, Rossella e20028, e20656
Bryl, Maciej e20514
Buchanan, Jacqueline 9561
Buckanovich, Ronald J. 5556
Buckley, Sarah A. e18528
Budd, G. Thomas 521
Budhathoki, Nibash e15643
Buechler, Steven Allen 579
Buecker, Rebecca e12088
Buelow, Ben 8017
Bueno, Orlando TPS8056
Bueno, Raphael 8555
Buess, Martin e23005
Buhl, Anna Sofie Kappel 1071
Bui, Nam e22513
Bukari, Sani Mohammed e12590
Bukowski, Alexandra 6544
Bulbul, Ajaz 569
Bumma, Naresh e19524, e20633
Buonerba, Carlo e16503
Burgess, Melissa Amber 11008
Burian, Rosemarie Anne 11618
Burke, John M. e14000
Burke, John M. e19008
Burks, Eric 8543
Burns, Karen Cristly 10568
Burris, Howard A. 105, TPS2606, TPS2608, 3033
Burstein, Danielle Suzanne 10531
Burtness, Barbara 6001
Bury, Danielle e13551
Butts, Alissa 2067
Buzaglo, Joanne S. 9588, e16587
Buzdin, Anton e23142
Byrd, John C. 7510
Byrd, Kenneth e14573
Byrne, Annette T. 3580

C

Cabanillas, Fernando 7556
Cabanillas, Gerardo e14598
Caceres, Maria V. e17010
Cadoo, Karen Anne TPS5606, e17119, e17121
Caffo, Orazio 5030, e16521
Caggiano, Vincent e12101
Cai, Beilei e15690
Cai, Chunlin e23002
Calabro, Luana 8558
Calip, Gregory Sampang e13032
Callahan, Margaret K. 3069
Calvo, Emiliano 2510
Calvo, Jorge e13057
Camejo, Natalia e18209
Cameron, Alison 10541
Campbell, Aleli e21679
Campbell, Brittany Morgan 1570
Canale, Thomas e18049
Cannon, Timothy Lewis e15515
Canzonieri, Vincenzo e14039
Cao, Yu e23016
Caparello, Chiara e15719
Capasso, Anna e14604
Capdevila, Jaume 6083
Carbognin, Luisa 539
Carcano, Flavio Mavignier e16039
Cárdenas Quesada, Nuria e20080
Cardoso, Fatima 516, 1010
Carlino, Matteo S. 9545
Carlo, Maria Isabel 4510, 4524
Carlson, Josh John e18311

Carrasco, Javier 11554
Carretero-González, Alberto e14576
Carroll, Kate 6026
Carter, Jordan Spencer 10083
Carthon, Bradley Curtis e16048
Cartwright, Thomas H. e15152, e18147
Cary, Clint e18235
Casadei Gardini, Andrea e15684
Cassidy, Richard John e18075
Cassier, Philippe Alexandre 11054
Cassinello, Javier e15150
Castaneda Altamirano, Carlos e13549, e15521
Castellano, Daniel e16536
Castellanos, Emily 6573
Castillo, Cecilia e21663
Castillo, Jorge J. 8043
Catenacci, Daniel V.T. 4067, 4124
Cathcart-Rake, Elizabeth Jane e20092
Cathomas, Richard 4521
Catic, Aida 1537
Cavalieri, Courtney Christine e23081
Cazzaniga, Marina Elena 1057
Cazzaniga, Marina Elena e12552
Ce Coelho, Juliano e13009, e20568
Cecchi, Fabiola 4068
Centers, Nicole Lee 1561
Cercek, Andrea 3519
Cerrito, Maria Grazia e14014
Cescon, David W. TPS2619
Chade, Daher Cezar 4539
Chae, Jung-Woo 10018
Chae, Young Kwang 8517, e23174
Chaft, Jamie E. 8508, TPS8575
Chakraborty, Rajshekhar 8020, e18154
Challa, Sreerupa Valli e14616
Chamberlain, Marc C. e13538
Chamberlin, Mary D. e18057
Chamoun, Kamal 7011, e18543
Chan, Anthony T. C. 6002
Chan, Anthony W.H. e15679
Chan, Daniel Boon Yeow e20537
Chan, Gloria HJ 1512
Chan, Jason Yongsheng 11049
Chan, John K. 5523
Chan, Joseph e15110
Chandana, Sreenivasa Rao e18097
Chang, Anne TPS9593
Chang, Boyang e15680
Chang, Rachael e18176
Chang, Won Jin e20561
Chao, Joseph TPS2600
Chapman, Brandon C. 4032
Chapman, Paul B. 9526
Chargin, Amanda e23172
Chari, Ajai 8031
Chatterjee, Sudeshna 1578
Chau, Ian 4046, 4047
Chaudhary, Ruchi e14529
Chaudhuri, Aadel 8519
Chauhan, Aman e15691, e15696
Chaul Barbosa, Caroline e19020
Chavarri Guerra, Yanin 1539, e13030
Chawla, Sant P. 11000
Check, Devon e16028
Chekerov, Radoslav 5558
Chen, Angela e20000
Chen, Anthony 6516
Chen, Eric Xueyu TPS3621
Chen, Fangjun 3046
Chen, Jia e15513
Chen, Jiaying 6037
Chen, Jing e18535
Chen, Jo-Pai e23217
Chen, Junqing e12023, e12587
Chen, Leo 6552
Chen, Lijuan e13002
Chen, Ling e15529
Chen, Meihua e14542
Chen, Ming Huang 3022
Chen, Ming-Yuan 6005
Chen, Qian e14073
Chen, Robert W. TPS7575
Chen, Rongrong 11527
Chen, Runzhe 8035
Chen, Ruthia 1513
Chen, Shin-Cheh e12503
Chen, Viola e16072
Chen, Wei-Shen 9579
Chen, Wendy Y. TPS586
Chen, Wenli e17012
Chen, William S. 6060
Chen, Wucheng e20076
Chen, Xiaohui e23179
Chen, Xinru e20595
Chen, Yun 4066
Chen, Zhan-Hong e15622
Chen, Zhong-ping e13530
Chen, Zhuo Georgia 6057
Chenard-Poirier, Maxime 2506, 2542, TPS2607
Cheng, Ann-Lii 4001
Cheng, Michael L. 4533, 5010
Cheng, Min-Yi e12125
Cheng, Sierra 6509
Cheng, Xiangdong e15545
Cheng, Ying e20012
Cheng, Zhigang e17593
Cher, Lawrence e13522
Chera, Bhishamjit S. 6044
Cherkashin, Mikhail A. e18289
Chern, Jing-Yi 5588
Cherniawsky, Hannah Marie e18219
Cherubini, Chiara e16519
Chesney, Jason Alan 9509
Cheung, Yee Him e13006
Cheung, Yin Ting 10521
Chhatrala, Hardik Satish e15644
Chi, Kim N. 5002, 5032
Chi, Zhihong 3067
Chiang, Nai-Jung 2531
Chien, Richard e23065
Chilaca Rosas, María Fátima e18532
Chin, Venessa T. e15759
Chintalacheruvu, Lakshmi Manogna e15058, e15632
Chiocca, E. Antonio 2044
Chiorean, E. Gabriela TPS4147, TPS4150
Chisti, Mohammad Muhsin e12502
Chitnis, Saurabh Deepak e12553
Cho, Byoung Chul 2069
Cho, Hearn J. TPS8053
Cho, Helen Kim e23084
Cho, Jinhyun 8521
Cho, Oyeon e13036
Choi, Jin 4117
Choi, Jonggwon e15702
Choi, Jung Hye e19031
Choi, Yong Won 4043
Choi, Yoon Young 4022
Choi, Young Jun e17547
Chooback, Negar e20567
Chopra, Anita e18516
Chou, Pei-Chun 6590
Chouaid, Christos e20548
Choucair, Marie-Louise 10551
Choudhary, Ishita 1100
Choueiri, Toni K. 4504, TPS4594
Chovanec, Michal e16042, e21607
Chow, Jennifer e23089
Chow, Pierce K. H. 4002
Chowdhury, Simon 4506, 5028
Christensen, Troels Dreier e12532
Chu, Li e20533
Chua, Kevin Lee Min e17545
Chun, Yun Shin TPS3625
Chung, Christine H. 11512
Chung, Jeffson Chia-Hsien e17568
Cicin, Irfan e15055
Cingam, Shashank Reddy 11570
Cisak, Kamila Izabela e19032
Claret, Laurent e14517
Clark, Joseph e21005
Clark, Leslie Horn e17114
Clarke, Emily e12557
Clifton, Katherine 576
Clingan, Philip R. 2529
Cloughesy, Timothy Francis e13504
Clouthier, Derek L. 11607
Cmelak, Anthony 6074
Cobain, Erin Frances 101
Cochin, Valérie e17564
Coelho, Rafael Correa e15511
Cohen, Deirdre Jill TPS3627
Cohen, Romain 3563
Colàs, Eva Colàs e17070
Colbert, Lauren Elizabeth 11557
Cole, Calvin e16580
Cole, Peter D. 7527
Colecchia, Maurizio e16019
Coleman, Morton TPS7578, TPS7579
Colia, Vittoria e22525
Colleoni, Marco 503
Colli, Leandro Machado 3056
Collins, Dearbhaile Catherine 8556
Colombo Bonadio, Renata R.C. e17115
Colombo, Ilaria 5581
Colombo, Nicoletta 5559
Comandone, Alessandro e22528
Combs, Susan E. e20056
Comolli, Giuditta e12562
Concha-Benavente, Fernando 6050
Conen, Katrin Lisa 2032, e13524
Connelly, Caitlin F. 1568
Conroy, Michael e13013
Conte, Pier Franco 501
Conteduca, Vincenza 5060
Conter, Henry Jacob e18295
Contreras, Sergio e12501
Cook, Rachel J. TPS7071
Cooney, Tabitha e14100
Copeland, Anureet 10048
Copher, Ronda 10109, e17589
Copur, Mehmet Sitki e18040
Cordeiro, Mauricio e16056
Corli, Oscar 10089
Corny, Jennifer e20543
Corrie, Philippa 4100, 9501
Cortes, Jorge E. 7002, 7051, TPS7068
Cortinovis, Diego Luigi 8513
Costa, Jose Iran e18253, e21533
Costa, Ricardo Lima Barros e12568
Cote, Gregory Michael 6032, 6036
Couetoux du Tertre, Mathilde e20588
Coughlan, Diarmuid e22011
Cousin, Sophie 11014
Covut, Fahrettin e19503
Cowan, Renee A. 5584
Cowey, Charles Lance e21015
Cowzer, Darren e17056
Coy, Heidi e16049
Craig, Paul e15627
Cranmer, Lee D. 11023, e21058
Creelan, Ben C. TPS3096
Crehange, Gilles 4037
Cremolini, Chiara 11508
Cristofanilli, Massimo 1050
Crocenzi, Todd S. 4013
Cronin-Fenton, Deirdre e20523
Crown, John P. e21576
Crowther, Jonathan e18023
Cui, Chuanliang e21013
Cui, Jiuwei e20015
Cullen, Jennifer 5048, 5066
Cunningham, David e14627
Currow, David Christopher 10097
Curti, Brendan D. 3014, TPS3100, 9528
Curtin, Thomas Patrick 10518

D

D'Angelo, Sandra P. TPS3097, 9530, 11007
D'arpino, Sara 6579
D'ippolito, Simona 10070
D'souza, Anishka e12554
Da Costa, Alexandre Andre B.A. 5576, 6061
Daaboul, Nathalie 3058
Dabbous, Firas M. e12081
Dabbous, Omar e15724
Dabbs, David J. 522
Dackus, Gwen 535
Dagogo-Jack, Ibiayi 8536, 9025
Dahiya, Saurabh 7552
Dahl, Christine 2029
Daigo, Yataro e23144

Daly, Robert Michael 6529, 6548
Dambrosio, Nina e21630
Danese, Mark D. e20026
Daneshmand, Siamak e16000
Daniel, Sugganth 1538, 5024
Dasari, A. e15699
Datar, Ila e14611
Daver, Naval Guastad 7026, e18505
David, Rachel Julie 7543
Davidoff, Amy J. 6527, e18004
Davids, Matthew Steven 7505, e19041
Davies, Michael A. 9506
Davis, Andrew A. 11537, e23028
Davis, Elizabeth J. e21000
Davis, Kara L. 10526
Davis, Katelynn e15735
Dawod, Mohammed Adam Ibrahim e15076
Dawson, George Anthony e17531, e17532
Day, Daphne 3070
Daye, Dania e15121
Dazzi, Claudio e20676
de Boer, Stephanie M. 5502
De Bono, Johann S. TPS5091
De Carlo, Elisa e21502
De Censi, Andrea 1557, e13040
De Giorgi, Ugo 4577
De la Cruz Ku, Gabriel Antonio e12100
De la LLave, Sandra e18014
De La Mora, Hector e21589
De Laere, Bram 5049
De Langen, Joop 9042
De Lemos, Mario e22535
De Los Santos, Rose Ann e14585
De Luise, Cynthia e13096
De Marinis, Filippo 9036
de Moraes, Rafael Vanin e21022
De Paepe, Annelies e20030
De Paepe, Katja 7534
De Souza, Jonas A. 6615, e21673
De Wit, Ronald 4530
Dean, Andrew Peter e14013, e15747
DeAngelo, Daniel J. 2520, 2560
Decker, William Karl e14539
Decoster, Lore 10010
DeHart, Jessica Noelle Clague e21592
Del Campo, Jose Maria 5560
Del Paggio, Joseph 6609
Del Priore, Giuseppe TPS2615, e14061, e16567
Del Re, Marzia e15794
Del Rosario, Michael 9568, e21049
Delaloge, Suzette 1078
DeLeon, Thomas e15626, e21057
Delord, Jean-Pierre 6025
Deming, Dustin A. e15082
Demircan, Nazim e15009
Demirci, Umut e15507
Den Brok, Wendie-Lou D. 1544
Denburg, Avram e18339
Deng, Bo e15579
Deng, David e18038
Deng, Gary E. 8021
Deng, Min e15555
Dengel, Lynn Thacher e21080
Denicoff, Andrea 6542
Denlinger, Nathan e19023
Denninger, John W. 10051
Dent, Rebecca Alexandra 1009
Derks, Jules 9061
Derosa, Lisa 3015, 4569
Desai, Jasmin Radhika e15630
Desai, Jayesh 3557
Desai, Meghna R. e21525
Desai, Poorvi Kirit e19034
Desantes, Kenneth TPS2596
Deshmukh, Sanjay P. e17558
Deshwar, Amar e15738
Desjardin, Jacqueline Talea 1515
Desjardin, Marie e15013
Desjardins, Annick e13533
DeVito, Nicholas C. 3053
Dewan, Ramita 2051
Dey, Nandini e23151
Dhakal, Ajay 1054
Dhakal, Binod 8012, 8022
Dhani, Neesha C. 5524
Dhawan, Mallika Sachdev 2527
Dhir, Aruna Alahari e19012
di Martino, Simona e16055
Di Mattei, Valentina E. e21557
Diab, Adi e14040
Diab, Maria e18547
Dias-Neto, Emmanuel e16578
Diaz Beveridge, Robert e15159
Diaz Duque, Adolfo Enrique TPS2080
Diaz, Luis A. 3071, TPS3618
Diaz, Marca e18249
Dibs, Khaled Nabil e13500
Dickerson, John F. 6551
Dieci, Maria Vittoria e12038
Diehl, Adam e14586
Diehn, Maximilian 3591
Dietrich, Martin Frederik e18224
Dietz, Andrew Charles 10523, 10559
Dimitriadi, Sergey N. e16077
Dinardo, Courtney Denton 7030
Ding, Naiqing e14543
Ding, Xiao e23192
Ding, Zhen-Yu e20531
Diniz, Clarissa P. 5047
Dioun, Shayan M. e18129
DiPerna, Costanzo A. e23126
Dirix, Luc Yves 11530
Distler, Allison 8029
Dittamore, Ryan Vance 5076
Do, Kevin e18245
Do, Khanh Tu TPS2617
Dogan, Mutlu e16040
Dohan, Anthony 3601
Doi, Toshihiko 108
Doll, Marie e21713
Dollar, Krista e12054
Dong, Jun e18287
Donskov, Frede 4578
Dood, Robert e17066
Doolittle, Gary C. 6546
Dorajoo, Sreemanee Raaj e21609
Doroudi, Maryam e18085
Dorsey, Colleen TPS7569
dos Santos, Marcos Tadeu e18510
Dowlati, Afshin 2523
Downey, Robert J. e21687
Drago, Joshua Z. 1013
Drake, Charles G. 5046
Drea, Edward Joseph e18321
Dredge, Keith 3083
Dresler, Hadas 1562
Dreyer, Stephan 4115, e15755
Dreyling, Martin H. 7535
Drilon, Alexander E. 9069
Dronca, Roxana Stefania 11534
Druy, Alexander e22014
Du Bois, Andreas 5501
Dubbink, Hendrikus J. e20055
Dubrovsky, Esther 544
Ducreux, Michel 3567
Dudnik, Elizabeth e18322
Duffaud, Florence 11041
Duffy, Austin G. e15786
Duhoux, Francois P. 1062
Duma, Narjust 2533, 8034
DuMontier, Clark e21548
Dunkel, Ira J. 10506
Dunn, Lara 6081
Dunyak, James e20040
Durani, Urshila e18091
Durborow, Michelle e21625
Dureau, Sylvain 11515
Durm, Greg Andrew 8523
Duska, Linda R. 5532, TPS5601
Dutto, Lorenzo 5073
Dvorak, Tomas e21672
Dwary, Ashish Dutta e13518

E

Eads, Jennifer Rachel 4075
Earl, Helena Margaret TPS591
Economides, Minas P. e17556
Edelman, Martin J. 9056
Edelstein, Kim 10064
Edenfield, William Jeffery 1084, 9553
Edwards, Beatrice Jara-Almonte e18140
Eeles, Ros A. 1520
Egle, Daniel e12061
Ehlers, Hans-Ulrich e21686
Eichler, Christian 582
Eigl, Bernhard J. 5021
Eilber, Frederick C. 11051
El Charif, Omar e18162
El Dakdouki, Yolla e23110
El Dika, Imane Hassan e15614, e15668
El Osta, Badi Edmond 9021
El-Jawahri, Areej 10005
El-Khoueiry, Anthony B. 2552, 3027
El-Rayes, Bassel F. 4077
El-Zeftawy, Hossam A. e17591
Elaidi, Reza-Thierry 10120
Elamin, Yasir e20654
ElChaarani, Bilal e12520
Eldadah, Saleem e18527
Elias, Rawad e21544
Elleray, Rebecca e17037
Ellethy, Tarek 568
Ellis, Peter G. e18189, e21680
Ellis, Peter Michael e20019
Ellsworth, Susannah G. e15760
Elshafeey, Nabil 2016
Elvin, Julia Andrea 5512
Engel-Nitz, Nicole e16539
Eniu, Alexandru E. e13116
Enriquez, Daniel 585, e12012
Enzinger, Andrea Catherine 6575
Eoli, Marica 2065
Epenetos, Agamemnon A. e14062
Epperla, Narendranath 7541
Epstein, Andrew S. e21571
Eraj, Salman Ali e21611
Erba, Harry Paul 7027
Erdem, Dilek e15502
Eriksson, Mikael 11028
Eroglu, Zeynep 9584
Escudier, Bernard J. 4508, 4563
Espejo Freire, Andrea Patricia e22521
Espinosa Fernandez, Jose Rodrigo e12123
Espinoza, Diego e18059
Espinoza-Portocarrero, Miguel Arturo e23205
Esplin, Edward 1577
Estevinho, Fernanda e13039
Ethier, Josee-Lyne e17049
Eto, Masatoshi e16086
Evans, T.R. Jeffry TPS3109
Even, Caroline 6024
Eveno, Clarisse 3565, e15064
Everett, Jessica e13020
Eyzaguirre, Eduardo 11077
Eze, Nnamdi e17520

F

Fadelu, Temidayo 3517
Faivre, Sandrine J. e15676
Fakhoury, Kareem e21629
Fakhrejahani, Farhad 5037
Falchook, Gerald Steven 2579
Faleiro, Ines e15717
Falkson, Carla Isadora e12075
Fallah-Rad, Nazanin e15613, e18297
Fan, Bin 4082
Fan, Frank (Xiaohu) LBA3001
Fan, Pang-Dian 9043
Fan, Yu e23190
Fan, Yun e20538
Fan, Zu-Yan 10107
Fang, Jian e20007
Fang, Mei-yu e23138
Fangusaro, Jason R. 10504, 10543
Farag, Kamel e12584
Farago, Anna F. 11580
Fares, Aline Fusco e16051
Fargnoli, Brenton e18279
Farha, Mark 2535
Farhangfar, Carol J. 6508, e18000
Färkkilä, Anniina 5582
Farrugia, Mark K. e12113
Fasching, Peter A. 1061
Fashoyin-Aje, Lola A. 6518, 6564
Fathi, Amir Tahmasb 7015
Fatiregun, Omolara A. e18198
Fay, Andre Poisl 4583
Febbo, Phillip G. 5074
Federico, Sara Michele 10542

Federman, Noah TPS10577, TPS11626
Fedyanin, Mikhail e15147, e18022
Fegan, Christopher 7518
Felip, Enriqueta 2502
Felip, Eudald e20556
Felix, Gabriela Espirito Santo 1572
Fellman, Bryan M. e14030
Feng, Mei 6030, e17522
Feng, Qin 2595, e20032
Feng, Zheng e20581
Fenioux, Charlotte e16022
Ferguson, Robert 3017
Fernandes, Ancilla e20589
Fernandez, Judith 6526
Ferrandina, Gabriella 5536
Ferrario, Cristiano 1067
Ferrarotto, Renata 6089
Ferris, Robert L. 6020
Ferrufino, Cheryl e15070
Fiala, Mark A. e18061, e21519
Fidler, Mary J. e20592
Fields, Jessica 1533
Fietkau, Rainer 6016
Filon, Olga e13537
Finn, Richard S. 1001, 1039, TPS4143
Fischer-Valuck, Benjamin Walker 4538
Fisher, George A. 4088
Fisher, Maxine D. e17512
Fishman, Sarah 10013
Fitzal, Florian 557
Fizazi, Karim LBA3
Flannery, Kyle e16016
Flaum, Nicola 4114
Fleming, Gini F. 5585
Fleming, Mark T. TPS5088
Fleming, Martin D. 9578
Flinn, Ian 7500
Flores, Claudio J. e20081
Florescu, Marie e20089
Florindi, Francesco e18021
Flowers, Christopher 7537
Foldi, Julia 577
Fong, Lawrence 3004
Font Pous, Albert 5052
Fontana, Maria Chiara 11622
Fontanilles, Maxime e17048
Foote, Jonathan 5544
Forde, Patrick M. TPS8577
Foreman, Leslie e18009
Forero-Torres, Andres TPS1113
Formica, Vincenzo 3552
Forschner, Andrea 9514
Forster, Martin David 5586
Forsythe, Anna e18526
Fortes, Fernanda Paschoal e13101
Foss, Francine M. 7564
Foster, Rebecca Hope 10049
Fountzilas, Christos e15615, e15663
Fournel, Ludovic e18266
Fowler, Nathan Hale 7531, TPS7576
Fox, Bernard A. e14639
Fox, Elizabeth e22013
Franceschi, Enrico 2017
Francini, Edoardo e16515
Francois, Eric 3547
Franke, Aaron J. e19047
Frankel, Arthur E. 9516
Frantsiyants, Elena Mikhaylovna e21066
Fraser, Sarah Anne e20546
Fraser, Steve e12110
Freedman, Rachel A. 1005, 1045
Freites-Martinez, Azael e12533
Frey, Melissa Kristen e13024
Frezza, Anna Maria 11065
Fribbens, Charlotte Victoria 1015
Friedlander, Michael 3013, 5507
Frilling, Andreja e15697
Fritscher, Carlos Cezar e20065
Frosch, Zachary Ak 6530
Fu, Siqing 2066
Fu, Yangyang e20074
Fuchs, Charles S. 4003
Fujimoto, Nobukazu e23098
Fukuoka, Shota 3540
Fukushima, Ryoji 4039
Fulcher, Nicole 5574
Fulk, Kelly e13109
Fundytus, Adam Michael e18080
Fung, Chunkit e21608
Funt, Samuel 4555
Furchtgott, Leon 3528
Furlanetto, Jenny 10068
Furman, Wayne Lee 10534

G

Gabriel, Susan e18568, e19007
Gadgeel, Shirish M. 8504
Gadi, Vijyakrishna e12521
Gaillard, Stephanie 5571
Gajra, Ajeet 9058
Gal, Omer e12046
Galanina, Natalie e23133
Galanis, Evanthia 2023
Gale, Kevin 5051
Gallego, Alejandro e21573
Galli, Giulia e21001
Gallicchio, Lisa e21619
Galligan, Derek e19514
Galon, Jerome 3025, e14615
Galvez, C. Lizette e21552
Gambichler, Thilo e21037
Gambôa, Nathalia e18256
Gamucci, Teresa e12504
Gandara, David R. 9001
Gandhi, Shipra 11565, e14590
Ganesh, Shanthi e14608
Gangadhar, Tara C. 9014
Ganguly, Sandip e15569
Gantke, Thorsten 8045
Gao, Jianjun 5081
Garcia Garcia, Yolanda 5508
Garcia Saenz, Jose Angel TPS1118
García Verdejo, Francisco José e15504
Garcia, Christine Ann e18179
Garcia, Gwenalyn e12022
Garcia, Jessica e23056
Garcia, Jorge A. 5041
Garcia-Alfonso, Pilar e15019
García-Donas, Jesús 5577
Gardiner, Jamie D. 11035
Garg, Mandeep K. e23113
Garlipp, Benjamin 3532
Garmezy, Benjamin e18286
Garrido-Laguna, Ignacio 2511
Garrigos, Carmen e16074, e16076
Garrone, Ornella e12510, e12561
Gartrell, Robyn Denise 9580
Gashonia, Lisa M. 7525
Gasol Cudós, Ariadna e12133
Gaspar, Nathalie 10544
Gasparetto, Cristina 8023
Gasparini, Elisa 1028
Gattoc, Leda Portia A. e17107
Gaudet, Robert E. e18538
Gaudy Marqueste, Caroline 9552, e21042
Gaughan, Elizabeth Mary e21009
Gaut, Daria 9031
Gauvin, Camille e20669
Gavilá, Joaquín TPS594
Gawlik, Anna e16556
Gay, Francesca Maria 8003
Gay, Laurie M. 3039, 4130
Gbolahan, Olumide B. e15748
Gebauer, Gerhard e17080
Geiger, Jessica Lyn 6072
Geller, Alan e21039
Geller, James I. 10537
Geng, Cuizhi e12106
Gennari, Alessandra 1086
Gentille Sanchez, Cesar Giancarlo e18110
Geoerger, Birgit 10524, 10525
George, Daniel J. 4522
George, Thomas J. TPS3629
Gerber, Amanda e12506
Gerber, David E. 2517, TPS8579, e18215
Gerds, Aaron Thomas 7061
Gernone, Angela e16508
Gerratana, Lorenzo 2048
Gerritsen, Winald R. 5525
Gervais, Claire 3055
Getz, Kelly D. 10515
Geukes Foppen, Marnix Heimen 9572, e21062
Geyer, Charles E. 520
Ghatalia, Pooja e16050
Ghate, Ketan 6067, e16025
Ghidini, Michele e15588
Gholami, Sepideh e15161
Ghose, Soumya e16579
Giaccone, Giuseppe 8573
Giannakis, Marios 3036
Gibson, Jordan e18148
Gibson, Todd M. LBA10500
Gil Deza, Ernesto 6594
Gil-Martin, Marta 2555, e17110
Gilbert, Amy e14550
Gilbert, Scott Michael e16010
Gill, Amitoj e19042
Gill, Jennifer TPS7570
Gill, Saar 7509
Gillespy, Kristen 6543
Gillison, Maura L. 6003, 6019, TPS6097
Girardi, Fabio 1558
Giri, Smith e15068
Giri, Upama 7551, 7554
Giri, Veda N. 1516
Giridhar, Karthik 5058
Giron, Philippe e23154
Giskeødegård, Guro Fanneløb e23043, e23095
Glaspy, John A. e21693
Glasspool, Rosalind Margaret 2594
Gleeson, Jack Patrick e13515
Glisson, Shawn Dana 6604
Gluz, Oleg 573
Godfrey, James K. 7508
Goere, Diane 4064
Goerig, Nicole Lydia 2036
Goetz, Matthew P. 1043
Goff, Laura Williams 2593
Goffin, John R. 1548
Gokmen, Ayla e18537
Gokmen-Polar, Yesim 11592
Gokul, Ashni e19018
Goldberg, Stuart L. 10025
Goldfarb, Lucas e20554
Goldinger, Simone M. 9590
Goldlust, Samuel Aaron 2021
Goldman, Jamie e21568
Goldman, Jonathan Wade 9093, e20525
Goldstein, Daniel A. 6601, 9013
Goldstein, David 4109
Goldstein, Jennifer Brooke 4116
Goldvaser, Hadar 549
Goller, Taylor Maxwell 6583
Golota, Janusz e22540
Golshan, Mehra 514
Gomes, Jessica Ribeiro e21044, e23166
Gomez Garcia, Susana e20067
Gomez, Andrea C. e23187
Gong, Inna Y. 10058
Gong, Jun 4544
Gonsalves, Wilson I. 8032
Gonzalez Pagan, Omayra J. e13052
Gonzalez Velez, Miguel 8044, e19525
Goodman, Aaron e14508, e14533
Goodman, Chelain Rae 11524
Gootjes, Elske C. 3553
Gopalakrishnan, Dharmesh e18324, e21586
Goparaju, Krishna e18092
Gordon, Brittaney-Belle Elizabeth 6517
Gordon, Joshua Ian e14536
Gordon, Noa 6624
Gore, Lia 10511
Gormley, Nicole 2541
Gornick, Michele Caroline e13016
Gorzelitz-Liebhauser, Jessica e21582
Gosain, Rahul e21076
Goudot, Francois-Xavier e21505
Goulart, Bernardo H. L. 6528
Gounder, Mrinal M. 11001, 11058
Gourley, Charlie 5533
Gowen, Michael 9559
Gowin, Krisstina L. e21684
Goy, Andre e19030
Goyal, Gaurav 8050, 9044
Gradishar, William John 1004
Graetz, Ilana e12044

Graham, Donna M. 4030
Graillon, Thomas 2011
Gramatzki, Dorothee 2038
Grande, Enrique 5016
Grande, Mathilde 6623
Grankina, Anastasia e23074
Grant, Robert C. e15784
Grassi, Paolo TPS4601
Gravel, Mathieu e20579
Gray, Jhanelle Elaine e20672
Gray, Stacy W. 1517
Graziani, Silvia Regina e21628, e21631
Green, Daniel M. 10567
Greenlee, Heather e13097
Greenup, Rachel Adams 6532
Greer, Joseph 10022, 10055
Gresham, Gillian 6571
Greto, Daniela e22530, e22531
Gridelli, Cesare 9002
Grigg, Claud 9082
Grimison, Peter S. TPS4592
Grisham, Rachel N. TPS5610
Grivas, Petros 4534
Groen, Harry J.M. 8502
Grohe, Christian e14526, e14528
Groisberg, Roman 2582, 2588
Grommes, Christian 7515, 7533
Gronchi, Alessandro 11061
Gross, Andrea M. e14070
Grothey, Axel 3551, TPS3619
Grover, Natalie Sophia 7548
Grunwald, Michael Richard 7039
Grupp, Stephan A. 7047
Gruslova, Aleksandra e14619
Gu, Jin 3610
Gu, Zhenyu e23140
Gubernick, Lindsay e13022
Gucalp, Ayca 1102
Guddati, Achuta Kumar 6578, e18101
Guevara, Andres e15565
Guibert, Nicolas Marie 11529
Guirgis, Helmy M. e20629, e20644
Gulati, Shuchi e17500
Gulhati, Pat e15799
Gulley, James L. 3006, 9086
Gumus, Mahmut e15028
Guo, Rong e20049
Guo, Wei e21021
Guo, Weijian e15066
Gupta, Abha A. 10047
Gupta, Kanika e16052
Gupta, Sameer e12583
Gupta, Sumit 10565, 10573
Gurman, Gunhan e18518
Guskova, Nailya e17018, e17020
Gutierrez, Martin e20622
Gutierrez-Barrera, Angelica M. e12057
Gutschenritter, Tyler e17587
Gyawali, Bishal e14036
Gyergyay, Fruzsina e16522
Gylfe, Alexandra E. e23118
Gyorffy, Balazs 1096

H

Ha, Hyerim 11542
Haaga, John e23176
Haas, Michael 4108
Habib, Nabil e16531, e20587
Haddad, Robert I. 6009
Hagiwara, May e18330
Hahm, Myung-Il e13045
Hahn, Noah M. 4525
Haider, Ahmad 5085
Haigentz, Missak e14077
Hainsworth, John D. 9073
Hakim, Nausheen Naila e18252
Halford, Sarah E. R. 2022, 2516
Hall, Evan Thomas 1528
Hall, Michael J. 1587, e13119
Halperin, Daniel M. e15693
Halwani, Ahmad Sami 7526
Ham, Janneke 6075
Hamid, Anis e21512
Hamid, Omid 3012, 6010
Hammad, Nazik e18213
Hammel, Pascal e15718
Hamrick, James e18278
Han, Baihui 9053
Han, Boram e15778
Han, Xuesong 6521
Han, Ying e23048
Hann, Christine L. TPS2598
Hansen, Aaron Richard 2570
Hansra, Damien Mikael 6568, e21671
Hao, Daxuan e15510
Haque, Sulsal e17572
Harb, Wael A. 2576, TPS3110, TPS3115
Harbeck, Nadia 504, e21701
Harbison, Richard A. e17517
Harmon, Gil Edward e14088
Harris, Joshua e15704
Harris, Tamira e18225
Harrison, Claire N. 7001
Harrison, Douglas James e22019
Harshman, Lauren Christine 4585, TPS4596
Harter, Philipp 5500
Haruna, Yoshimichi e15665
Harvey, R Donald e14035
Hashemi Sadraei, Nooshin e23083
Hashibe, Mia 10073
Hashida, Hiroki e15015
Hashimoto, Kenji TPS3112
Hassan, Bilal e13501
Hassel, Jessica Cecile 9570
Hassett, Michael J. 6621
Hata, Akito 9034
Hathaway, Amanda Redden 4589
Haugnes, Hege Sagstuen e16047
Hawkins, Makenzie L. 10074
Hawley, Sarah T. 6500
Hayakawa, Nozomi e16090
Hayashi, Hideyuki e13115
Hayashi, Takuo 11600
Hayes, Sandra Christine 10067
Hazenberg, Mette D. 7009
He, Yue e17002
Hearn, Jason W.D. 5050
Hecht, J. Randolph 4111
Heeke, Arielle Lutterman 1502
Hegde, Aparna Madhukeshwar e20624
Hegde, Meenakshi 10508
Hegde, Upendra P. e14603, e17534
Hehlmann, Ruediger 7049
Heilbroner, Samuel P. 2590
Heinrich, Bernhard 2056
Heinrich, Michael C. 11011, e22508
Heinzelmann-Schwarz, Viola A. 5563
Heitz, Florian 5521, 5555
Heller, Glenn 5007
Hellmann, Matthew David 8503, 9015
Henderson, Tara O. 10566
Hendifar, Andrew Eugene e15700
Henick, Brian S. e20652
Hennenfent, Kristin L. e15658
Heong, Valerie 2550
Hepp, Julia e14626
Herbst, Roy S. 9090
Herden, Jan e16577
Hermann, Frank e14096
Hermens, Rosella 6570
Herms, Florian 9535
Hernandez Blanquisett, Abraham e17104
Hernandez Cruz, Irwin Alejandro e17045
Hernandez Torres, Catalina 10031
Hernando-Cubero, Jorge e15603
Herrera, Marytere e15535
Herrmann, Tara e20663, e21669
Hershman, Dawn L. 10093
Herskovic, Arnold M. e15514
Hertz, Daniel Louis 1063
Hess, Dominique TPS2621
Hess, Viviane LBA10002
Hibbitts, Emily 10528
Hicks, Krystal e15710
Hierro, Cinta 2581
Higano, Celestia S. 5042
Higgins, Kristin Ann 8565
Higham, Christine e14067
Hile, Elizabeth TPS10127, e21640
Hiley, Crispin T. TPS9099
Hillier, Kirsty e22008
Hillman, Robert Tyler 5509
Hiltermann, Thijo Jeroen Nicolaas 3030, e14505
Hingorani, Sunil R. 4008
Hinkel, Jennifer M. 6549, e18298
Hinrichs, Christian S. 3009
Hiraki, Masayuki e14053
Hirata, Kenro 1542
Hirsch, Heather Anne 11602
Hirschey, Rachel e21584
Hitron, Matthew e20001
Hittson, Lauren 10546
Hlubocky, Fay J. 10115
Ho, Alan Loh TPS2618
Ho, Gwo Yaw 5583
Hobbs, Evthokia 10105
Hobbs, Gabriela e18561
Hochberg, Jessica 10532
Hochhegger, Bruno e20083
Hoffman, Kenneth Robert e18192
Hoffman, Steve e14060, e16540
Hofheinz, Ralf TPS4133
Hofman, Paul e20500
Hofstatter, Erin Wysong 1522
Hofstraat, Hans e16573
Hogg, David 9522
Hohenberger, Peter 11042
Holch, Julian 3586
Hollebecque, Antoine TPS3626, 5504
Holmskov Hansen, Karin e20014
Holsey Gramkow, Mathias e15078
Holzem, Alessandra e20059
Homicsko, Krisztian 9571
Hong, David S. 2507, TPS3098
Hong, Min Hee 4051
Hong, Sook-hee e20638
Hong, Theodore S. 4118
Hool, Kristina e15170
Hooper, Ellen e22002
Hope, Tom 5057
Hopkins, Thomas e18246
Hoppmann, Anna Lynn 10514
Horcasitas, Darling J. e23218
Horii, Rie 1036
Horn, Leora TPS8578, TPS8584
Hortobagyi, Gabriel N. 1038
Horvath, Lisa 5055
Hoskin, Peter LBA10004
Hosokawa, Shinobu e20677
Hosry, Jeff 7553
Hosseini, Ava e13048
Hou, Li e21696
House, Linda S. e15583
Howard, Alexander e13079
Howard, Candace M. e13544
Howard, Scott C. e18025
Hsieh, Chih-Yi e15671
Hsu, Joy C. e20616
Hsueh, Eddy C. 9573
Hu, Bei e19019
Hu, Mingyue e15741
Hu, Wei e13034
Hu, Weiheng e20574
Hu, Xingsheng e20642
Hu, Yi e15554, 15765
Hu, Yongxian e14549
Hu, Zishuo Ian e15791
Hu-Lieskovan, Siwen 9558
Huang, I-Chan 10570, e21563
Huang, Jing e15572
Huang, Na e15026
Huang, Ping e21617
Huang, Po-Hsiang e15656
Huang, Ta-Chen 4042
Huang, Xin 1058
Huang, Xiu e13104
Huang, Yecai e17521
Huberty, Jennifer e21704
Hudgens, Stacie e15132
Hudson, Jessica Lynn 8526
Huffman, Brandon M. e15797
Hughes, Elisha 1579
Hughley, Raymond Wesley e14537
Hui, David 10003, 10085
Huijberts, Sanne TPS3622
Huillard, Olivier e17594
Humeniuk, Michael Sandon e16532
Hummert, Shelly E. e18268
Hung, Chia-Yen e12009

Hunter, Mark e17027
Hunter, Sarah e20678
Huntington, Scott F. 6593
Huober, Jens Bodo 512
Hurvitz, Sara A. e18196
Huselton, Eric 7044
Hussain, Maha 5001, 5019
Hussain, Muhammad Azam 4535
Hussain, Syed A. 4527
Hussaini, Azra e16538
Husson, Olga 1567
Hwang, In Gyu 3605
Hwang, Jessica 6503
Hwang, Larn e15065
Hwang, Victoria e17506
Hwang, William L. 9079
Hyman, David Michael 2004, LBA2501

I

Iachetta, Francesco 2567
Iafolla, Marco Adelmo James e21064
Iams, Wade Thomas 8571
Ibraheem, Abiola Falilat e18126
Ichida, Kosuke e23216
Ichikawa, Hiroshi e15592
Idbaih, Ahmed 2034, e13510
Iddawela, Mahesh Y. e21036
Idos, Gregory 1523, 1525
Iglesias, Jose Luis TPS3105
Ikeda, Masafumi TPS4144
Ileana Dumbrava, Ecaterina Elena 1524, 11567
Ilhan, Aysegul e15050
Ilhan, Osman e18530
Ilie, Marius e20632
Ilowite, Maya 6562
Imianitov, Evgenii 9040
Imoto, Shigeru e12094
In, Gino Kim e21063
Inagaki, Daisuke e15109
Inci, Guelhan e18255
Infante, Jeffrey R. 2574, 3571
Ingham, Matthew TPS11082
Ingles Garces, Alvaro Henrique TPS2601, TPS2613
Iniguez-Ariza, Nicole M. 6087
Innocenti, Federico 3504
Inocencio, Rowena Torres e23092
Inoue, Akira e21715
Ionescu, Dana e14011, e14012, e22536
Iqbal, Muhammad e21527, e21528
Iqbal, Syma 4009
Irie, Hanna e23070
Iruku, Praveena e18207
Isaac, Krista e19043
Isakoff, Steven J. TPS1121, TPS1126
Isenalumhe, Leidy Lismeri 7542
Ishiguro, Megumi 3611
Ishikawa, Toshiaki e15155
Islam, Mohammad Ariful 11582
Islam, Prioty 7557
Ismail, Hibah e15604
Ismaila, Nofisat e18211
Issa, Ghayas C. 7037
Itahashi, Kota e14037
Italiano, Antoine 11002
Itani, Yoshio e17074
Ito, Ken-ichi e12107
Ito, Kimihiko e17065
Ito, Shuhei 11531
Ivanov, Olga e13004
Iveson, Timothy 3502
Iwamoto, Mitsuhiko e14045
Iwase, Toshiaki 584
Iwata, Tomomi Nakayama 1031
Iyengar, Arjun e18112
Iyengar, Neil M. 1037
Iyer, Gopa 4511
Iyer, Renuka V. e15641
Iyer, Veena 8524, e19533
Iznaga Escobar, N. E. e15787
Izsak, Allison 9534

J

Jabbarian, Lea Jasmina e21501
Jabo, Brice e15575
Jackisch, Christian e12547
Jackson, Graham H. 8009
Jackson, Sarah A. 1518
Jacobs, Bart e15127
Jacobs, Jamie M. 10023
Jacobs, Linda A. e21604
Jacques, Flawendjee Djaweelentz e13061
Jafri, Syed Hasan Raza 1575
Jafri, Syed Imran Mustafa e18104
Jaganathan, Hamsa e18271, e18280
Jagannath, Sundar 8040
Jagsi, Reshma 10052
Jain, Apurva 4086
Jain, Nitin 7522
Jain, Prantesh e20646
Jain, Rishi e21700
Jain, Rohit K. e16544
Jain, Sarika 1026
Jain, Shanu 3570
Jaiswal, Deepna Deepak e15146
Jakopovic, Marko e20518
Jaksa, Ashley 6545, e18052
Jakubowiak, Andrzej J. 8000
Jalali, Ali 8538
Jalali, Rakesh 2063
James, Alena Talia e18277
James, Nicholas D. LBA5003
Jamshed, Saad e21695
Janelsins, Michelle Christine 10014
Jani, Prashant Mukesh e15115
Janikova, Katarina e17060
Janjigian, Yelena Yuriy 4014
Jankilevich, Gustavo e16059
Janku, Filip 2515, 11609
Janni, Wolfgang 1047
Janowitz, Tobias e14074
Jansen, Yanina 9539, e21072
Janssen, Sanne e21077
Jaroszewski, Dawn E. e15567
Jarry, Anne e23087
Javed, Muhammad Ahsan e15774
Javle, Milind M. 4076
Jayaram, Anuradha 5071
Jayson, Gordon C. 11521
Jean-Pierre, Pascal e18088
Jensen, Benny Vittrup e15060
Jensen, Lars Henrik e21555
Jentzsch, Madlen 7042
Jeon, So Yeon e21699
Jeong, Jae-Hwan e23058
Jeurkar, Chetan 10015, 10086
Jha, Gautam Gopalji 3066
Jhaveri, Jaymin 2031
Jhaveri, Tulip A. e14017
Ji, Jiafu e15519
Ji, Shengjun e13545, e15725
Jia, Ruinuo 4063
Jiagge, Evelyn Mawunyo 1101
Jiang, Ben-Yuan 9022
Jiang, Di Maria 3600
Jiang, Shan e12589
Jimenez, Rachel B. 10053
Jin, Chaoyu 2568
Jin, Chunzi Jenny e16551
Jin, Jing e15006
Jin, Michael C. 7507
Jin, Shenying e15609
Jin, Ying e20576
Jin, Zhaohui e15030, e15703
Jing, Yu e15542
Joerger, Markus TPS2602
John, Elizabeth S. e21531
John, Preethi e12071
Johns, Claire e15758
Johnson, Benny 3556, e15045
Johnson, Connor e18275
Johnson, Douglas Buckner 9517, 9536
Johnson, Eric e23188
Johnson, Martin e20536
Johnson, Melissa Lynne 9529
Johnson, Skyler Bryce e18175
Johnston, Emily E. 10574, e18047
Johnstone, Cameron e21078
Joly, Florence 5538, TPS10126
Jonasch, Eric 4513, 4516
Jones, Clare Frances 6606
Jones, Jennifer M. 6584
Jones, Maris S. 550
Jones, Meredith e18203
Jones, Robin Lewis TPS11081, e22516
Jones, Veronica e18070
Jonker, Derek J. e14637
Jordan, Emma J. e14028
Jordan, Emmet 4102, e15728
Jorgensen, Jennifer 1589
Joseph, Ranjit e18539
Joseph, Vijai 1529
Joshi, Amit 6018
Joshi, Monika 4547
Joshua, Anthony M. 2562, TPS5095
Joy, Anil A. e12534
Judson, Ian Robert 11004
Jung, Ahrang e16027
Jung, Hyun Ae e19516
Jung, Kyung Hae 1082
Jung, Kyungsuk e13025
Jung, Sora e21664
Juratli, Tareq A. 2047
Juric, Dejan TPS3104
Justiniano, Carla Francesca e15139, e18084
Jørgensen, Jan Trøst e15600

K

Kabraji, Sheheryar Kairas 11579
Kachesova, Polina S. e23160
Kadakia, Kunal C. e21618
Kaderbhai, Coureche Guillaume 3026
Kadia, Tapan M. 7017
Kadowaki, Shigenori 4041
Kaehler, Katharina C. e21615
Kagamu, Hiroshi 11525
Kaidarova, Dilyara e17008
Kailasam, Karthik 6534, e13114
Kaira, Kyoichi e20615
Kaiser, Adeel 5082
Kaito, Hidekuni e14007
Kajiura, Shinya e21665
Kakizawa, Nao e23202
Kaklamani, Virginia G. e12576
Kalinsky, Kevin TPS1112
Kallich, Joel D. e18157
Kallinteris, Nikoletta Lea 11603
Kalra, Maitri 4558
Kam, Audrey E. e18146
Kamada, Yoshihiko e12084
Kamath, Suneel Deepak e23023
Kambhampati, Swetha e15767
Kamen, Charles Stewart 10021
Kamihara, Junne 1581
Kamran, Sophia C. e15165
Kanaloupitis, Dimitra Konstantinos e14607
Kanao, Kent e16581
Kanapuru, Bindu 2539, e14024
Kane, Michael Joel 6617
Kang, Hyunseok 6088
Kang, Irene e12558
Kang, Jin 9063, 11591
Kang, Kai 11552
Kang, Min 6063
Kang, Xiaozheng e15525, e23069
Kang, Yoon-Koo TPS4138
Kanjanapan, Yada TPS5608
Kanji, Zaheer S. e15771
Kankeu Fonkoua, Lionel Aurelien e15582
Kann, Benjamin H. e15162
Kannarkatt, Joseph e23156
Kantarjian, Hagop M. 7012
Kantor, Guy e22501
Kaplieva, Irina V. e23010
Kappeler, Christian e22509
Karaboue, Abdoulaye e14082
Karaca, Mustafa e12018
Karachaliou, Niki 11504
Karadurmus, Nuri e19027
Karagiannis, Tom e18138
Karam, Dhauna e15096
Karamouzis, Michalis e14554
Karampeazis, Athanasios e15053
Karim, Safiya 6591, e15148
Karn, Ambuj e18042
Karp, Daniel D. 2519
Karri, Saradasri e20582
Karthaus, Meinolf 10101
Karzai, Fatima 5026
Kasamatsu, Yuka e17075
Kasangian, Anaid Anna e12087

Kaseb, Ahmed Omar 4083, e15662
Kasi, Anup e15744
Kasner, Margaret T. 7043
Kasuga, Akiyoshi e15768
Kasumova, Gyulnara G. e15669
Kataoka, Kozo TPS3633
Kato, Ken 4069
Kato, Shumei 11511, 11578
Kato, Terufumi 9077
Kato, Tomoaki e15705
Katsuda, Masahiro TPS4153
Katsumata, Kenji 3549
Katz, Daniela e12512
Katz, Matthew H.G. 4125, TPS4151
Katz, Steven J. e18145
Kaufman, Howard e14557, e21065
Kavalerchik, Edward TPS2597
Kavecansky, Juraj e21040
Kawashima, Yosuke e20583
Kawazoe, Akihito 4040
Kaye, James A. e13080
Kazan, Eyad e17553
Kazlow, Esther 1535
Keating, Karen N. e18123
Kebriaei, Partow 7007
Kebudi, Rejin e22009
Keegan, Niamh M. 583
Keegan, Theresa 6565, e18037
Kegel, Thomas 4552
Keizman, Daniel e16588
Kell, Malcolm R. e21577
Kelley, Michael J. 6507, 8544
Kelley, Robin Kate 4073, 4097
Kelly, Ciara Marie 11010, 11039
Kelly, Deirdre e20557
Kelly, Karen 3059
Kelly, Ronan Joseph 4060, TPS4131
Kelsen, David Paul e15010
Kemal, Yasemin e17538
Kempf, Emmanuelle e14023
Kendra, Kari Lynn e21014
Kenmotsu, Hirotsugu 9078
Kennecke, Hagen F. 3602
Kennedy, Andrew S. e15040
Kenzik, Kelly 10011
Kerber, Anne e14001
Kernan, Nancy A. 10513
Kerns, Sarah L. 10075
Kerr, David e20071
Kerr, Keith 8516
Kesari, Santosh e14004
Kessler, Elizabeth Riley e16510
Keung, Emily TPS9594
Khagi, Yulian e14504
Khalaf, Daniel 5036
Khalid, Arifa e22004
Khan, Muhammad Saad e13033
Khan, Omar Farooq 10084
Khan, Saad A. 9051
Khan, Sajid A. 3588
Khan, Seema Ahsan 534
Kharchenko, Evgeniya Vladimirovna e19050
Khashab, Tamer e19040
Khattri, Arun 6054
Khodova, Kristina e23158
Khomiakov, Vladimir e15532
Khorana, Alok A. 6557
Khozin, Sean 11596
Khudayar, Humnah e13087
Khunger, Monica 11566, e20647
Khushalani, Nikhil I. 9547
Khushman, Moh'd M. e15730
Kibel, Adam S. e16516
Kiesewetter, Barbara e18151
Kieszkowska-Grudny, Anna e21550
Kikuchi, Eiji 4545
Kikuchi, Hiroshi e23004
Kilbridge, Kerry L. e18222
Kilickap, Saadettin e12517
Kim, AeRang TPS10579
Kim, Alexander Y. e15745
Kim, Beom Kyung e15678
Kim, Byung Moon e15620
Kim, Chul e20545
Kim, Clara H. e20033
Kim, Edward S. TPS9103
Kim, Gun Min TPS587
Kim, hee Jeong 517
Kim, Hee Kyung e20584
Kim, Hye Sook 8564
Kim, Hyo Song 1571
Kim, Jee Hyun e21539
Kim, Jeong-Oh e20610
Kim, Ji-Yeon 1041, 10108
Kim, Jin Won e21540
Kim, Jong Gwang e15590
Kim, Kevin e21033
Kim, Ki Hyang e21530
Kim, Lyndon J. e13519
Kim, Min Ji 10027
Kim, Min Kyu e13000
Kim, Rebecca H. 3011
Kim, Richard D. 3081, 4016
Kim, S. Rim 3514
Kim, Se Hyun 10041
Kim, Seo-Hyun e20594
Kim, Seung Tae e14622, e15686
Kim, Sooha e18232
Kim, Su Mi 4045
Kim, Sun Young 3606
Kim, Tae Hyun e12540
Kim, Tae Won 3561
Kim, Won Seog 7532
Kim, Yeul Hong 10008
Kim, Yong-Man e13046
Kim, Youn H. 7517
Kimmick, Gretchen Genevieve TPS10128
Kinders, Robert J. 11588
Kindler, Hedy L. 8557
King, Jennifer C. e20671
King, Rebecca L. 7547
Kinoshita, Takayuki e12098
Kirchberger, Michael Constantin e21024, e21035
Kirschbrown, Whitney Paige 2525
Kirstein, Martha e15625
Kit, Oleg I. e15153
Kit, Oleg Ivanovich e23180
Klabusay, Martin e19006
Kleckner, Ian 10095
Kline, J Bradford e23082
Klinkhammer-Schalke, Monika e18200
Klug, Lillian Rose 11044
Knapen, Lotte Marieke 9540
Knipprath-Meszaros, Alexandra Maria 5515
Knoerl, Robert e21710
Knop, Stefan 8001
Ko, Beom Seok e12093
Ko, Heidi Chwan e18050
Kobayashi, Keigo e20577
Kobayashi, Yoshie 11614
Kobrinski, Daniel Allen 7558
Koch, Christine e15029
Koeda, Keisuke 4010
Koehne, Guenther 8016
Koenig, Kristin Lynn e15168
Koga, Noriko e16584
Koganemaru, Shigehiro e14032
Kogawa, Takahiro TPS1116
Kogiku, Ai e17064
Kohli, Manish 5053
Kolberg, Hans-Christian e12090
Kolesnikov, Evgeniy N. e15093, e15111
Kolitz, Jonathan E. 7036
Kolyadina, Irina Vladimirovna e12121
Komarnitsky, Philip B. TPS8583
Komarov, Yuriy 11075
Komarova, Ekaterina e17530
Komatsubara, Kimberly Mayumi TPS9597
Konda, Bhavana e17580
Kong, Feng Ming 4080, 8572
Kong, Yan 9589
Konner, Jason A. 5572
Kono, Scott Arthur e21553
Konstantinopoulos, Panagiotis A. TPS5615
Kopetz, Scott 3505, 3548
Kopp, Lisa M. 10519
Korn, Wolfgang Michael 11575
Kornelsen, Emily e21677
Korphaisarn, Krittiya 3590
Kosaka, Takeo e14010
Koscielniak, Ewa 10527
Koshkin, Vadim S. 4529, 4586
Kosmin, Michael e12544
Kostenko, Anna e20596
Kota, Karthik Joshua e23047
Kotani, Daisuke e15570
Kotecha, Rupesh 2071
Kotecki, Nuria 11052
Kothadia, Sejal e21621, e21642
Kothari, Prachi 10552
Kothari, Shalin e16513
Kotoula, Vassiliki e13055
Kottorou, Anastasia E. e15130
Kourelis, Taxiarchis e19530, e19534
Kovic, Bruno 6574
Kowalkowski, Marc e18303
Koyama, Junji e20063
Kozaric, Amina Kurtovic e18549
Kozlova, Larisa e13542, e13543
Kozono, David E. 8546
Kraft, Ira Lignugaris 10540
Kraj, Leszek e15756
Kraja, Shuajp e14633
Kramer, Kim 10545
Kratz, Jeremy D. e15054
Kravtsova, Oksana E. e17036
Krendyukov, Andriy 10116
Kris, Mark G. 9039
Krishnamurthy, Anuradha 2587
Krishnan, Subha e23153
Krishnasamy, Shalini R. e12570
Kristeleit, Rebecca Sophie 2532
Kruithof-de Julio, Marianna e16576, e23135
Krzyzanowska, Monika K. e18269
Ku, Geoffrey Yuyat 4025
Ku, Kimberly Peihsi 5045
Kuba, Sayaka e21668
Kubo, Toshio e20057
Kuboki, Yasutoshi TPS3623
Kubota, Kaoru 8534
Kuehnle, Elna e18132
Kuhl, Christiane K. 2528
Kuhlman, Patrick 10043
Kujtan, Lara Ann 8529, e23121
Kulangara, Karina e14584, e14589
Kulkarni, Girish S. e16003
Kumar Tyagi, Nidhi e12030
Kumar, Rajesh e17061
Kumar, Rohit e21692
Kummel, Sherko 555
Kundranda, Madappa N. e14524
Kunk, Paul Raymond e15650
Kunte, Siddharth e15736
Kunthur, Anuradha e16023
Kunwor, Ranju 9555
Kurian, Allison W. 541, 1576
Kurk, Sophie 10087
Kurkul, Charles Vincent e15624
Kurokawa, Tetsuji e17025
Kurzrock, Razelle 6086
Kushner, Carolyn J. e12103
Kushwaha, Anne C. 1507
Kusick, Karissa N. e22023
Kusumoto, Tetsuya e15540
Kutilin, Denis S. e23094
Kutluk, M. Tezer e22015
Kutsevalova, Olga Yu. e14084
Kuziora, Michael 11538
Kvammen, Oivind 4553
Kwa, Maryann J. TPS1124
Kwan, Marilyn L. 4543
Kwapisz, Dorota Malgorzata e21028
Kwok, Gin Wai e15049
Kwon, Daniel e15689
Kwong, Dora Lai Wan e17555
Kyi, Chrisann TPS3114

L

Labomascus, Stephanie e14530
Lachowiez, Curtis Andrew 7048, 7055
Lacouture, Mario E. e14064
Laderian, Bahar e13023
Ladwa, Rahul e21020, e21027
Laes, Jean-Francois e23097, e23099
Laetsch, Theodore Willis 10510
Lafay-Cousin, Lucie 10505
Lafeuille, Marie-Helene e18529
Lage, Daniel E. 6504
Lai, Wei-Chu Victoria 9029, 9071
Laing, Lance G. e23203
Lakhani, Nehal 2524
Lakshman, Arjun 8014, 8038

Laktionov, Konstantin K. e14593
Lalani, Aly-Khan A. 4573
Lambertini, Matteo LBA10066
Lamble, Nina Mosallaei e16501
Lammers, Austin J. e20621
Lamy, Pierre-Jean e17059
Lancet, Jeffrey E. 7031, 7035
Landau, Danny e19045
Landre, Thierry e15034
Lang, Benjamin Joseph 7060
Lang, Frederick F. 2002
Lang, Jin Yi 5530, e18136
Langabeer, Denise Manon 5565
Langer, Corey J. 9059, 9066
Lanman, Tyler A. e13546
Lansigan, Frederick e18086
Lara, Primo 4515
Larkin, James M. G. 9556
Larsen, Stig Einride e12581, e15708
Lassen, Ulrik Niels TPS2605
Lassman, Andrew B. 2003
Lathan, Christopher S. 6553
Latif, Nida e18223
Latosinsky, Steven e12104
Lattanzi, Michael 9577
Lau, Loretta 10539
Lau, Sally C. e18030
Lau-Min, Kelsey S. 6592, e18039
Laubach, Jacob 8002
Laubli, Heinz Philipp e14523
Lauer, Richard C. e16582, e16583
Lavoie, Jean-Michel e20062
Lawsin, Catalina Rosario e21597
Lazutin, Yuriy N. e20064
LE Goux, Constance e16029
Le Rhun, Emilie 2076
Le Saux, Olivia 1052
Le Tourneau, Christophe 6021, 6080
Le, Tri Cao e16070
Le-Rademacher, Jennifer e21545
Leal, Alexis Diane 3554, 3558
Leamon, John e13099
Lebellec, Loic 11024
LeBlanc, Thomas William 10054
Ledermann, Jonathan A. 5506, 5518
Ledet, Elisa M. e16548
Lee, Banghyun e17013
Lee, Belinda 4101
Lee, Chee Khoon 1104
Lee, Dylan E. e14072
Lee, Hyun Woo e15558
Lee, Jae Kwan e14623
Lee, James Chi-Chiang 3072
Lee, James J. 3054, TPS3099
Lee, Jeeyun 4024, e15610
Lee, Jenny HJ 9546
Lee, Jessica 1503
Lee, Jieun e23019
Lee, Jin Hwa e20051
Lee, John J. 11510, e15118
Lee, Jung-Yun e17015
Lee, Kris M. e13015
Lee, Larissa Janeen 5599, e17116
Lee, Margaret e12515, e15106
Lee, Michael Sangmin e15120
Lee, Nancy Y. TPS6093
Lee, Rebecca 9583
Lee, Ru Min e13056
Lee, Sang-Woong 4029
Lee, Shin Yin e15090
Lee, Soo Jung 11548, e15126
Lee, Steve Young e18244
Lee, Valerie TPS4154
Lee, Victor HF e20521
Lee, Won-Chul 8541, e20077
Lee, Yeh Chen e18024
Lee, Yun-Gyoo e20661
Leeman, Jonathan Eric 6029
Lefebvre, Alexandra e13005
Lega, Iliana Carolina 10558
Leger, Paul Denis 9084
Legoux, Jean-Louis 3550
Leighl, Natasha B. 9011
Leleu, Xavier 8004
Lemdani, Katia e14540
Lentini, Nicole e22024
Lentzsch, Suzanne 8036
Lenz, Georg 7536
Lenz, Heinz-Josef 3511
Leo, Patrick e16559
Leon-Ferre, Roberto Antonio 533
Leonardi, Giulia Costanza 9081
Leone, Jose Pablo 1070
Leone, Julieta 1069
Leopold, Christine 1029, 10072
Lerner, Andrew 11615
Lerner, Seth P. 4500
Lesluyes, Tom 11067
Lesokhin, Alexander M. TPS3102, TPS8051
Lesser, Glenn Jay e21643
Lestingi, Jean Felipe Prodocimo 5018
Leung, Abraham C.F. 9550
LeVasseur, Nathalie 581
Levi, Francis 2569
Levin, Victor A. TPS2081
Levine, Oren Hannun 10024
Levy, Mia Alyce 6533, e18182
Lewin, Jeremy Howard 4559
Lewis, Spencer B. e13511
Lheureux, Stephanie 5522
Li, Ailin e14103
Li, Allen e20586
Li, Bin 4036
Li, Bo e12079
Li, Bob T. 2508, 8510
Li, Daneng e21523
Li, Dawei e15123
Li, Edward C. 6618
Li, Fang e20086
Li, Haoran e16500
Li, Hongli e15508
Li, Jin 3508
LI, Kai e20530
Li, Lingyu e15038
Li, Longjiang e17561
Li, Meng-Xia e14582
Li, Min e15125
Li, Qingdi Quentin e16024, e16030
Li, Rutian e20535
Li, Shaoying 7559
Li, Sophia S. e16534
Li, Su e12567
Li, Tao 4033
Li, Wen-Feng e20636
Li, Xin e12571
Li, Xinyi e13044
Li, Yi e17562
Li, Yintao e23006
Li, Yuan e15587
Lian, Bin 9569
Liang, Hu 6006
Liang, Li e20529
Liang, Spencer 3074
Liang, Wenhua 8540
Liang, Zhiyong TPS9104
Liao, Wangjun e15556
Lichterman, Jake N. e23012
Liedtke, Cornelia 560
Lim, Chiew Woon 11069
Lim, Howard John e13113
Lim, Joline Si Jing 2573
Lim, Kian-Huat 2553
Lim, Myong Cheol 5520
Lim, Soon Thye 7549
Lim, Soyi 5527
Lim, Stephanie Hui-Su e15081
Lin, Chia-Chin e21657
Lin, Daniel 1569, e18060
Lin, Emily Pei-Ying e20087
Lin, Frank Po-Yen 6596, e18137
Lin, Gen e20507
Lin, Jeffery Shyh-Jye e16089
Lin, Jeffrey e16017
Lin, Jennifer H. e16525
Lin, Jianqing e16058
Lin, Jin-Xiang e15031
Lin, Li e15550
Lin, Minglin e15647
Lin, Nancy U. 2074
Lin, Po Lin e23175
Lin, Po-Ju 10007
Lin, Richard Jirui 10039
Lin, Steven H. 3064
Lin, Ze-xiao e15634
Lindeman, Geoffrey John 1044
Lindsay, Daniel Paul 11533
Lindsay, James 6620
Litière, Saskia 2534
Litton, Jennifer Keating TPS595
Liu, Bingshan e19518
Liu, Binliang e21606
Liu, Chia-Jen e15119
Liu, David 4512
Liu, Dazhi 10575, e18228
Liu, Fangqi e15051
Liu, Fei-Fei e12048
Liu, Guizhong e23079
Liu, Hsingjin Eugene e14078
Liu, Jilong 1588
Liu, Jingdong e15544
Liu, Joyce F. 5535
Liu, Laiyu e20573
Liu, Shiru Lucy 3613
Liu, Stephen V. 9092
Liu, Wenli 10078
Liu, Xi e14095
Liu, Xiao-Ran 1105, e12542
Liu, Xinyang 4052, e21059
Liu, Yichu 2045
Liu, Ying e12117, e12136
Liu, Yingmiao 11546
Liu, Yong e13541
Liu, Yong-Mei e20571
Livingston, John Andrew 11019
Lo Monaco, Silvia 11611
Lo Re, Giovanni e14621
Locatelli, Franco 10530
Locke, Frederick Lundry 3023, 7512, TPS7572
Lockwood, Matthew Blake e18281
Lode, Holger N. 10548
Loehrer, Patrick J. 8520
Loges, Sonja 7059
Loh, Kah Poh 6536, 10019
Loibl, Sibylle 571, TPS1115, 3062
Lokhandwala, Tasneem e18314
Lomauro, Timothy A. e21562
Lombardi, Giuseppe TPS2085
Long, Georgina V. 9505, 9508
Longcor, Jarrod e14087
Lonial, Sagar 8028, TPS8052, TPS8055
Lontos, Konstantinos 8039
Looney, Timothy e14518
Loparco, Dario e12016
Lopategui, Diana Maria e21587
López Saucedo, Raúl Alejandro e17586
Lopez, Rafael e18260
Lopez-Martin, Jose A. TPS9599
Lopez-Pousa, Antonio 6014
Lorandi, Vinicius e18343
Loree, Jonathan M. 3589
Lorenzen, Sylvie 4027
Lotz, Jean-Pierre 4557
Lou, Yuqing e13007
Love, Neil e18186, e18187
Lowe, Kimberly e15136, e15169
Lowery, Maeve Aine 4015, 4085, TPS4142
Lu, Cheng e17536, e20052
Lu, Heming e17000
Lu, Hongyang e15503
Lu, Huifang 10080
Lu, Man e12095
Lu, Shun 9067, 11033, 11528
Lu, Yen-Jung e20522
Lu, Yi e21578
Lu, Yue Christine e17557
Lu, Yun e15005
Lu-Yao, Grace L. e16553, e16563
Luan, Xiaohui e20558
Lubberts, Sjoukje 4550
Lucas, John Thomas 10557
Luciani, Andrea e20600
Luis, Ines Maria Vaz Duarte 1034, TPS10125
Lum, Sarah e18043
Lumen, Nicolaas e16537
Lung, Mei Sim e15694
Luo, Hong Lei e15523
Luo, Jia e20025
Luo, Leo 5590
Luo, Shuangling TPS3631
Luo, Yuhao e15581
Lupak, Oleksandra e17571
Lv, Wangxia e15003
Ly, Ina 2050
Lycette, Jennifer L. e21614
Lyle, Stephen e23108
Lyman, Gary H. 6582
Lynam-Scherr, Courtney e13047
Lynch, Julie Ann e18051
Lynch, Kristine E. e18248
Lysenko, Irina B. e19510, e19511

M

Ma, Fei 11543
Ma, Jennifer 7065
Ma, Joseph 10104
Ma, Qinli e18290
Ma, Yu e15080
Macarulla, Teresa Mercade 4127
Machiels, Jean-Pascal H. TPS6090
Mackall, Crystal 3000
Macomson, Brian 5027
Madan, Ankit TPS2614
Madani, Julia e17023
Maddocks, Kami J. 7514
Madenci, Arin L. 10562
Madu, Max Fullah e21549
Maeda, Shigeto e17590
Maejima, Aiko e21511
Magis, Quentin 9525
Magnan, Heather D. 11050
Magno, Stefano e21570, e21697
Magnuson, Allison e21532
Mahajan, Abhishek e17588
Mahalingam, Devalingam e15753, e16502
Maher, Ian e21079
Maher, Jedi e15089
Mahner, Sven TPS5602
Mahon, Kate Lynette 5014
Mahtani, Reshma L. 551
Maia, João Raphael e18257
Maia, Manuel Caitano 4582
Maiese, Eric 8042, 8046
Mainor, Candace Barette e23194
Maiti, Abhishek 7033
Maitland, Michael L. 2563
Majithia, Neil e21054
Mak, Milena Perez e17546
Makker, Vicky 5598
Makosiej, Frank e18055
Malangone-Monaco, Elisabetta e16009
Malani, Rachna 11549
Malec, Monica 10026
Malhotra, Jyoti 1547, 10017
Malik, Faizan e18094, e18108
Malin, Jennifer e18099, e18106
Malissen, Nausicaa e14591
Malorni, Luca 1002
Malouf, Gabriel G. 4571
Malpartida, Juan Carlos e23141
Maltese, Mariangela e14532
Maluccio, Mary A. e15652
Maly, Joseph J. e19026
Mamdani, Hirva Mansurali 11013
Mamesaya, Nobuaki e20010
Mammatas, Lemonitsa Hillegonda TPS2620
Mamounas, Eleftherios P. TPS589
Man, Muran e19039
Manahan, Kelly J. e17042
Manda, Rohini e17113
Mandair, Dalvinder 4090, 8528
Mandaliya, Hiren A. e20630
Mandilaras, Victoria 5587
Mangano, Chiara 7528
Mangaonkar, Abhishek Avinash 7058
Mangla, Ankit e16518
Manguso, Nicholas e12130, e15688
Manikhas, Alexey e12580
Manikhas, Georgy M. e15505, e17519
Manjappa, Shivaprasad e18127
Manjon, Nuria e20045
Manne, Ashish e15714
Manthri, Sukesh e21526, e21546
Manzyuk, Valentina e12579
Mao, Kai e15642
Mao, Yan e12530
Mao, Yuan e20085
Maor, Ronny e12064
Maoz, Asaf e15133
Marcello, Krista e18131
Marconi, Giovanni 7038
Maria, Blazquez Arroyo e21683
Marinelli, Luca e16575
Marino, Natascia e13065
Marino, Patricia 6588
Mariotti, Veronica e13521, e15722
Marisa, Laetitia 3509
Marisi, Giorgia e15666
Markovic, Svetomir 3034
Markowska, Janina e13017
Markowski, Mark Christopher 5075
Marks, Douglas Kanter e12109
Marquez Rodas, Ivan 3082
Martin Broto, Javier 11003, 11071
Martin, Amber L. e22001
Martin, Miguel 1012
Martin, Petra e15134
Martin, Philip 3079
Martina, Diah e21709
Martinello, Rossella e12043
Martinez de Castro, Ana e23103
Martinez Garcia, Jeronimo 5566
Martinez Lago, Nieves e15548
Martinez-Trufero, Javier 11070
Martini, Rachel e23072
Mas, Luis e13076
Masarova, Lucia 7063, e18562
Mascarenhas, Leo TPS2599
Masci, Giovanna e12566
Maslan, Annie e23068
Maslov, Andrey A. e22007
Maslyukova, Elizaveta e12092
Mason, Neil Thomas e18292
Mason, Robert 9537
Mason, Warren P. e13525
Massett, Holly A. 6585, e18259
Masson, Eric e18130
Master, Samip R. e19035
Masumoto, Norio e12097
Mateen, Abdul 4541
Matei, Daniela 5505
Mateos, Maria-Victoria 8033
Matera, Robert M. 10112
Matias, Margarida 10069
Matikas, Alexios e12036
Matos Garcia, Ignacio TPS4146
Matsui, Hiroto 3086
Matsumoto, Seiji e23078
Matsuura, Hiroko 11056
Matulonis, Ursula A. 5534
Maubec, Eve TPS9596
Maude, Shannon L. 103
Maughan, Benjamin Louis 5064
Maurea, Nicola e23102
Maurer, Stephen M. e13095
Mayadev, Jyoti 5526
Mayer, Ingrid A. e12527
Mayer, Robert J. 3559
Mayor, Paul 5551, e18093
Mazul, Angela e17525
Mazzaferro, Vincenzo 4017
McBride, Ali e18264, e18334
McCabe, Nuala 11616
McCabe, Vita e13035
McCammack, Erin e12115
McCarthy, Anne Marie 1521
McCarthy, Fiona Margaret e14612
McCarthy, Philip L. 8037
McCaul, James Anthony 6065
McClain, James Thompson e18068
McCoach, Caroline Elizabeth TPS9100
McDonald, Erica e16509
McDonald, Kerrie Leanne 2062
McDougall, Jean A. e18067
McGehee, Elizabeth e20027
McGuinness, Julia 1586
McKay, Rana R. 5040
McKean, Meredith Ann 9574
McKie, Kerri e20053
McKillop, Sarah Jane e22505
Meadows, Jason e18185
Medeiros, Bruno C. e18507, e18524
Mediavilla-Varela, Melanie e23090, e23091
Medrano Guzman, Rafael 11045, e15687
Meehan, Robert S. 2518
Meerten, Esther Van e17559
Mego, Michal e23022
Mehanna, Hisham Mohamed 6004, TPS6091
Mehta, Minesh P. TPS9106
Mehta, Rutika Jitesh e13081
Meier, Friedegund Elke TPS9595
Meissner, Carl e15057, e15059
Melamed, Alexander 5537
Melero, Ignacio 2549
Melisko, Michelle E. TPS6626
Mell, Loren K. TPS5600
Mellado-Lagarde, Marcia e23212
Mellemgaard, Anders TPS2610, e20020
Mellert, Hestia S. e23063
Melotek, James 6066
Menapace, Laurel Anne e15140
Mendenhall, Nancy P. e16555
Menderes, Gulden e14009
Mendez, Eduardo 6034
Mendez, Joe Sammy 2040
Mendivil, Alberto e17094
Meneses Medina, Mónica Isabel e15618
Meng, Xue e23100
Menon, Manoj e18006
Menon, Roopika e23146
Menzies, Alexander M. 9581
Meric-Bernstam, Funda 1035, 2505
Meriggi, Fausto e23045
Merriman, Joseph 1543
Mesa, Ruben A. 7000
Messina, Carlo e16069
Metcalfe, Kelly A. 1527
Metzger Filho, Otto 1030
Meurer, Marie e17109
Meyer, Francois e17560
Meyer, Larissa 5557
Meyerhardt, Jeffrey A. 10059
Mezey, Jason e23195
Mezquita, Laura 9089
Miao, Diana 3016
Michael, Michael 2564
Michaelson, M Dror 2551
Michalaki, Vasiliki e12578
Michels, Sebastian Yves Friedrich 9041
Micke, Patrick e20637
Miftakhova, Regina R. e14068, e23018
Mihalcik, Stephen Andrew 5078
Mikhael, Joseph 8007
Miklos, David Bernard TPS7072
Milano, Gerard A. 1079
Milbar, Niv 4546
Miles, Randy C. e18337
Miller, Dave P. 537
Miller, Eirwen M. 5593, e17099
Miller, Eirwen Murray e17103
Miller, Kelly LR e16011
Miller, Kimberly Ann e21043
Miller, Kirsten e18193
Miller, Rowan 5597
Miller, Wilson H. 3057
Millis, Sherri Z. 11585
Milton, Valderrama e15171
Min, Jun e13003
Minarik, Marek e23040
Minarik, Tomas e17092
Minkovsky, Alissa e18517
Minocha, Vinay Nikhil e18064
Minson, Katherine Ashley 10533
Mir, Romaana e21010
Mirabile, Aurora e18251, e18301
Mirghani, Haitham e17535
Mirza, Abu-Sayeef e13062
Mirza, Mansoor Raza 5517, TPS5611, TPS5612, TPS5613
Mishkin, Grace e18072
Mita, Monica M. 2577
Mitchell, Aaron Philip 6510
Mitchell, Edith P. e18001
Mitchell, Paul TPS9097
Mitne-Neto, Miguel e18511
Mittal, Karuna e23170
Mittal, Nupur e18188, e22005
Mittra, Arjun e15616
Miyamoto, Kenichi e18304
Miyamoto, Ryoichi e15560
Miyamoto, Yuji 3585, 11608
Mizuno, Nobumasa 4123
Mobley, Erin Michele e18238
Modest, Dominik Paul 3525
Moehler, Markus H. 4011, TPS4132
Moehrmann, Lino 11551
Mogushkova, Khava A. e23085
Mohan, Raj e20005
Mohapatra, Suryanarayan e13514
Mohi El.Din, Ahmed M. e20516
Mohile, Supriya Gupta 10042
Mohyuddin, Ghulam Rehman e19001
Moik, Florian e15621

Moiseenko, Tatiana e17030, e17067
Mok, Tony 9005, LBA9007
Molenaar, Remco Jurriaan 4049, e14020
Molmenti, Christine Louise Sardo 1554
Moniz, Camila Motta Venchiarutti 3577
Montalban-Bravo, Guillermo 7020, 7053
Moon, Hanlim e21698
Moon, Jung Joo e22542
Mooradian, Meghan e14565, e20041
Moore, Assaf e15163
Moore, Christine Ann e13043
Moore, Kathleen N. 5547, TPS5607
Moore, Sara 9045
Morales, Serafin e12120
Moran, Bruce e23201
Moreno, Amy Catherine 4035
Moreno-Aspitia, Alvaro 502
Morgan, Todd Matthew 5072
Morgenfeld, Eduardo L. e16073
Morin, Sophie e18326
Morita, Kiyomi 7023
Moroney, Claire Elizabeth e21529
Morozova, Olena TPS10578
Morris, Lindsay Kaye 1080, e16084
Morris, Michael J. 5038
Morrow, Monica 508, 561
Mortimer, Joanne E. e12524, e12525
Morton, Lindsay M. 10520
Moschini, Marco e16034
Moschos, Stergios J. 2575, TPS9592
Moses, Kelvin A. e16542
Mosgaard, Camilla Stedstrup e15131
Moss, Haley 6608
Motz, Benjamin Mitchell 3608
Motzer, Robert J. 4507, TPS4595
Mougalian, Sarah Schellhorn e12129
Movva, Sujana 11027
Mozzilli, Simone Lehwess e18231
Mpima, Sheila e19004
Mrad, Chebli 6614
Muchtar, Eli e19532
Mueller, Daniel Wilhelm TPS4140
Mueller, Martin 7050
Mukesh, S. e21670
Mukherjee, Kalyan Kusum e23155
Mukherjee, Sarbajit e15761
Mukkamala, Suresh 5552
Müller, Hermann L. 10554
Mulrooney, Daniel A. 10564
Mumby, Patricia B. 10046
Muñoz, Miguel Angel e15158
Munoz-Zuluaga, Carlos A. 4098
Murakami, Haruyasu 8518, e20542
Murakami, Ryusuke 5510
Murakami, Takashi e23164
Murata, Satoshi 4050
Murawski, Niels 7539
Muro, Johanny F. e15157
Murphy, Brittany L. 11559
Murphy, Janet E. 4113
Murray, Drew Carl Drennan e13108
Murthy, Rashmi Krishna 580
Musolino, Antonino 1095
Musselwhite, Laura W. e15135
Mustacchi, Giorgio 1049, 1055
Mustafa Ali, Moaath Khader e21599
Mustian, Karen Michelle 10020
Mutonga, Martin Boniface Gitobu e12050
Muzaffar, Mahvish e12034

N

Nabbout, Nassim H. e18531
Nabhan, Chadi 6613
Nabid, Abdenour 5008
Nadeem, Rashid e21591
Nadler, Eric S. 6033, e20643
Naffouje, Rand 4044
Naffouje, Samer A. e15067
Nagahashi, Masayuki e23122
Nagao, Shoji e17022
Nagasaka, Misako e14575
Nagpal, Seema e13509
Naing, Aung TPS2603, TPS2604, 3084, TPS3116, 4567
Nair, Nita S. 527
Nakagawa, Akio e14577
Nakano, Takayuki e23152
Nakashima, Nariyasu e20054
Nakashima, Yuichiro 4062
Nakatsukasa, Katsuhiko 552
Nam, Jooyeon e13539
Namireddy, Praveen e18063
Namuche, Fernando e12011
Nanah, Rama e18556, e18559
Nanda, Rita 506
Nangia, Julie R. 10088
Nanni, Jacopo e23207
Naqvi, Kiran 7019, e18551
Narayan, Anand 1564
Narayan, Preeti e20539
Narayana, Swapna 7062
Narayanan, Siva e21073, e21075
Narita, Yukiya 3051
Narloch, Jessie 2049
Narra, Ravi Kishore 7045
Narui, Kazutaka 1025
Nastoupil, Loretta J. 7511, 7519
Nathwani, Nitya e21703
Natori, Akina 10037
Navarro Manzano, Esther e12559
Naya, Yoshio 4536
Nazarian, Angelica e15046
Nead, Kevin Thomas 5044
Necchi, Andrea 4526, e16018
Nejadnik, Bijan e18565
Nelius, Thomas e23149
Neoptolemos, John P. 4104
Nepomnyashchaya, Evgeniya M. e17038
Nerodo, Galina Andreevna e17001, e17041
Neron, Mathias 11055
Nesselhut, Jan e13531
Neuwirth, Madalyn G. e18062
Newcomb, Polly A. 3604
Newcomer, Lee N. 9046
Ng, Kimmie 3506
Ng, Matthew 2584
Ng, Sweet Ping 6610
NG, Terence 10096
Ng, Terry L. e20683
Nghiemphu, Phioanh Leia 2012
Nguyen, Huy Tram N. 2052
Nguyen, Timothy K. e18241
Ni, Chao e23024
Ni, Shujuan e15099
Nichols, Christine Ida e12083
Nicolosi, Piper L.W. 5009
Nie, Gang e12019
Nie, Keke 9017
Nielsen, Morten e14545
Niemeijer, Anna-Larissa N. e20047
Niesvizky, Ruben 8041
Nieto, Yago 4519
Niewiadomski, Dario e16075
Nikanjam, Mina e14620
Nikipelova, Elena Alekseevna e15128
Niphadkar, Seema e13077
Nishida, Toshirou e22510
Nishijima, Tomohiro F. 10030
Nishimura, Reiki e12020
Nishino, Mizuki 9087, 9521
Nishio, Shin e17029
Nitta, Hidetoshi 4079
Niwinska, Anna 2078
Noeparast, Amir e23197
Noepel-Duennebacke, Stefanie 3595
Nogova, Lucia e20664
Nomura, Hiroyuki 5503
Nonemacher, Henrique T. S. e16079
Noor, Alfiah e14104
Noro, Rintaro e21660
Noronha, Vanita 6007
Nosaki, Kaname e20505
Novikova, Inna Arnoldovna e21067, e22538
Novotny, Jan e15075
Nowak, Anna K. 8506
Nowakowski, Grzegorz S. TPS7571, TPS7573
Nowsheen, Somaira e12522
Nugent, Francis Warren e15677
Numan, Yazan e18550
Nunes Filho, Paulo Ricardo Santos e20552
Nunes, Ana Tablante TPS3092
Nunes, Hugo SM e13100
Nunes, Raquel e12025
Nusrat, Maliha e15143
Nuti, Marianna e14506
Nyrop, Kirsten A. e12069

O

O'Brien, Ciara e15043
O'Connor, Brenda e21645
O'Connor, Jeremy 3068, e14583
O'Connor, Owen A. 7521
O'Donnell, Peter H. 4502
O'Donoghue, Niamh e21655
O'Hara, Mark H. 3545
O'Kane, Grainne M. 2073
O'Leary, Ben 1018
O'Malley, David M. 5553
O'Malley, Dennis e21050
O'Neal, Richard e13041
O'Reilly, Eileen Mary 4110
O'Rourke, Mark Allen 10099
O'Sullivan Coyne, Geraldine Helen 2558, TPS2609
Oakley, Catherine Mary e21560
Obeid, Elias 11563
Ocal, Muge e23013
Ocen, Joanita e17051
Ocio, Enrique M. 8015
Ocvirk, Janja e21016
Odunsi, Kunle TPS3094
Offin, Michael e23150
Ogasawara, Sadahisa e15629
Ogden, Angela 11604, 11612
Ogi, Sayaka e14085
Ogiya, Rin 1081
Ogunleye, Foluso Nelson 4061
Ogunniyi, Adebayo e22518
Oguri, Tomoyo e20540
Oh, Jonathan TPS5604
Oh, Melissa S. e13084
Ohanian, Maro 7029
Ohashi, Kadoaki e20659
Ohmae, Masatoshi e17567, e17569
Oinino, Sarah e13550
Oizumi, Satoshi 9038
Ojima, Toshiyasu e14538
Oka, Suguru e16080
Okabe, Hiroshi e15574
Okada, Yuki e21688
Oke, Oluchi e12059
Oki, Eiji e15585
Oksuzoglu, Berna e15116
Okumatsu, Koki e21658
Oliva, Stefania 8011
Oliveira, Julio e14056
Oliver, Katherine e14089, e14091
Oliver, Matthew T. e21572
Olivieri, Nicholas D. e18305
Olopade, Olufunmilayo I. e13107
Olsson, Hakan Lars e13088
Olszanski, Anthony J. 2592
Olszewski, Adam J. 6522
Olufade, Temitope O. e12537
Olugbile, Sope Omowale 3061
Omae, Kenji e16067
Omesi, Lenore 6555
Omodaka, Toshikazu e21068
Omstead, Ashten N. e15598
Ong, Cecilia Tuongquang 532
Ono, Takeharu e17528
Onukwugha, Ebere 7563
Onuma, Kazuhiro e14086
Orbach, Daniel 10529
Ore, Martin 5594
Oren, Michal e18053
Oren, Ohad e14038, e18344
Ornstein, Moshe Chaim 4548, e16005
Ortega Granados, Ana Laura e20515
Ortiz-Cuaran, Sandra e23060
Orucevic, Amila e15172
Osei-Tutu, Akosua 2585
Oseledchyk, Anton e12536
Osipov, Arsen 4031

Osman, Diaa e14600
Osmulski, Pawel A. e23066
Osorio, Juan Carlos e16071
Osterman, Chelsea K. e16021
Otaibi, Zachary e18181
Otsubo, Kohei 9027
Ott, Patrick Alexander 109
Ou, Fang-Shu 3535
Ou, Junwen e20078
Ou, Qiuxiang 2572
Ou, Sai-Hong Ignatius 9010, e20502
Overman, Michael J. 3522
Owada, Yuki e23184
Owen, Dwight Hall TPS8580, 9080, e16088
Owonikoko, Taofeek Kunle 8505
Oyan, Basak 2035
Oza, Amit M. TPS5603
Ozaslan, Ersin e21656
Ozkan, Metin e15023
Ozmen, Tolga 563

P

Page, Ray D. e18306
Pai, Sara I. 6040, 6058
Paik, Paul K. e20541
Painter, Corrie 1519
Pak, Linda Ma e15675
Pal, Sumanta K. 4517, TPS4599
Pal, Tuya e13090
Palacio, Sofia e18002
Palacka, Patrik e16015
Palesh, Oxana 10094
Palhares, Daniel Moore Freitas e17507
Palmer, Daniel H. 4119
Palmerini, Emanuela 11025, 11030
Palmieri, Giuseppe e21047
Pan, Kevin e18076
Pan, Shujuan e13014
Panattoni, Laura Elizabeth 6505
Pandha, Hardev S. TPS3108
Pandya, Bhavik J. e18525
Pang, Angela e22522
Paniagua Cruz, Alan 4056
Panjabi, Sumeet e19513
Pankov, Aleksandr e23208
Pannier, Diane e14015
Panou, Vasiliki 8560
Pant, Manisha e18139
Pant, Shubham 2583, e18134
Papadimitrakopoulou, Vassiliki 9094
Papadopoulos, Kyriakos P. 3005, 9503
Papasotiriou, Ioannis e13001
Pappo, Alberto S. e21006
Parameswaran, Janaki e14105
Paranagama, Dilan e18031
Paraskevaidi, Maria 5596
Parchment, Ralph E. 2540
Pardo Aranda, Nuria e20526, e20555
Parikh, Kaushal 6576
Parikh, Kinjal e18210
Parikh, Ravi Bharat 6538
Parise, Carol 1098
Park, Hyo K. 5589
Park, Jae Hong 7008, 7024, TPS7568
Park, Jeong-Yeol 5578
Park, Ji Won 3518
Park, Jihwan e16549
Park, Jun Won e15534
Park, Soo e14553, e14556
Park, Sook Ryun 4020
Park, Steven I. TPS3095
Park, Tristen Sinae 554
Park, Wungki e14636
Parkes, Amanda Marie 1072
Parkes, Eileen E. 4023
Parmar, Ambika e21060
Parra-Herran, Carlos e17081
Parrondo, Ricardo Daniel e12037
Partridge, Savannah C. 11520
Pasquali, Sandro 11016
Pasquinelli, Mary e21646
Patel, Anuj K. e15000
Patel, Dilan Anil e12591
Patel, Jaymin M. 1097
Patel, Ketan e18098
Patel, Kiran e12073
Patel, Kruti e14563
Patel, Manali I. 6525
Patel, Nisha Subhash e14569
Patel, Poras e18087
Patel, Rishi e15685
Patel, Sandip Pravin e23213
Patel, Sapna Pradyuman 9554
Patel, Shahina e18563
Paterson, Carly Lynn e21711
Pathak, Surabhi e14609
Patil, Pradnya Dinkar 11547
Patil, Vijay Maruti 2024
Patsouris, Anne TPS1117
Paty, Jean 11022
Paulson, Kelly Garneski 3044
Pawar, Dilip e17505
Pawlyn, Charlotte 8026
Paximadis, Peter Alexander 8566
Paxton, Raheem e12573
Payne, David 10057
Paz-Ares, Luis G. 3038, TPS8586
Peace, Kaitlin M. 3088
Pearlstein, Kevin A. 10081
Pease, Daniel Fellows e18074
Pecora, Irene e15754
Pedrazzoli, Paolo 10098
Pedregal, Manuel e12007
Peereboom, David M. e13507
Pegg, Neil 11590
Pegourie, Brigitte 8019
Pelekanou, Vasiliki 519
Peña-Curiel, Omar e23173
Pendharkar, Dinesh e18003
Pentz, Rebecca D. TPS6625, e18046, e18217
Peoples, Anita Roselyn 10119
Peppercorn, Jeffrey M. e21603
Peppone, Luke Joseph 10113
Percac-Lima, Sanja 1506
Peretz, Idit 1077
Perez, Edith A. 1003
Perez, Raymond P. 3003
Pergolotti, Mackenzi 10038
Perimbeti, Stuthi e15141, e15564
Perl, Alexander E. TPS7067
Pernot, Simon e15061
Perol, Maurice 9003
Perrone, Francesco 515
Pesco Koplowitz, Luana e14049
Petekkaya, H. Ibrahim e18027
Peterfy, Charles 11048
Peters, Geoffrey David e17551
Peters, Katherine B. e21636
Peters, Mary Linton Bounetheau 1501
Petersen, Christopher Thomas e19017
Peterson, Lanell M. 11572
Peterson, Susan K. 1555
Petracci, Elisabetta 3546
Petrera, Marilena TPS1591
Petrylak, Daniel Peter 106
Pezzullo, Luciano e17577
Pfeffer, Raphael M. 2077
Pfeiffer, Boris 9049, e20609
Pfreundschuh, Michael 7506
Phan, Alexandria T. 4095
Philip, Philip Agop e15039
Phillips, Melissa Mary 8553
Phillips, Nicholas Steve 10517
Phillips, Ryan TPS5094
Picone, Antonio e23052
Pierce, Andrew e14063, e17542
Pietzner, Klaus e13058
Pignon, Jean-Christophe 4576
Piha-Paul, Sarina Anne 2565, TPS2616
Pilie, Patrick Glen 4581
Pillai, Rathi Narayana TPS9102, e20648
Pilon, Dominic e16528, e16529
Pinato, David James 11597, e14614
Pineda-Roman, Mauricio 7529
Pinnamaneni, Ramya e20665
Pintova, Sofya e21675
Piotrowska, Zofia 9020
Piperno-Neumann, Sophie 9502
Pires Da Silva, Ines Esteves Domingues 9513, 9541
Piulats, Josep M. 9533
Pivkova Veljanovska, Aleksandra e19502
Pivot, Xavier B. 509
Pizon, Monika e23143
Planchard, David 9075
Plichta, Jennifer Kay e18144
Poddar, Jyoti e17006
Pohl, Esther 1526
Pokataev, Ilya e15733
Pole, Jason D. e18168
Pollack, Craig Evan 6550, e18048
Pollack, Megan 9544
Pollack, Seth 3090
Pollan, Marina 1505
Pollyea, Daniel Aaron 7022
Poniewierski, Marek S. e21517
Poorvu, Philip Daniel 10065
Popat, Uday R. 7046
Pophali, Priyanka Avinash 1573, e13083
Porceddu, Sandro Virgilio 6008
Porneczy, Edit e14595
Porta, Camillo e16081
Porter, Ashleigh e17516
Posadas, Edwin M. 5031
Posch, Florian e15083
Postow, Michael Andrew TPS9591
Potikyan, Gary e20511
Potluri, Jalaja TPS7069
Poveda, Andres 5573
Powell, Steven Francis 6011
Powles, Thomas 3035, TPS4590, TPS5090
Prabhash, Kumar e13111
Prajapati, Hasmukh J. e15649
Prasanna, Thiruvarudsothy 3560
Prasongsook, Naiyarat e12006
Preeshagul, Isabel Ruth e20634
Presley, Carolyn Jean 6563, e21547
Press, Robert H. e20604
Price, Timothy Jay 3569, 3584
Prieske, Katharina e21520
Prieur, Alexandre 11545
Primrose, John Neil 4006
Prince, Grace 2072
Princic, Nicole e12528, e12546
Privalov, Alexey e15501, e17040
Procaccio, Letizia e21654
Prodehl, Leanne e13067
Provencher, Louise e13078
Psyrri, Amanda TPS6096
Pu, Jie e23196
Puca, Loredana 5029
Puig, Oscar e13105
Purdum, Anna e18333
Purim, Ofer e15537
Pusztai, Lajos 572, 1016
Pyltsin, Sergey P. e20090

Q

Qi, Fei 7540
Qi, Xiaolong e15594
Qi, Yunxiang e17011
Qian, Yuan e15709
Qin, Angel e20607
Qin, Shukui 4087, e15595
Qiu, Haibo e22507
Qiu, Miaozhen 4065
Qiu, Ying e21003, e21011
Qu, Feilin e12032
Qu, Xiujuan e15024
Quain, Katharine e21601
Quek, Kelly 8545
Quek, Ruben G.W. e16524
Quidde, Julia 3544
Quist, Jelmar 1006
Qureshi, Mahin Iqbal 6600

R

Raab, Marc 8024
Radeke, Erika K. e18018
Radford, Diane Mary 10063
Radhakrishnan, Padhma e20035, e21041
Radkiewicz, Cecilia e13074
Radovich, Milan 1531
Radtchenko, Janna e20551, e20593
Raez, Luis E. 11550
Rafei, Hind 6042
Rafiullah, Fnu e19523
Rahimi-Nedjat, Roman e17566

Rainey, Hope 6069
Raje, Noopur S. 8005
Rajpar, Shanna 5012
Rakovitch, Eileen 528
Raleigh, Ruth e18247
Ramalingam, Sri 6051
Ramamurthy, Chethan 1585
Ramanathan, Sabarina e15154
Ramchandren, Rod 7530
Ramey, Stephen 6077, 11017
Ramirez, Jacqueline e14066
Ramnarine, Sabrina e21595
Ramos Vazquez, Manuel e12563
Ramos, Corinne 11619, 11620
Ramsay, Robert George 3573
Randazzo, Dina e13532
Rao, Vishal Uchila Shishir e17549
Raphael, Jacques e18331
Rapposelli, Ilario Giovanni e18190
Raque, Kathleen e12045
Rasco, Drew W. 7545, e14102
Rashad, Sadaf e15712
Rasschaert, Marika Anna e18208
Rastogi, Sameer 11064
Rathinagopal, Jenny e15114
Ratta, Raffaele e16064
Ratti, Maria monica e21551
Rauenzahn, Sherri L. e18201
Raufi, Ali Mehmood e12005
Raut, Chandrajit P. 11009
Ray, Meredith 8522
Ray-Coquard, Isabelle Laure TPS5605
Raybould, Alison L. e15646
Raymond, Chris e16002, e16546
Razavi, Pedram LBA11516, 11526
Reardon, David A. 2042
Recchia, Francesco 3021
Recine, Federica e12055
Reckamp, Karen L. e20675
Reddy, Amit e22000
Reddy, Sangeetha Meda 11501
Reddy, Venkataprasanth P. 9072
Ree, Anne Hansen e14033
Reichek, Jennifer e22022
Reichert, Zachery TPS5086
Reid, Robert e16564
Reidy, Diane Lauren 4094
Reilley, Matthew 3574
Reinacher-Schick, Anke C. 3543, e15086
Reinbolt, Raquel E. 10102
Reis, Diego e21627
Reiss, Samantha 2033
Remon, Jordi 11532
Ren, Gang e15720
Ren, Ruimei e12091
Renfrow, Jaclyn e13534
Renne, Salvatore Lorenzo 11074, e22006
Renouf, Daniel John TPS4149
Reuben, Alexandre 9575, 11500
Reuter, Christoph 5039
Rho, Mi Jung e16552
Riaz, Nadeem 6076
Ribeiro, Karina Braga e18150
Ricciardi, Giuseppina e12516
Rice, Stephanie 5079
Richard, Nadine M. TPS2086
Richardet, Eduardo e12042
Richardson, Paul G. TPS8054, TPS8057
Richter, Joshua Ryan e19500
Richters, Lisa Katharina 5546
Ricigliano, Mark e14018, e15749
Rick, Oliver 10061
Riedl, Jakob M. e15084
Rieke, Damian Tobias e14613
Riess, Jonathan 9030
Rifkin, Robert M. e19517, e19527
Rijntjes, Jos 5069
Rimassa, Lorenza 4000
Rincon, Maria Andrea 6595
Ring, Sorcha e18125
Rini, Brian I. 4584, TPS4597, TPS4600
Rioja, Patricia Elizabeth e15576
Ritchie, Ellen K. 7052
Rivalland, Gareth 8514, 8569
Rivera Duarte, Alfonso Alfredo e18566
Riviere, Paul 11574
Robert, Caroline 9504
Roberts, Megan 6554
Robertson, John Forsyth Russell 1048
Robinson, Jeffrey D. 6566
Robson, Mark E. LBA4
Roc, Anne e18096, e18109
Roca, Enrique Luis e14065
Rocca, Andrea 1042
Rocha Lima, Caio Max S. 8568
Rodica Maricela, Anghel e17047
Rodig, Scott 9515
Rodin, Gary 7041, LBA10001
Rodney, Simon 4518
Rodriguez Freixinos, Victor 5569
Rodriguez Gomez Hidalgo, Natalia e17105
Rodriguez, Cesar Augusto e12062
Rodriguez, Cristina P. e17575
Rodriguez, Jorge Alberto e18078
Rodriguez, Maria Alma e18262, e21602
Rodriguez-Rodriguez, Lorna 5592, e18015
Roeper, Julia e20560
Roger, Anissa e21008
Rogers, Brittany Kayla e18274
Rohanizadegan, Mersedeh e13027
Rohr, Irena e17096
Rojas, Luis e17082
Rolfo, Christian Diego e20043, e20569
Roman Bassaure, Edgar e17005
Romanov, Ilya e17518
Romejko-Jarosinska, Joanna 7560
Romero, Ignacio 5543, e13106
Roncolato, Felicia 5575
Roper, Nitin 9023
Rosen, Sheri e21583
Rosenberg, Shoshana M. 531
Rosner, Samuel 9548
Ross, Jeffrey S. 3583, 11595
Ross, Masey Marie e21565
Rossetti, Sabrina e16054
Rossi, Alessandro e21556
Rossi, Sabrina e20608, e20662
Rossini, Daniele 3542
Rostorguev, Eduard Evgenevich e13540
Roszik, Jason 5528
Rotenstein, Lisa 6524
Roth, Joshua A. e18267
Roth, Patrick e13528
Rovithi, Maria 2591
Rowe, Julie Haewon e15142
Rowland, John Christopher e21649
Roy, Rajasree e20509
Royal, Richard Eldon 9582
Royce, Trevor Joseph 11021
Rozeman, Elisa A. 9586, TPS9600
Rozenblit, Mariya e12541
Ruban, Cynthiya e20038
Ruda, Roberta 2026
Ruddy, Kathryn Jean 6531
Rudnick, Jeremy David 2059
Rugo, Hope S. TPS1111
Ruhstaller, Thomas 4019
Ruiz Mendoza, Rossana Esther 548
Rule, Simon e14101
Rulli, Eliana e20631
Rummel, Mathias J. 7501
Ruppert, Amy S. 7503
Russo, Alessandro e14617
Russo, Antonio e12508
Rust, Kelly 553
Rutkowski, Piotr 11026
Rutledge, Brian 1540
Ryan, Charles J. 5067, TPS5087
Ryckewaert, Thomas 11047
Ryu, Keun Won 4028
Røe, Oluf D. e23059

S

Saba, Nabil F. 6052, e15607
Sabari, Joshua K. 8512, 11536
Sablin, Marie-Paule e12592
Sablon, Erwin e20519
Sacco, Assuntina Gesualda TPS6092
Sackey, Korkor e16569
Sadaps, Meena e18118
Sadek, Ramses F. e12575
Saeki, Sho e20559
Safran, Howard 4007, e15072
Sagar, Bhuvana e18340
Sagiraju, Hari Krishna Raju e13093
Saha, Sukamal 5567
Sahai, Vaibhav 4072
Sahebjam, Solmaz 2001, TPS2084
Sahgal, Arjun TPS10129
Sahota, Sheena 2557
Saif, Wasif M. 2559
Saiki, Masafumi e23104
Sakai, Daisuke e21624
Sakdejayont, Siwat 11617
Salah, Samer 11059
Salama, Monica e18282
Salami, Simpa Samuel 5061
Salanova, Ruben e20565
Salas, S Bastien 11063
Saleh, Ramy e12127
Salem, Mohamed E. 3578, 11517
Salloum, Ralph 10516
Salmasi, Amirali 5063
Salmon, John Stuart e15751
Saloura, Vassiliki 3080
Saluja, Ronak 6598
Salvador, Javier e23041
Salz, Talya 10082, e21596
Sam, Davis e18242, e21004
Samaha, Heba 2053
Samalin, Emmanuelle e15048
Samawi, Haider e15653, e18163
Sanai, Nader TPS2083
Sanborn, Rachel E. 3007, e20605
Sánchez Rovira, Pedro e23053
Sanchez, Marta e20008
Sanfilippo, Roberta 11072
Sanhueza, Cristobal T. e15757
Sankhala, Kamalesh Kumar 11078
Santa-Maria, Cesar Augusto TPS1110, 3052
Santini, Fernando Costa 9012
Santomasso, Bianca 3019
Santos Pinheiro, Fernando 2068
Santos, Lúcio Lara e13075
Santos, Vanessa Montes e21676
Saramon, Laurie e20048
Sarangarajan, Rangaprasad e14042
Sarangdhar, Mayur 2538
Sareen, Srishti 1536
Sarfaty, Michal e18338
Sarker, Debashis TPS2612
Sarnaik, Amod 3045
Sarre-Lazcano, Catherine e18166
Satake, Hironaga e18263
Sato, Jun e20002
Sato, Takami 9531
Sato, Yozo e15648
Satram-Hoang, Sacha 538
Savaraj, Niramol e23165
Sawa, Kenji e20060
Sawada, Takeshi e15077
Saxton, Claire e21554
Sayers, Louise 9563
Scagliotti, Giorgio V. 9019
Schadendorf, Dirk 9524, 9527
Schats, Kelly 3028, e21030
Scheel, Andreas H. e20508
Scheinberg, Tahlia 3060
Schellens, Jan H.M. 5514
Schenk, Erin Lynn e14597
Schenkel, Brad e19009
Scher, Howard I. 5015, 5070
Schernberg, Antoine 4120
Scherpereel, Arnaud LBA8507
Scheulen, Max E. 9511
Schlack, Katrin e16507
Schlappe, Brooke A. 5531
Schluckebier, Luciene 9068
Schmalenberg, Harald 4054
Schmid, Peter 556, 2548
Schmidt, Manuel e14625
Schmitz, Sandra 6013
Schmoll, Hans-Joachim 3533
Schnarr, Kenna e12082
Schneeweiss, Andreas 518
Schoen, Martin W. e18519, e22503
Schoffski, Patrick 11057
Schott, Dorothea 11558
Schroeder, Jan e12555
Schuler, Martin H. 4038, 9519

Schumacher, Jessica R. 6520
Schuurhuizen, Claudia 3564
Schvartsman, Gustavo 9083, 9532
Schwaederle, Maria Clemence 11593
Schwartsmann, Gilberto e14019
Schwartz, Anthony L. e21025
Schwartz, Candice e18567
Schwartz, Kenneth A. e13529
Schwartz, Melissa e17073
Schwartz, Sarit 11601
Schwartz, Theresa Lynn e13059
Scilla, Katherine Ann 11606
Scoggins, Marion e13049
Scott, Marietta L. e14502, e14503
Scotte, Florian e18276
Seby, Sandra e17527
Seckl, Michael 1059
Secondino, Simona 4549
Sedhom, Ramy e18541, e21506
Seepana, Jyothirmai e20036
Sehdev, Amikar TPS11628
Sehouli, Jalid 5562
Seidel, Christoph Alexander 4560
Seiden, Danielle 1552, e21690
Seidman, Andrew David 1073
Seitz, Rob e23073
Seiwert, Tanguy Y. 6049, TPS6099
Selim, Ranya 2028
Sella, Avishay e16561
Sella, Tal e12051
Selmy, Mohamed e23009
Sen, Shiraj 2526, 2537
Senbetta, Mekre e19037
Sener Dede, Didem e13536
Sepesi, Boris e20034
Sero, Valeria e23161
Seth, Sahil e20058
Seufferlein, Thomas e15037, e15769
Sever, Ozlem Nuray e14605
Severson, Eric Allan e13031
Sha, Huizi e14047
Shabason, Emily Kauvar 10572
Shafer, Danielle A. 2060
Shah, Bijal D. 3024
Shah, Carisa M. e16545
Shah, Chintan e21622, e21674
Shah, Manish A. TPS4135, TPS4141
Shah, Manisha H. 6022
Shah, Paras Hemant e16572
Shah, Parth e18545, e23120
Shah, Sandip 7550, e18315
Shah, Shweta e18107, e18117
Shahda, Safi 3541
Shaheen, Shagufta e20061
Shahrokni, Armin e21536, e21543
Shaikh, Marwan Elahi e23051
Shakya, Sachin e12008
Shalashnaya, Elena V. e15512
Shamah, Corey J. e18220
Shamai, Sivan 11060
Shamp, Stephen 8542
Shang, Jinbiao e17502
Shango, Maryann e23169
Shankaran, Veena e18079
Shanshal, Mohamed e14093
Shapiro, Irina 9557
Shapiro, Jeremy David 3572
Sharma, Anurag e18294
Sharma, Nitika e14606, e20513
Sharma, Priyanka 529
Sharma, Ricky A. 3507
Sharma, Rohini 4093
Sharman, Jeff Porter 7504, 7523
Shaulov, Adir e21633
Shaw, Alice Tsang 9006, LBA9008
Sheiko, Elena A. e12124
Shelat, Anang 10556
Shen, Chan 4092
Shen, Jie e15628
Shen, John P. 5561
Shen, Lujun e15636
Shen, Yinchen e15098
Sheng, Xinan 4575
Shenolikar, Rahul A. e16032
Shenoy, Niraj Konchady e13073
Shepherd, Scott Thomas Colville e16061
Shepshelovich, Daniel 6514
Sher, David Jonathan e18124
Sherman, Eric Jeffrey 6085
Sheth, Siddharth 6045
Shi, Feng e15635
Shi, Qian LBA1
Shi, Tingyan 1583
Shi, Yan e15788
Shi, Yu-Mei e23020
Shi, Yuankai 3513, e20655
Shibaki, Ryota 11541
Shien, Tadahiko TPS588
Shiga, Kiyoto e17574
Shigematsu, Fumie e20620
Shikhlyarova, Alla Ivanovna e14052
Shim, Hyun Jeong e21503
Shimada, Midori e20023
Shimada, Yoshifumi e15101
Shimanovsky, Alexei e20003
Shin, Hee-Chul e13110
Shin, Junghoon e19024
Shin, Sarah 8525
Shinde, Arvind Manohar e21689
Shinozaki, Katsunori 4059
Shiota, Masaki e16570
Shiradkar, Rakesh e16554
Shore, Neal D. TPS5097, e14634
Short, Nicholas James 7013, 7014
Shrestha, Anju 1553
Shroff, Rachna T. 4018
Shulman, David Stephen TPS10576
Shum, Elaine e18073
Shumway, Dean Alden 562
Shusterman, Michael e15729
Sicklick, Jason K. 2512
Sidana, Surbhi 8047, 8048
Siddiqui, Mohammad Rashid e16026
Siebenaller, Caitlin e18513
Siegel, David 8027
Siegel, Robert S. 6078
Signorovitch, James 6599, 6605
Sikaria, Swati e16036
Silletta, Marianna e22517
Silva, Wania Cristina e15008
Silverman, Lewis R. TPS7074
Sim, Hao-Wen 2037, 4053
Simpson, Danny 9567
Simpson, Rachael e18558
Sineshaw, Helmneh M. 3587
Singal, Gaurav 2514, 6539
Singer, Christian F. 536
Singh, Harpreet 10009
Singh, Jasmine e17533
Singh, Navneet e20024
Singh, Parminder TPS4591
Singh, Sareena e17054
Singh, Sunanda e13547, e15727
Singh, Veena M. e23033, e23036
Singh, Vijendra e18540
Sinicrope, Frank A. 3516, 3579, TPS3630
Siontis, Brittany 11018
Sita-Lumsden, Ailsa Roberg e16558
Siu, Lillian L. 104
Sivaraj, Dharshan 8008
Sivendran, Shanthi e21605
Sivsammye, Suceil e15596
Sjoquist, Katrin Marie TPS4136
Skelton, William Paul e17021
Skinner, Karen E. e20590
Skoulidis, Ferdinandos 9016
Skrzypski, Marcin Tomasz 11556
Skubitz, Keith M. e14016
Slavin, Thomas Paul 1514
Sledge, George W. 1000
Slim, Jennifer Nadine e18180
Slingluff, Craig L. TPS3106
Slovin, Susan F. 5034
Smaletz, Oren e17039
Smeltzer, Matthew e20079
Smetanay, Katharina 525
Smit, Egbert F. 9070
Smit, Marie-Anne Damiette 2544
Smith, David C. 4503
Smith, Derek e18010
Smith, Jess Louise e21641
Smith, Jesse Joshua 3581
Smith, Karen L. 10076
Smith, Lia J. e18095
Smith, Matthew K. 6537
Smith, Matthew Raymond TPS5092
Smith, Roger 11583
Smyth, Robert 9032
Snider, Jeremy Williams e15011
Snyder, Rebecca 10016
Sobhani, Iradj 3520, 3615
Sobol, Robert E. e14610
Sobrero, Alberto F. 3501
Sochor, Marek e23021
Socinski, Mark A. e14034
Sogono, Paolo Generato e17563
Sohal, Davendra TPS4152, 6558
Soldera, Sara V. 8559
Soliman, Hatem Hussein e12569
Soliman, Ranin e18310
Solis Hernandez, Maria Del Pilar e15138
Solman, Isabelle 7524
Solomon, Rachel 6541
Somaiah, Neeta 11006
Somashekhar, S.P. 8527
Somlo, George 8010
Sonbol, Mohamad Bassam e15779
Song, Paul Y. 1091
Song, Yeohan e15032
Song, Yong 9035
Song, Zhangfa e15105
Soni, Payal Dilip e18135
Sonmez, Ozlem e14601
Sonoda, Tomoaki e20575
Sonpavde, Guru e16012
Sonugur, Fatma Gizem e23014
Soo, Joanne 7538
Soria, Jean-Charles 4074, TPS11625
Sormunen, Jorma Tauno Juhani 1565
Soto Parra, Hector J. TPS9107
Soto Perez De Celis, Enrique 10035, 10036
Soule, Tomas Jose e17016
Sousa, Nuno 6616
Souweidane, Mark M. 2010
Souza, Juliana e22524, e22541
Soyano, Aixa Elena 530, e20599
Spahn, Martin e16535, e23008
Sparano, Joseph A. TPS1114
Speers, Corey Wayne e12102
Spencer, Jennifer e18299
Sperk, Elena e12014
Spicer, James F. 3085
Spicer, Jonathan D. 8537
Spira, Alexander I. 1103, TPS3107
Sporkmann, Mareike e17046
Spratt, Daniel Eidelberg 5000
Spring, Laura 1046, TPS1106
Srinivasalu, Vijay Kumar e12033, e17565
Srinivasamaharaj, Srividya e15124
Srivastava, Arnav 4588
St. Louis, Jessica 6556
Stacchiotti, Silvia 11062
Stack, Brendan C. 6041
Stacoffe, Marion e12577
Stebbing, Justin 510
Steensma, David P. TPS7075
Stein, Alexander TPS3620
Stein, Anthony Selwyn 7032
Stein, Eytan M. 7004
Stein, Mark N. 2586
Stein, Matthew K. e15012, e20506
Steinberg, Gary D. 4531
Stellato, Daniel R. e18553
Stemhagen, Annette TPS7073
Stemmer, Salomon M. 543, e12053
Stern, Jennifer e15752
Sternberg, Cora N. 4564
Steuer, Conor Ernst 6082
Stewart, Elizabeth 10535
Stiff, Andrew e12126
Stinchcombe, Tom 8509
Stintzing, Sebastian 3510
Stone, Richard M. 7016
Stone, Steven e16566
Stoumbos, Dionisios e19033
Stover, Daniel G. 1092
Streck, Mitchell e18501
Streicher, Katie 3041, 11505
Strickler, John H. TPS3624
Stringer, Erica Michelle 1083
Stroud, Chipman Robert Geoffrey e13072, e2171 2
Strulov Shachar, Shlomit 10060, e21707
Stuebs, Patrick e15566

Stuessy, Peter e18273
Su, Christopher e18017
Su, Kang-Yi e13103
Su, Ying-Wen e17503
Su, Yun e18500, e18504
Subbiah, Ishwaria Mohan 10034
Subbiah, Vivek 6023, 9074
Subramaniam, Deepa Suresh 2019
Subudhi, Sumit Kumar 5065
Sudo, Kazuki e14511
Suenaga, Mitsukuni 3594, 11564
Sugawara, Shunichi 9037
Sugiyama, Eri 9057
Suhy, David e14551
Sui, Jane Sze Yin 11587
Suidan, Rudy Sam 6602
Sullivan, Ryan J. 3063
Sumrall, Ashley Love e13523
Sun, Der Sheng e15578
Sun, Lova e19003
Sun, Maxine e16506
Sun, Ruobai e13011
Sun, Shengjie e20658
Sun, Wan 1053
Sun, Weijing 4081
Sun, Yuanjue e22506
Sunakawa, Yu 11613
Sundar, Raghav 2571, 10536
Sundar, Santhanam 10111
Sura, Karna Tushar 4034
Sureda, Manuel 11573
Suwanvecho, Suthida 6589
Suzman, Daniel L. e18236
Suzuki, Kenji 8561
Suzuki, Maya 10550
Suzuki, Rei e15726
Suzuki, Yusuke e13082
Sweeney, Christopher 5062
Swick, Adam D. e17509
Syed, Binafsha Manzoor e12031, e13060
Sym, Sun Jin e15047
Symonds, Erin L. 3597
Synnott, Naoise C. e14098, e14099
Synold, Timothy W. 4566
Szabados, Bernadett e16004
Szablewska, Sylwia e20082
Szekely, Borbala e13028
Szeto, Christopher 1093
Szlosarek, Peter Wojciech TPS8582

T

Tabatabaie, Omidreza 4058
Taber, Angela Marie e21678
Tabernero, Josep 3002
Tacyildiz, Nurdan e22010, e22020
Tadros, Audree 559
Tagawa, Scott T. TPS5093
Taha, Mahdi e16547
Taieb, Julien 3515
Takahashi, Koichi 7005, 7034
Takahashi, Shinichiro 4107
Takano, Atsushi e14057
Takano, Masashi 5550
Takano, Natsuki e23101
Takayama, Yuji e23025
Takekuma, Munetaka e17024
Takiguchi, Yuichi 9064
Taku, Nicolette e18019
Talamo, Giampaolo e19504
Talati, Chetasi e18546
Taleb, Amina B. e18258
Talekar, Mala Kiran 10507, e19016
Tam, Constantine Si Lun 7520
Tamaki, Keita e19036
Tamiya, Motohiro e20679
Tamragouri, Keerthi 11621
Tan, Aaron e21653
Tan, Antoinette R. 11581
Tan, Daniel Shao-Weng 11506
Tan, Teng Hwee e17552, e17573
Tan, Yen Yen e12588
Tanco, Kimberson e21694
Tancredi, Richard e21509
Tandon, Nidhi 8049
Tandstad, Torgrim TPS4593
Tang, Bixia e21055
Tang, Boxiong e18522, e19010
Tang, Derek e12535
Tang, Ming 8570
Tang, Shou-Ching e23209
Tanioka, Maki 1065
Tannir, Nizar M. 4570, 4572
Tano, Sheeba V. e12586
Tao, Yungan 6070
Tapia, Christopher e18005
Taplin, Mary-Ellen 5005
Tardy, Magalie Pascale e17524
Tarhini, Ahmad A. 9500, 9542
Tariq, Khurram Bilal e15775
Tarter, Thomas H. e16586
Tawbi, Hussein Abdul-Hassan 9507
Tawfik, Bernard TPS6098
Tawfik, Cindy 5591
Tayshetye, Pritam e23111
Tchou, Wen-Wei e16589
Teck, Anja-Tatjana e23080
Teixeira, Luis 3087
Telford, Claire e12545
Telfort, Jersen e13038
Telles O Lima, Jurema e21534, e21537
Temel, Brandon 10040
Temkin, Sarah Madhu 5564, 5579
Teo, MinYuen 4509
Teoh, Deanna Gek Koon e13037
Teplinsky, Eleonora e17058
Teply, Benjamin A. 5017
ter Veer, Emil 4048
Terasaki, Mizuhiko 2000
Terawaki, Hiromi e18164
Tergas, Ana Isabel 10028
Teufel, Michael 4078
Tey, Jeremy Chee Seong e21667
Thaker, Premal H. 5568
Thamlikitkul, Lucksamon e17582
Thapa, Bibhusal 8515
Thatcher, Nick 9050
Thekkekara, Romy Jose e20635
Thibaud, Santiago e18557
Thibault, Constance 5033
Thillai, Kiruthikah e23139
Thomas, Alexandra 1032
Thomas, Christian A. e12065
Thomas, Colin e19005
Thomas, Fabienne 4554
Thomas, Reena Parada 2058
Thomas, Robert J. 10103
Thompson, John A. TPS3101
Thompson, Michael A. 7562
Thomsen, Caroline Brenner 3593
Thoreson, Nick e16557
Thorsen, Lene 4551
Thress, Kenneth Stephen 9018
Tian, Geng e23057
Tian, Jie e23093
Tie, Jeanne 3521
Tinhofer, Inge 6059
Tiseo, Marcello TPS9098, e14514
Tiwari, Shristi e21500
Tjan-Heijnen, Vivianne C. 523
Tjulandin, Sergei 5541
Todd, Sarah e17072
Todorova, Valentina K. e12013
Toh, Han Chong 6047
Toh, Uhi e12072
Toki, Maria 9076
Tokunaga, Masanori TPS4134
Tolaney, Sara M. 511, 1019, TPS1109
Tolcher, Anthony W. 2580
Tomasevic, Zoran e12523
Tomasevic, Zorica e12509
Tonetti, Debra A. e14090
Tong, Zhongsheng 1087
Toomey, Sinead 3616
Toppo, Laura e15538
Torrejon, Davis Yuri 3077
Torres, Harrys A. e18152
Torres-Roman, Junior Smith e18113
Tota, Jennifer e18230
Touat, Mehdi e23159
Tougeron, David 3536
Toulmonde, Maud 11053
Traina, Tiffany A. 1089
Tramontano, Angela e18071
Tran, Ben 2521
Tran, Krystel e18013
Tran, Phuoc T. 5020
Trapp, Elisabeth Katharina e23061
Trebeschi, Stefano e14520
Tredan, Olivier LBA100
Trieu, Vuong N. e15742
Trillsch, Fabian e17050
Trinh, Quoc-Dien e18308
Tripathi, Abhishek e16001
Tripathy, Debu TPS1120
Trivedi, Sumita e17111
Trone, Jane-Chloe e14058
Trosman, Julia Rachel e18032, e21644
Troy, Jesse D. e21564
Truong, Judy 6607, e18312
Tsai, Katy K. e21593, e21594
Tsang, Derek S. 10549
Tsang, Erica S. e20563
Tsao, Anne S. 9062
Tseng, Ju-Yu e23029
Tsimafeyeu, Ilya e18240
Tsimberidou, Apostolia Maria 2513
Tsoulos, Nikolaos e23193
Tsuchiya, Kaoru e15664
Tsukita, Yoko e23001
Tsuneizumi, Michiko 6587
Tsunoda, Nobuyuki e12505
Tsuyoshi, Hideaki e17014
Tu, Haiyan 9028
Tu, Yan e15597
Tun, Aung e18284
Tun, Han W. 7516
Tureci, Özlem e15584
Turkington, Richard C. 4026
Turner, Nicholas C. 1007
Turner, Simon R. 8535
Turtle, Cameron John 3020
Twelves, Chris 2046
Tyker, Albina e13063
Tyulyandina, Alexandra e23109

U

Ueno, Hideki 3609
Ueno, Makoto 4099
Ugidos, Lisardo e14029
Ulmasov, Firdavs e22537
Unal, Emel Cabi e22018
Underwood, Jenny e18194
Ung, Brian e19519
Unger, Evan C. 2561
Unger, Joseph M. 1541, 6513
Unnikrishnan, Athira e13070
Uppaluri, Ravindra 6012
Urruticoechea, Ander 1023
Usman, Sadaf 6027
Uttamapinan, Suleepon e12015
Uzzo, Robert TPS4598

V

Vadhan-Raj, Saroj e18191
Vadola, Lisa Ambrosini e18270
Vaishampayan, Ulka N. TPS3111
Valderrama, Adriana e18341
Valdivieso, Natalia e17004
Valencia, Omaira e18288
Vallabhaneni, Priyanka 9585
Vallet, Anais 9538
Valpione, Sara 9512
Van Blarigan, Erin 10006
van Bussel, Mark 2556
Van Cann, Thomas e22523
Van Den Bent, Martin J. 2009
Van den Bergh, Magali 7555
Van Den Eynde, Marc 3599
Van Der Graaf, Winette T.A. 11076
Van Der Noordaa, Marieke Emma Marguerite TPS593
Van Der Velden, Daphne Liselotte 2547
Van Dievel, Julie e22532
Van Driel, Willemien 5519
Van Helden, Erik Jacobus 11519, e15117
van Oostrum, Ilse e18506
Van Ramshorst, Mette S. 507
Van Triest, Baukelien e14048
Vanderwalde, Ari M. e20618
Vang, Alia 11073
Varadhachary, Gauri R. TPS3103
Varallyay, Peter e13517
Varga, Andrea 5513
Varghese, Anna M. 1064
Varlotto, John M. 8539

Vasquez, Juan e22012
Veitch, Zachary William Neil 547
Velcheti, Vamsidhar 11518
Vendrell, Ines e15743
Venook, Alan P. 3503
Vera, Jesus e21038
Verbiest, Annelies e16085
Vereskunova, Marina I. e17032
Vergote, Ignace 5580
Verheijen, Remy B. 11535
Verma, Amit e23096
Verma, Ashish e13068
Verma, Bikash TPS3093
Verma, Kamlesh e15156
Verma, Sunil 1020
Vernieri, Claudio e12556
Vetto, John T. 9576
Vey, Norbert TPS7070
Viana, Publio C. C. 5084
Viator, John Andrew e21053
Vidal Boixader, Laura 2543
Vidaurre, Tatiana 6547
Vidula, Neelima 1075, e12001
Vigil, Carlos Enrique e18515
Vilarino, Noelia e13526
Villarreal-Garza, Cynthia Mayte e12003, e21714
Vincent, Benjamin Garrett TPS1125
Vincenzi, Bruno 11038
Vishnubhotla, Priya e23163
Vissotto, Eduardo De Figueiredo e12024
Vitale, Maria Giuseppa e16063
Vivaldi, Caterina e15777
Vladimirova, Liubov Yu e17578, e17579
Vocka, Michal e23038
Vodolazhsky, Dmitriy I. e23007
Volyanskyy, Konstantin e23162
Von Minckwitz, Gunter LBA500
Von Pawel, Joachim TPS8585
Vos, Melissa 11068
Voss, Martin Henner 2500, 4523
Vuong, Brooke e15707
Vuzman, Dana e23077
Vyas, Ojas Harihar e18089

W

Wade, James Lloyd 9054
Wagg, Jonathan e15108
Wagle, Nikhil 1076
Wainberg, Zev A. 4071
Wakamiya, Karen 7561
Wakelee, Heather A. TPS8576
Waks, Adrienne Gropper e12134
Walcott, Farzana L. 1556
Walker, John WT e14587
Walker, Paul R. 6560, e20512
Wallner, Lauren P. e18012
Walsh, Robert John 1056
Wan, Jonathan e21032
Wang 1, Xicheng e14079
Wang, Andrew e15144
Wang, Changzheng 8550
Wang, Chao-Jie e15102
Wang, Chunmeng e14555
Wang, Daniel Ying 9566
Wang, Di 11032
Wang, Dian 11012
Wang, Eunice S. TPS7066
Wang, Guangji e12028
Wang, Hanping e20613
Wang, Haotong 11020
Wang, Jianfei 2070
Wang, Jie e16585, e20603
Wang, Jin 11029
Wang, Jinghui 8567
Wang, Jiping 4129
Wang, Lisa I. e20627
Wang, Meng-Yun e15552
Wang, Qian 1563
Wang, Qifeng e15559
Wang, Rui 540
Wang, Shiqing e15580
Wang, Shusen 1066
Wang, Si-Yu e20626
Wang, Siao-Yi e14552
Wang, Victoria 7040
Wang, Wei e15071, e15528
Wang, Weili 8574
Wang, Wen-xian e13120
Wang, Xin e15025
Wang, Xin Shelley 10100
Wang, Xinxin 3048
Wang, Yao 3042
Wang, Ying 566, e12538, e21588
Wang, Yuzi e14541
Wang, Zheng e15637
Wang, Ziqiang 3537
Wang-Gillam, Andrea e15795
Wangjam, Tamna e18233
Wapnir, Irene 513
Ward, Kenneth Daniel e18254
Wargo, Jennifer Ann 3008, 9587
Warren, Joan 5540, e18081
Warsame, Rahma M. 6512, 6572
Wassermann, Johanna 526
Watanabe, Akie e18237
Watanabe, Fumiaki e23042
Watanabe, Hiromi e20601
Watanabe, Junichiro e12529
Watanabe, Masahito e16530
Waterhouse, David Michael 9095
Watson, Sarah e14025
Waxman, Adam Justin 8018
Weber, Jeffrey S. 3031, 9523
Wedde, Trude Baastad 5059
Wei, Jia e15586
Wei, Jingwei 2043
Wei, Ping e20050
Wei, Xiao e16533, e16565
Wei, Ye 3603
Wei, Yuchun e23011
Wei, Zhig 9048
Weichenthal, Michael 9565
Weickert, Martin O. e15692
Weidhaas, Joanne B. 3040
Weil, Brent 10563
Weinberg, Benjamin Adam 3592
Weinmann, Arndt e15651
Weinstein, Cindy e21685
Weinstock, Chana 3018
Weisel, Katja C. 8006
Weiss, Anna 570, e23186
Weiss, Jared 6064, e20623
Weiss, Sarah A. 4565
Weldon, Christine B. e12067, e18205
Weller, Michael 2013
Wells, Connor 3555
Wells, Keith Ryan e21048
Welsh, James William 11562
Welsh, Sarah e16087
Wen, Song e14567
Wendtner, Clemens-Martin TPS7567
Weng, Li e23062
Wenz, Frederik K. e12105
Wenzel, Lari B. 5549
Weppler, Alison M. e21074
Wermke, Martin TPS3091
Werner, Theresa Louise e17071
Wesolowski, Robert TPS1127
West, Derek L. e15623
West, Howard Jack TPS9101
Westin, Gustavo Figueiredo Marcondes 8533, 8549
Weston, Erica 10079
Wheeler, Stephanie B. e18293
White, Richard Edward e18156
Whitworth, Pat W. 10117
Wick, Wolfgang 2061
Wieduwilt, Matthew Joseph e21626
Wildes, Tanya Marya e18020
Wildiers, Hans e13066
Wilking, Nils Erik 6535
Wilkinson, Anne e21507
Wilky, Breelyn A. 3075
William, William Nassib 1545, 6017
Williams, AnnaLynn 10045
Williams, Grant Richard 10033
Williams, Kirstin Anne e21648
Williams, Norman R. e12085
Williams, Scott TPS5096
Willumsen, Nicholas 1085
Wilson, Carmen Louise 10561
Wilson, Michelle K. e17034
Wimberger, Pauline e17077
Winther, Stine Brændegaard 10032
Wirapati, Pratyaksha 3538
Wirsching, Hans-Georg 2014
Wirth, Lori J. 6053
Wise, David 5054
Witzig, Thomas E. TPS7574
Woelber, Linn Lena e17033
Woff, Erwin 11569
Wolf, Ido 1549
Wolford, Juliet Elizabeth 5516
Wolin, Edward M. 4089
Wolters-Eisfeld, Gerrit e15739
Wong, Andrea Li Ann e12122
Wong, Angelique 10121
Wong, Deborah Jean Lee 9091
Wong, Kevin e16571
Wong, Martin CS e13091
Wong, Melisa L. 6519
Wong, Risa 10050
Wong, William Bruce 6511, e18317
Wong, Yao 1021
Woo, In Sook e15107
Wood, Lauren Virginia 3089
Wookey, Vanessa 6046, e17511
Woopen, Hannah e17062
Worst, Barbara Christine 10509
Wright, Alexi A. 6567
Wright, Frances Catriona e18234
Wright, Jesse P. 4122
Wroblewski, Mark 11522
Wu, Bin e15531
Wu, Christina Sing-Ying 3612
Wu, Elise e19011
Wu, Junjie e23131
Wu, Shang-Gin e20572
Wu, Shengyang 11034
Wu, Wenchuan e18216
Wu, Ya-Lan e20625
Wu, Yi-Long 8500, 8547
Wu, Yuan e17523
Wu, Zhiyong e20549
Wulff-Burchfield, Elizabeth Marie e21575
Wyrwicz, Lucjan 3530

X

Xianmin, Mu e23000
Xiao, Kun e14568
Xiao, Lei 7028, e18512
Xie, Congying e17009, e20046
Xie, Jipan e19509
Xie, Yuanqi e14534
Xing, Ligang 8531
Xing, Yan e18016
Xiong, Jian e15506
Xiong, Wenjun e22512
Xiu, Joanne 11066
Xu, Binghe e12017
Xu, Chunwei 11623, e14050
Xu, Haipeng e14515
Xu, Haiyan e20527
Xu, Jianmin 3575
Xu, Jianping e20528, e20562
Xu, Mengmeng e23148
Xu, Qiang 11605
Xu, Rui-hua e15772
Xu, Zhaomin 3596, e17101

Y

Yaeger, Rona 3534
Yam, Clinton TPS590
Yamada, Michiyo e13092
Yamada, Takeshi 3598
Yamagami, Kazuhiko e12108
Yamaguchi, Motoko 7546
Yamashita, Nami 1560
Yamauchi, Hideko e13051
Yamaura, Takumi e23136
Yan, Ning e15562
Yanagitani, Noriko 2546
Yang, Andrew Chung 4105
Yang, David Dewei 5080
Yang, Houpu e12099
Yang, James Chih-Hsin 2020
Yang, Jessica e21026
Yang, Joanna C. 6619, 10122
Yang, Lin e15546
Yang, Liu e15166
Yang, Mengdi e20534
Yang, Shan 1584
Yang, Sheng e14581
Yang, Sherry X. 11599
Yang, Wuwei e22502
Yang, Yan e15526
Yang, Yang 4021
Yanjun, Xu e23181
Yao, Yihong e14548
Yao, Zengwu e15577

Yap, Jason e17035
Yap, Kelly Khai Li 5023
Yarchoan, Mark e14512
Yashima, Jun e22539
Yasmeen, Samia e16044
Yasuda, Takushi e14635
Yates, Melinda S. 1551, 5511
Ye, Botian e15541
Ye, Feng e13112
Yeh, Chau-Ting e15657
Yeku, Oladapo O. 3050
Yellapragada, Sarvari e19515
Yendala, Rachana e14107
Yennu, Sriram 10114, 10118
Yerushalmi, Rinat 11561
Yi, Zongbi e23039
Ying, Jianming e20591, e20651
Ying, Jieer e15509
Ying, Xiaozhen e20667
Ying, Zheng ming e20510
Yip, Steven 4580, e16020
Yip, Walter e12049
Yogarajah, Meera e14572, e18542
Yokom, Daniel e15137
Yokota, Tomoya 2536
Yoneda, Kazue 8548, e23044
Yoo, Ji Geun e17003
Yoo, Shin Hye 10106
Yoon, Sung-Soo TPS8058
Yoshida, Taichi e15518
Yoshimoto, Nobuyasu e13086
Yoshitsugu, Kanako e20570
Yoshizawa, Ayuha e23215
You, Benoit 5554
Yu, Chu-Ling 10569
Yu, Evan Y. TPS5089
Yu, Helena Alexandra 9033
Yu, Hui e14525
Yu, Irene 3576
Yu, Jianjun e14527
Yu, Jingbo e18544
Yu, Tiffany e23106
Yu, Wenxi 11031
Yu, Xingfei 11539
Yu, Yunfang e12511
Yuan, Yuan 546
Yucel, Idris e17592
Yui, Jennifer C. e18514
Yusuf, Dimas e15746
Yuza, Kizuki e23191

Z

Zafar, Yousuf e18296
Zage, Peter E. 10553
Zahoor, Haris 4587
Zaidi, S. H. Manzoor e17513
Zalcberg, John Raymond 3582
Zalcman, Gerard TPS8581
Zamagni, Claudio TPS11627
Zamarin, Dmitriy e17087
Zamzam, Manal e18226
Zanelli, Francesca e20524
Zanotti, Giovanni e17526
Zanwar, Saurabh e20628
Zapotocky, Michal 10503
Zarkar, Anjali 4542
Zarrabi, Kevin e14559
Zauderer, Marjorie Glass 8554, e13118
Zaw, Myo e18265
Zdenkowski, Nicholas e14031
Zeidan, Amer M. 7010, 7057
Zenda, Sadamoto 6071
Zeng, Ming e16523
Zeng, Yuan e15561
Zenzola, Victor e12118
Zerdes, Ioannis e23088
Zerhouni, Yasmin A. e15094
Zhai, Bo 3049
Zhang, Alison Yan 11046
Zhang, Bo e15701
Zhang, C. e14535, e23127
Zhang, Gong-Yi 5570
Zhang, Haijun e20544
Zhang, Hanbo e12000, e15723
Zhang, Henghui e23086
Zhang, Jianjun e20042
Zhang, Jianwei 3607
Zhang, Jie e20011
Zhang, Jin e23003
Zhang, Li 10090
Zhang, Lianru e14076
Zhang, Meiling e23115, e23123
Zhang, Mingjuan Lisa 8551
Zhang, Pei e16007
Zhang, Qingyuan e12543
Zhang, Qisu e18161
Zhang, Rong e20066
Zhang, Rong-xin e15002, e15112
Zhang, Shuchao 11036
Zhang, Songan e14501
Zhang, Tengfei e23075
Zhang, Tong e15069
Zhang, Xiaodong e15573
Zhang, Xueyan e14578
Zhang, Yang e15095
Zhao, Chong 6028
Zhao, Grace Q. e23067
Zhao, Lan 6056
Zhao, Lianjun e23200
Zhao, Lingdi 3047
Zhao, Xiao-Liang e20009
Zheng, Daniel 10522
Zheng, Haoyi e21600
Zheng, Qiuhong e23177
Zheng, Wang Fang 6079
Zheng, Weihui e17583
Zheng, Yanan 11555
Zhong, Jim 4103
Zhou, Caicun e20660
Zhou, Fang e14069
Zhou, Jiaojiao 1530
Zhou, Jifang e19049
Zhou, Mingyi e15018
Zhou, Na e14059
Zhou, Rui e15557, e20069
Zhou, Tian 10110
Zhou, Tie e16511
Zhou, Yong e22500
Zhou, Zhen Ni 1580
Zhou, Zhenzhen e23206
Zhu, Anjie TPS1123, e12507
Zhu, Ji 3614, TPS3632
Zhu, Jingqiang e17585
Zhu, Xiaodong 4070
Zhu, Yahui e15524
Zhu, Yingming e14083, e15517, e15602
Zhuang, Wei 11043
Zhukova, Galina Vitalyevna e14051, e15619
Ziegler, Matthew e19508
Ziel, Kathryn e18195
Ziemer, Mirjana 3073
Ziemke, Michael e20550
Zinnen, Shawn 2589
Ziranu, Pina e17540
Zlatnik, Elena Yurievna e20018, e21081
Zuckerman, Tsila e18520
Zykova, Tatiana e15516, e17026

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